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Review

Review of Antibiotic Pollution in the Seven Watersheds in China

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Abstract

China consumes 0.15-0.2 million tons of antibiotics yearly, which takes up 50% of the world's consumption. In this paper, 7 watersheds in China were investigated in order to show a clear picture of the antibiotic distribution in the environment, seasonal variation, and sources. We find that the majority of the aquatic antibiotics come from livestock and aquaculture, followed by medical waste, wastewater treatment plants, and domestic sewage. The spatial distribution of antibiotics varies greatly. Antibiotic concentrations were the lowest in the Yangtze River while the highest was in the Liaohe River and the Pearl River. Songhua watershed and the Southwest River, influenced by the economy and population in the northwest region, displayed a lower quantity of antibiotics. Seasonal variance showed dry season concentrations that were higher than the wet season. Additionally, antibiotics exist not only in the water but also in the sediments. Overall, the distribution of antibiotics in China is uneven due to the economy and population levels. Public health risk and ecological impacts are big concerns regarding the great deal of antibiotic consumption and discharge.

Keywords: antibiotics; China; contamination; distribution; sources; watershed

For decades, humans and animals have been using antibiotics on a large scale to prevent or treat diseases and promote the growth of livestock and aquaculture [1]. The annual use of antibiotics in the world is estimated at between 100,000 and 200,000 tons [2]; China alone uses more than 25,000 tons of antibiotics a year [3]. Antibiotic-resistant genes have been recognized as an emerging pollutant in the environment. The potential toxicity of antibiotics to aquatic organisms and humans is also attracting scholars' interest [4]. Furthermore, medical antibiotic abuse situations are becoming a concern in China. The outpatient antibiotic utilization rate is 75% of patients with colds, 95% of surgical procedures, and 80% of hospitalized patients – far more than the international standard of no more than 30% [2].

Untreated antibiotics by sewage treatment plant, landfill leachate, and agricultural runoff are three

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leading sources of antibiotics into the environment. Once in the environment, antibiotics are frequently detected in surface waters, sediments, and biota [5]. This presence can cause ecological risk [6], poisoning of aquatic organisms, and can even threaten human health. However, antibiotic pollution and management has not been given enough attention. Based on the harsh realities of antibiotics, the distribution and sources of antibiotics were reviewed in a large number of studies, and the data is summarized according to watersheds and reflected in this paper in order to present a clear picture of antibiotic pollution in China.

Contamination Sources of Antibiotics in Chinese Watersheds

Table 1 shows different sources of antibiotics in major Chinese watersheds. Livestock and aquaculture remain an important source of antibiotic contamination. There are a variety of sources of antibiotics in the environment, most of which are deposited from livestock and aquaculture. Due to incomplete treatment, medical waste and sewage treatment plants discharge many antibiotics. In sewage treatment, the wastewater is partially biochemically degraded during the treatment process [7]. However, some antibiotics are not easily degraded and can be transformed during the disinfection process, leading to transformation products. Some of these transformation products have even been shown to retain their antibiotic potency [8]. Some higher concentrations of antibiotics have been shown to be linked to the contamination of agricultural antibiotics in tributaries.

The Haihe watershed covers Beijing, Tianjin, Hebei, and part of Shandong, with more than 120 million people. Around the Haihe River, antibiotic input is high mostly from aquaculture and livestock excrement. It has been reported that 57% of the city's gross agricultural production comes from animal husbandry and aquaculture. Discharge from sewage treatment plants has also been shown to be an important source of antibiotics in the river. Furthermore, the main source of antibiotic contamination in the Haihe River may result from its tributaries [9].

The Pearl River Delta (PRD) is a region heavily affected by urban, industrial and agricultural activities. Discharges of treated or untreated wastewater significantly increase the detection rate of common antibiotics in the Pearl River Estuary (PRE). Human antibiotic usage volumes in the PRD region (including Hong Kong) has reached 15,770 tons in 2004, with equal or possibly larger quantities used in the agricultural sector [10]. It was estimated that about 1.73×10^{10} t per year of wastewater is discharged from the PRD into the PRE and the South China Sea (SCS) [11]. More than 20 antibiotic compounds can be found in sewage and sediment, vegetables and soil, river water and even drinking water in the PRD [10, 12].

As for the Yellow River, high concentrations and frequencies of antibiotics were observed. These areas are densely polluted by industrial and municipal wastewater and are a public health concern.

In the Three Gorges Reservoir area, the number of livestock and poultry farms was close to 12,000 in 2015. Antibiotics in animals are not completely absorbed and can be discharged into waterways, the soil, and surface runoff from animal manure and urine, through sewage irrigation, or waste fertilizer utilization [13]. As a highly developed area located on the east coast of China, the Yangtze estuary has become an important industrial and economic center of China, accounting for 18.7% of gross national production. At the same time, rapid development has brought heavy environmental burdens to the region. The estuary region can obtain considerable pollutant input from land-based sources through river runoff and sewage discharge.

The Liaohe watershed is located in the northeast region of China, and it includes a high degree of urbanization with a population of 33 million (2007) [14]. A large amount of wastewater containing antibiotics will greatly affect concentrations in the Liaohe watershed. From the samples of the Liaohe River, there were a lot of quinolone class antibiotics. This could be attributed to biological utilization and absorption from aquaculture and livestock excretion.

Table 1. Sources of antibiotics in major Chinese watersheds.

Watershed	Agricultural activities	Sewage treatment plants	Medical waste	Livestock / Aquaculture	Industrial waste	Sludge	Domestic sewage	Tributaries
Haihe River	√	√		√		√		
Songhua River		√	√	√	√			
Liaohe River	√	√	√	√			√	
Yangtze River		√	√	√	√		√	
Yellow River		√		√	√			√
Northwest Flow Area (2 lakes)	√	√	√	√			√	
Pearl River		√	√	√			√	√

Distribution of Antibiotics in Chinese Watersheds

According to the literature reviewed by the authors, various antibiotics have been detected in the Bohai Sea [6], the Yellow Sea [6], the Liaohe River [5], and the Haihe River [15] due to the large-scale abuse of antibiotics (the full name and abbreviation for each antibiotic can be found in Table 2). The Liaohe and Haihe rivers are particularly concerning as they have the highest antibiotics concentrations detected in China.

Antibiotics Distribution in Haihe River Watershed

The Haihe watershed covers Beijing, Tianjin, Hebei, and parts of Shandong, with a drainage area of 318,000 km^2, serving a total population of more than 120 million. Previous studies have investigated the presence of 12 antibiotics in the water and sediment of the Haihe, in the range of 0.3-173.2 mg/kg [15]. The research was conducted within the territory of the Haihe in Tianjin (the mainstream and tributaries), Dagu Drainage River, Chentaizi Drainage River, Duliujian River, and fish ponds. In the surface water, sediment, and fish pond samples, the study found 22 different types of antibiotics, including 8 fluoroquinolones(FQs), 9 sulphonamides(SAs), and 5 macrolides(MLs) based on EPA Method 1694 with some modifications.

In the mainstream surface water samples of the Haihe, 16 antibiotics were found, including 8 FQs, 5 SAs, and 3 MLs. Several major antibiotics and their concentrations are shown in Fig. 1. In all the water samples, 6 antibiotics were found, including ofloxacin (OFL), sulfamethoxazole (SMX), sulfadiazine (SDZ), roxithromycin (ROX), sulfamonomethoxine (SMM), and erythromycin (ERY). The concentrations of ∑FQs, ∑SAs, and ∑MLs were, respectively: 26.5 to 196 ng/L (mean: 121 ng/L), from 27.4 to 317 ng/L (mean: 187 ng/L), and from 6.6 to 33.4% (mean: 17.1 ng/L). SAs are the more prominent antibiotics, accounting for 57.1% of the total antibiotic concentrations, followed by FQs with 37.1%.

The range of the antibiotics in the surface water of the Haihe was not very high. In the mainstream of the Haihe, SMX was detected with an average concentration

Table 2. Abbreviations of antibiotics.

Full name	Abbreviations
Amoxicillin	AMX
Azithromycin	AZI
Cefazolin	CAL
Cefmetazole	CMZ
Cefotaxime	COX
Cephalosporins	CEs
Chloramphenicol	CAP
Chlorotetracycline	CTC
Ciprofloxacin	CIP
Clarithromycin	CLA
Doxycycline hyclate	DXC
Enrofloxacin	ENR
Erythromycin	ERY
Florfenicol	FF
Flumequine	FLU
Fluoroquinolones	FQs
Lincomycin	LIN
Lomefloxacin	LOM
Macrolides	MLs
Norfloxacin	NOR
Ofloxacin	OFL
Oxytetracycline	OTC
Quinolones	QNs
Roxithromycin	ROX
Sulfacetamide	SCT
Sulfachinoxaline	SCX
Sulfachloropyridazine	SCP
Sulfadiazine	SDZ
Sulfadimethoxine	SDX
Sulfisoxazole	SIZ
Sulfadimidine	SMD
Sulfamethazine	SMZ
Sulfamethoxazole	SMX
Sulfamethoxypyridazine	SMP
Sulfamonomethoxine	SMM
Sulfapyridine	SPD
Spiramycin	SPI
Sulfaquinoxaline	SQ
Sulfathiazole	STZ
Sulphonamides	SAs
Tetracycline	TC
Thiophenol	TAP
Trinethoprim	TMP
Tylosin	TYL

of 114 ng/L (median: 137 ng/L), followed by norfloxacin (NOR) and OFL, with average concentrations of 65.5 ng/L (median: 58.5 ng/L) and 36.4 ng/L (median: 30.9 ng/L), respectively. SMX concentrations in the Haihe are similar to those previously reported in the Cache La Poudre River (mean: 110 ng/L) [7]. However, the results of SMX concentrations were above observations within the Huangpu River (median: 6.78 ng/L in June and December 28.34 ng/L) and surface water in Germany (median: 30 ng/L) [1] and watersheds of southeast Queensland, Australia (median: 8 ng/L) [4], but lower than those found in the Rio Grande River (300 ng/L) in the United States [16]. The concentration of OFL was similar to that of the Seine River in France (mean: 30 ng/L) [17], but lower than in the Haihe River found in previous studies (average: 170 ng/L) [9]. The average concentrations of FQs and MLs in urban areas were higher, while SAs were found at higher concentrations in urban and rural areas. FQs and MLs are drugs used primarily for humans, while SAs are drugs used for humans and animals. In addition, FQs are easier to absorb in sediments than SAs [2], and MLs tend to be hydrolyzed in water [9], therefore weakening FQ and ML transport in water.

In total, 19 antibiotics were detectable in the sediment samples. FQs were found at the highest frequencies and average concentrations, followed by MLs. The lowest mean concentrations were obtained for SAs [7]. However, FQs had a strong affinity for soil particles. Compared with the antibiotic concentrations in 2008 and 2010, there were a large number of antibiotics in the Haihe watershed, but in the Dagu and Chentaizi tributaries the number of antibiotics decreased. In the present studies, NOR and OFL were found in all the sediment samples. Ciprofloxacin (CIP) and lomefloxacin (LOM) were found in 46, 45, and 36 samples, respectively, out of 47 sediment samples. In the mainstream of the Haihe River, average concentrations of NOR, OFL, CIP, enrofloxacin (ENR), and LOM were: 67.2 (56.6) mg/kg, 36.8 (33.4) mg/kg, 23.2 (13.8) mg/kg, 19.8 (15.5) mg/kg, and 4.8 (3.8) mg/kg, respectively. These results are higher than those detected in the Yellow, Liaohe, and Haihe [18] rivers, and lower than in previous studies [9]. In the sediments, FQs are the main detectable antibiotic and their concentration is several orders of magnitude higher than their concentration in surface waters. Here it is evidenced that sediment can be an important reservoir of FQs.

During the winter, the concentration of antibiotics in surface water increased significantly ($p<0.01$), except for tetracycline (TC) and oxytetracycline (OTC). Lower concentrations in the summer can be attributed to higher runoff (increased flow rate), faster photolysis [17], thermal degradation (water temperature in summer is about 26ºC and 5ºC in winter), and biodegradation. These conditions were also associated with higher microbial activity during the summer season [19].

Antibiotics Distribution in the Pearl River Estuary

PRE is sent from the Pearl River (PR) to the South China Sea. PRD is one of the most economically developed regions in China. Liang et al. [20] investigated that antibiotics released into the aquatic environment play an important role in the spread of antibiotic resistance. Environmental conditions can significantly affect the distribution of antibiotics between water and sediment.

Through the study of Xu et al. [11], 10 antibiotics were all detected at least once in the riverine outlets during the three sampling seasons (June 2009, October 2009, and January 2010, which are representative months for the wet season, intermediate season and dry season, respectively). Most antibiotics showed a downward trend from the PRE towards SCS, strongly confirming that riverine runoff is the most important source for these contaminants.

From all the target antibiotics, 7 were detected in both wet and dry seasons. During the dry season,

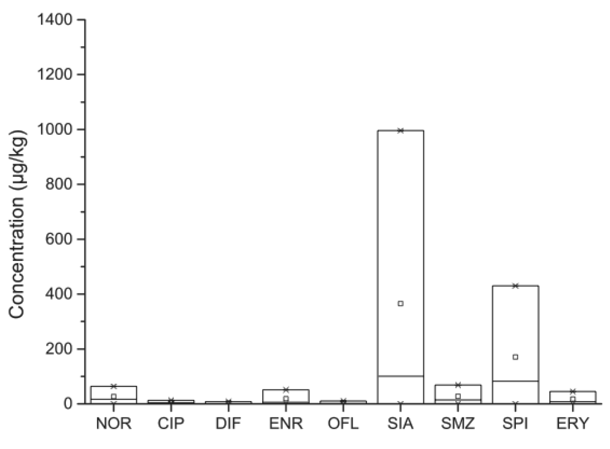

Fig. 1. Main antibiotics and their concentrations found in the Haihe River.

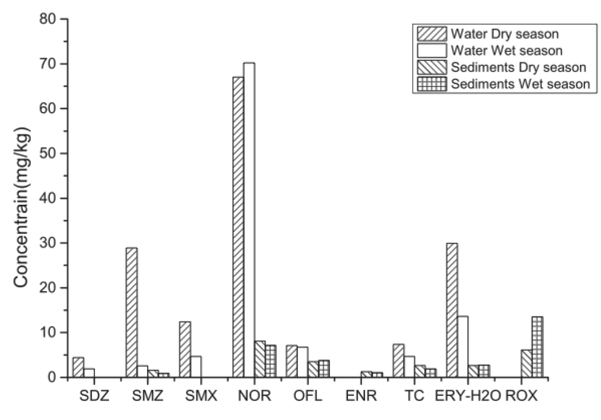

Fig. 2. Main antibiotics and concentrations of wet and dry seasons in water and sediment samples in the Pearl River.

4 antibiotics in water and sediments were detected at more than 50% frequency, indicating widespread use of these antibiotics in the PRD region. In the PRE region, as Fig. 2 shows, there are a large number of differences in antibiotic distribution between water and sediment. Among them, ENR and ROX were detected only in sediments, while SDZ and SMX were only detected in water. As reported, SAs showed the lowest detection frequency and average concentration in sediments. ROX was detected in about 30% of the sediment samples, but not in the water samples [7]. These patterns were likely due to the interaction between sediments and water in the aquatic environment.

On the whole, the concentration of antibiotics in the water in the wet season was significantly higher than that in the dry season. Seasonal changes can be influenced by a range of environmental factors such as discharge volumes, water flow rates, and rates of photolysis and biodegradation [9, 20]. In the summer, higher temperatures can accelerate the degradation of antibiotics in the water [21]. Also, the high water through-flow rates can dilute the concentration of antibiotics. However, the maximum concentration of several antibiotics in wet or intermediate seasons were found to be higher than those in the dry season. This may be a result of seasonal variation of antibiotic usage, precipitation (flow rate or tidal effects), or runoff during the wet season [11]. The concentrations of antibiotics in sediments did not have significant seasonal variations, which indicates that the antibiotics absorbed in sediments are not affected by changes in the source input or the short-term environmental conditions of the seasons. The spatial distribution of the antibiotic concentrations for PRE were largely dependent on the main source of pollution, the highly dense population in the PRD and the low treatment rate of domestic sewage (below 70%). Increased population growth, larger livestock populations, and intensive agricultural production contributed significantly to elevated levels of common antibiotics in the river and estuary.

Antibiotics Distribution in the Yellow River Watershed

The Yellow River is China's second longest river with antibiotic pollution amounting to 2×10^6 tons per year. Research has found 2 FQs (OFL and NOR), 2 MLs (ROX and ERY), and SMX detected in the six tributaries of the Yellow River. The remaining four antibiotics of interest, SDZ, sulfadimidine (SMD), chloramphenicol (CAP), and amoxicillin (AMX), were not detected in all water samples. There were five antibiotics detected, the highest was NOR, with a concentration of 327 ng/L in the tributary. Sulfonamide was detected in 38% of the samples in the range of 11-68 ng/L. The detection frequencies of OFL and NOR in the tributaries were 50% and 25%, respectively. The mean concentration of OFL from the six tributaries was 109 ng/L, while the maximum concentration found in the tributary of the Sishui River was 129 ng/L. The maximum concentration for NOR was 327 ng/L. MLs were the most frequently detected class of antibiotics. The frequencies of ERY-H_2O and ROX were 63% and 75%, respectively. However, compared with FQs, MLs had lower concentrations in the six tributaries, with a maximum detected concentration of 91 ng/L [22].

From 16 sampling sites in the Yellow River, in the mainstream, five types of antibiotics OFL, ROX, ERY-H_2O, and SMX were detected, consistent with its tributaries [22]. The water samples also showed trace levels of SMX concentrations ranging from 3-56 ng/L. The largest concentrations of SMX were discovered in the Sishui tributary at 56 ng/L. This suggests that the tributary is likely to be the main source of pollution for the Yellow River. Water samples containing OFL and NOR had testing frequencies of 81% and 75% respectively. ERY-H_2O and ROX had testing frequencies of 50% and 44% respectively.

According to research by Zhou et al. [18], among the 17 targeted antibiotics, seven were detected within the sediments of the Yellow River during the wet season. NOR, OFL, and ERY were found with detection frequencies of 60%, 67%, and 73%, respectively, with mean concentrations of 7.76, 3.49, and 8.11 ng/g respectively. However, the detection frequencies of SDZ, OTC, and TC were all below 33%.

As Fig. 3 shows, in the wet season the concentrations of MLs were affected by TOC, pH, and texture of the sediments, while the concentrations of TCs were only affected by pH. Low TOC levels and high sand contents in the sediments of the Yellow River resulted in a low distribution of antibiotics onto the sandy sediments. FQs were detected in the sediments with high concentrations and frequencies. TCs were also detected in some sampling sites with high concentrations, but SAs were often found with low concentrations and frequencies [18]. Few studies have shown the presence of TC deposits in China and Cache La Poudre River in the USA [23]. Sediments are important to study because of their strong adsorption capacity onto particles [17].

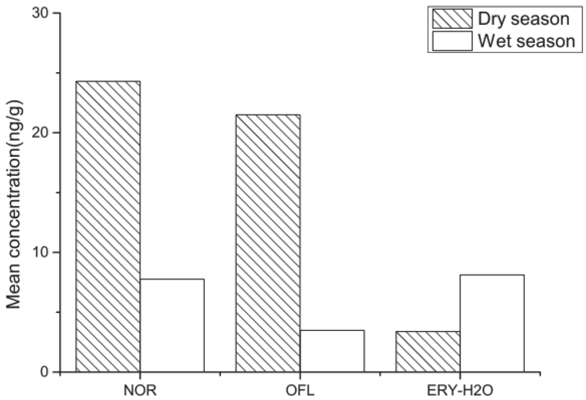

Fig. 3. Antibiotic concentrations detected in the Yellow River during dry and wet seasons.

In the dry season, ROX was detected with a frequency of 86% but was not detected in the wet season. The detection frequencies of enoxacin, OFL, and ERY-H_2O were 93%, 93%, and 14% respectively with mean concentrations of 24.3, 21.5, and 3.39 ng/g, respectively. The total concentration of FQs found in the Yellow River was significantly higher than those of SAs and MLs [18,22].

Antibiotics Distribution in the Yangtze River Watershed

At 6,397 km, the Yangtze River is Asia's longest and the third longest in the world. The river covers 1/5 of China's land area, with about 1/3 of the population of China. The basin area of the Yangtze River Economic Zone accounted for nearly 45% GDP in 2014 [24]. It is a good source of water for industrial and agricultural production, and also an ideal habitat for the growth and reproduction of aquatic organisms.

Concentrations of 6 types and 28 kinds of antibiotics in the Yangtze and main tributaries in the Three Gorges Reservoir area were analyzed. There were 10 antibiotics of 4 types detected, including SDZ, SMX, and sulfamethazine (SMZ) of SAs, ERY, ROX, tylosin (TYL) of MLs, OFL of FQs, other classes of CAP, florfenicol (FF), and lincomycin (LIN), which is shown in Fig. 4. Except for OFL and CAP, the other eight antibiotics are used in animal and poultry products. The detection rates of FF and LIN were the highest among the 10 antibiotics detected, both up to 80.65%. The detection rate of ERY, ROX, and CAP were above 60%; SDZ had the lowest detection rate at less than 10% [25].

There were 10 antibiotics detected in the Three Gorges Reservoir area. Eight of the ten are used in livestock and poultry: SDZ, SMX, SMZ, ERY, ROX, TYL, FF, and LIN. LIN and FF have higher levels of concentration (median: 7.05 and 24.3 ng/L respectively) and a detection rate of 80.65% for both. The SA (SDZ, SMX, SMZ) detection rate was not high, but the combined concentration was higher. The concentration of SDZ (90.7 ng/L) was the highest of the other 3 SAs detected and is the dominant component in supernatant of pig manure. In comparison with ERY (5.8 ng/L), ROX (16.4 ng/L), and TYL (9.2 ng/L) did not have high concentrations, but the detection rates are at 40% or more [25].

In the water samples, SAs and LIN were mainly detected, followed by FQs and MLs. Concentrations of antibiotics in the three gorges reservoir area was lower than other watersheds. SDZ, ROX, and OFL were the only antibiotics that had a higher concentration than that of the Yangtze estuary [26] and the Huangpu River [3]. However, the concentrations were lower than in the Yellow [22] and Pearl [12, 27] rivers.

Shi et al. [28] studied the occurrence and distribution of five classes of antibiotics in the surface sediments of the Yangtze estuary. Fig. 5 shows the range of detected antibiotics. In Shi's study, 20 antibiotics were detected in surface sediments, with more than half of the sampling points within the four seasons, including FQs, TCs, MLs, and CAPs. TCs, sulfaquinoxaline (SQ), ENR, and thiophenol (TAP) were the highest detected compounds with a detection rate of 100%. FQs had the lowest detection frequency among the target antibiotics, only in May 2012 were four antibiotics of FQs all detected. TCs, SQ, ENR, OFL, and TAP were detected in all samples of all four seasons.

Four FQs, including NOR, CIP, ENR, and OFL, were seldom detected among the compounds, with the detection frequency less than 57%. The maximum concentration ranges of FQs were from 20.2-69.3 ng/g of NOR, 12.1-42.9 ng/g of CIP, up to 4.8 ng/g of ENR, and 48.1-458.2 ng/g of OFL. The detection rate of TC, OTC, doxycycline hyclate (DXC), and chlorotetracycline (CTC) was 100%, which means antibiotics are widely used in the area. Compared to the other antibiotics, SA levels in the surface sediments of the study area were generally lower, with concentrations below 1 ng/L. Although the detection rate of SQ is 100%, its maximum concentration is less than 1 ng/g at all the sampling points. In addition, all the target antibiotics were detected within ng/g concentrations. FQs were

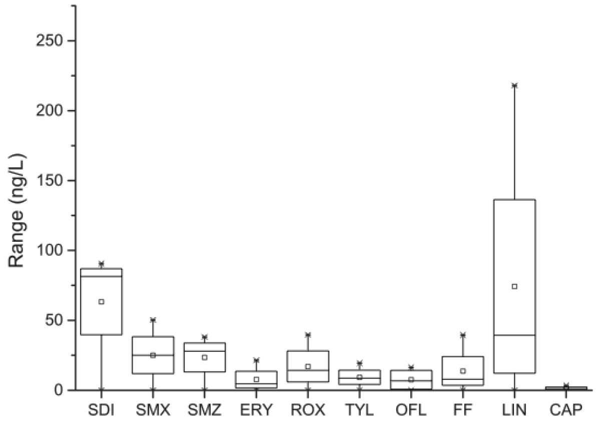

Fig. 4. Range of detected antibiotics in the Three Gorges Reservoir area.

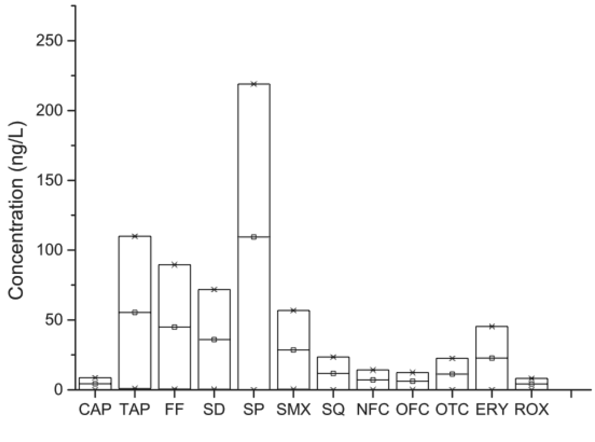

Fig. 5. Range of detected antibiotics in the Yangtze estuary.

the main detected antibiotics, accounting for 58.5-85% of the total sampled antibiotics, while TCs and MLs accounted for 4-25% and 9.3-13.5% respectively. SAs had the smallest detection rate of 1.8-4.5% from the sampled antibiotics.

Known to be influenced by hydrodynamics and temperature changes [9], the concentration of antibiotics varied greatly within the 4 different seasons. The concentrations of SAs and MLs were higher in January and May than concentrations in July and October. Relative to January 2012, TCs were rarely found in 3 out of the 4 seasons. Due to relatively high water solubility, SAs have become the main antibiotic in the surface water of the Yangtze estuary [26].

Antibiotics Distribution in the Liaohe River Watershed

In May 2012, emphasis was placed on 21 antibiotics with five different classes: SAs, quinolones (QNs), TCs, MLs, and trinethoprim (TMP). Antibiotic concentrations of water samples in the Liaohe River can be seen in Fig. 6.

From Bai's study [5] focusing on antibiotic occurrence, distribution, and bioaccumulation, 50 sediment samples were taken with a total of 13 antibiotics detected. The maximum concentrations of ∑SAs, ∑QNs, ∑TCs, and ∑MLs were up to 2.63, 116.99, 404.82, and 375.13 μg/kg, respectively. The dry weight (mean 0.42, 20.91, 32.11, 32.77 mg/kg, respectively), and proportion accounted for 0.3%, 24.3%, 37.3%, and 38.1% of the total antibiotics. The highest level of total antibiotics (742.8 mg/kg) was found at a site near a sewage treatment plant in the Hunhe River. While the lowest level (0.04 mg/kg) was found in the Liaohe River, where we observed a confluence of the Eastern and Western Liaohe Rivers.

Furthermore, SAs were detected in the sediments of the Liaohe watershed at low levels and detection frequencies. The concentrations of sulfapyridine (SPD), SMD, SMX, and sulfadimethoxine (SDX) were in the range of 0.02-0.14 mg/kg, with detection frequencies below 15%. Sulfacetamide (SCT), sulfathiazole (STZ), SMA, sulfamethoxypyridazine (SMP), sulfachloropyridazine (SCP), and sulfachinoxaline (SCX) were not detected in all the sediment samples. Among the TCs, OTC had a mean concentration of 29.12 mg/kg with the highest frequency of 74%, followed by CTC (mean concentration of 2 mg/kg and detection frequency of 40%) and TC (mean concentration of 0.98 mg/kg and detection frequency of 30%) [5]. For the QNs, the mean concentrations of OFL, ENR, CIP, and NOR were 5.62, 2.71, 0.88, and 11.7 mg/kg, respectively, with detection frequencies of 46%, 50%, 18%, and 76%, respectively, in the Liaohe sediments. The mean concentrations of the two MLs, ERY-H_2O and ROX, were 11.45 and 21.31 mg/kg, respectively, with detection frequencies of 48% and 64%, respectively. The concentrations of ERY–H_2O and ROX in the Liaohe River were higher than those in the Cache La Poudre River in the USA (maximum concentrations of 25.6 and 5.9 mg/kg, respectively) [7], but lower than those in the Pearl River (maximum concentrations of 385 and 336 mg/kg, respectively). In the surface water of the Liaohe watershed, spatial population distribution of antibiotics is closely related to the river pollution level. In cites upstream from the Liaohe watershed, the concentration level for antibiotics is higher than those in the suburban and rural areas [29].

The presence of antibiotic industries and the large use of antibiotics (for human and animals) are the main causes of pollution in the Liaohe watershed. There are three places where antibiotic pollution is more severe: Xinmin city (drainage for total antibiotic concentration in the basin at the highest point is 4,532.23 ng/L), and near the outlet of urban sewage treatment plants in Shenyang and Anshan [30]. This indicates that in densely populated urban areas, urban sewage discharge is the main source of antibiotics in the watershed.

According to the results from Deming Dong et al., in the Liaohe River in Jilin Province, MLs and QNs were the dominant antibiotic classes in the summer (July 2015). However, TCs and MLs were the main antibiotic

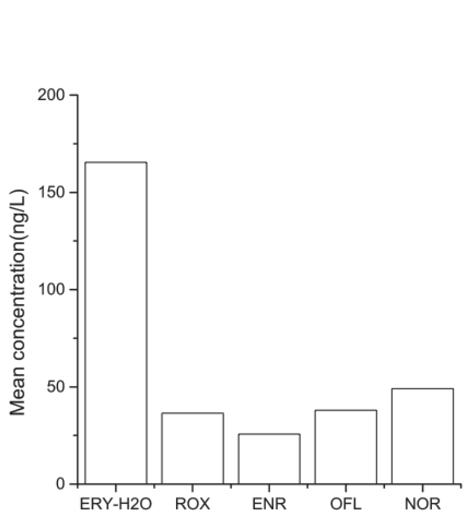

Fig. 6. Antibiotic concentrations of water samples in the Liaohe River.

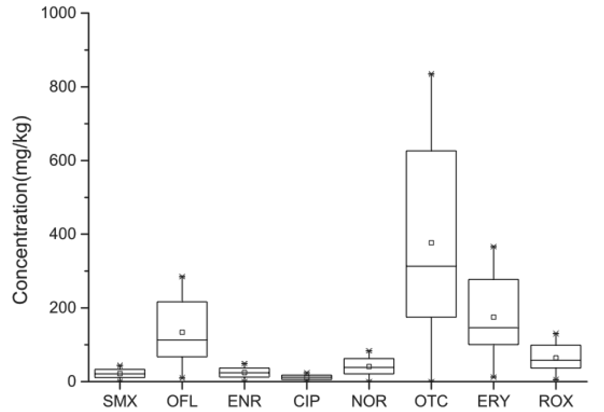

Fig. 7. Range of antibiotics in the Liaohe River in Jilin Province.

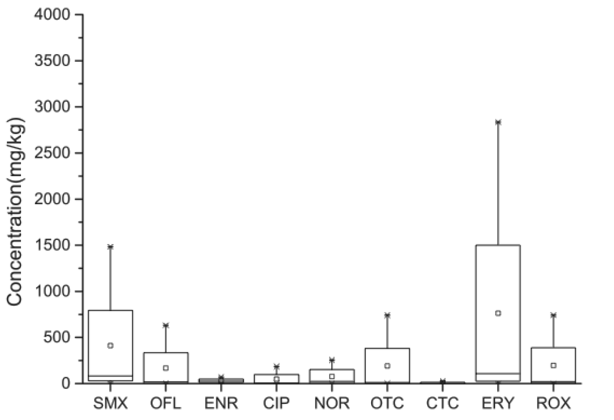

Fig. 8. Range of antibiotics in the Liaohe River in Liaoning Province.

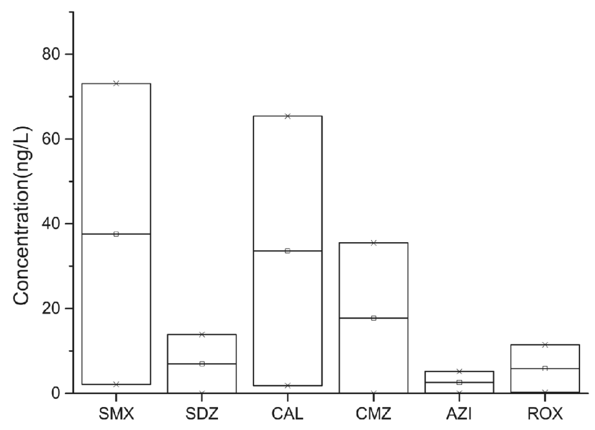

Fig. 9. Range of target antibiotic concentrations in the Songhua River mainstream.

classes in the fall (November 2015). The antibiotic concentrations in sediments at each sampling site showed no significant seasonal variations. These results are consistent with previous studies on the Liaoning Section of the Liao River [18]. Figs. 7 and 8 display the range of antibiotics in the Liaohe River in Jinlin and Liaoning provinces.

Antibiotics Distribution in the Songhua River Watershed

The Songhua watershed is located in northeastern China, with a total length of 1900 km and an area of 545,600 km^2. Wang et al. studied the occurrence of 12 types of antibiotics and their distribution in the mainstream of the Songhua River and its tributaries. These antibiotics include three cephalosporins (CEs) (cefazolin(CAL), cefmetazole (CMZ), cefotaxime (COX)), three MLs (azithromycin(AZI), clarithromycin (CLA), ROX), three FQs (OFL, NOR, flumequine(FLU)), and three SAs (SDZ, SPD, SMX). Fig. 9 shows the range of target antibiotic concentrations in the Songhua River mainstream.

The study collected 152 surface water samples in January, May, July, and October of 2016. Results showed that 12 antibiotics were detected in the mainstream of the Songhua River. Among the 12, SMX and CAL were the highest detected with a maximum concentration of 73.1 and 65.4 ng/L, respectively. The average concentrations of the other antibiotics were less than 15 ng/L, except for CMZ with a concentration of 35.6 ng/L.

AZI, ROX, and OFL were detected at all sampling sites (detection frequency was 100%). Also, CLA and NOR were detected at high frequencies (96.8 and 84.3%). ROX was the highest concentration (0.20-11.5 ng/L) detected, followed by AZI, CLA, and FLU at concentrations of 0.06-5.14 ng/L, up to 4.17 ng/L, and 0.02-4.21 ng/L respectively. NOR and OFL were present at much lower levels, with concentrations of up to 2.40 ng/L and 0.01-1.80 ng/L, respectively, in the mainstream. In the tributaries, the detection frequencies of these six target antibiotics were lower than frequencies in the mainstream; however, the maximum concentrations in the tributaries were higher than in the mainstream [31]. SAs had the highest frequency (86.4%) detected, with concentrations of up to 60.9 ng/L. Compared with the PRE, the Yangtze Estuary, and the Seiner River in France, SA, ML, and FQ antibiotic concentrations in the Songhua River watershed were detected at a lower concentration levels.

The Songhua River freezes for nearly six months starting in November and ending in April. The average thickness of ice covering the river is about 0.7-1.5 m. In deep freeze conditions, sulfa drugs and CEs are the main antibiotics detected (Fig. 10). Concentrations of mainstream antibiotics (i.e., CEs, SAs, FQs and MLs) are significantly higher than other months. In the icebound season, the downstream antibiotic concentrations are higher than the upstream, which is due to the significant decrease in the flow of the Songhua River from the ice. Runoff accounted for 20% of the total flow for the year. This greatly reduces the dilution effect, leading to an

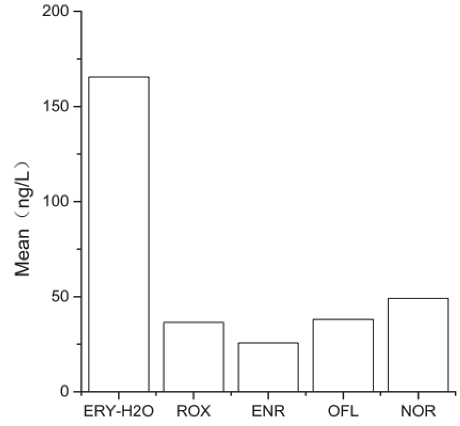

Fig. 10. Concentrations of target antibiotics in the Songhua River in the ice season.

increase in the concentration of antibiotics. Snow and ice cover on the surface of the river is another factor, as it significantly reduces the degradation of antibiotics, especially through photodecomposition [32].

Antibiotics Distribution in Bosten and Ulungur Lakes

Bosten Lake lies on the south slope of the Tianshan Mountains in Xinjiang, and is the biggest inland freshwater lake in China. Ulungur Lake is located in the city of Altai, in Xinjiang, and is the 10th largest freshwater lake in China and the second largest freshwater lake in Xinjiang [33]. As the two most important lakes in the northwest inner flow region, they have a profound impact on the region's environment.

From Lei's study [34], there were 18 antibiotics detected on the surface water and sediment samples. The average concentration of antibiotics detected in water samples ranged between 0.28 ng/L (TYL)-39.22 ng/L (CIP). The average concentration of antibiotics in sediment samples was up to 76.51μg/kg (CIP). The maximum concentration of antibiotics in both water and sediments samples were 112.30 ng/L (CIP) and 213.38μg/kg (CIP). In the water samples, the detection frequency of the four QNs were very high, with the average concentration ranging from 6.03-39.22 ng/L. The pollution levels of ENR (mean 6.03 ng/L) and OFL (mean 9.29 ng/L) in Bosten Lake are comparable to that of the Hong Kong coast (2.3 ng/L-8.0 ng/L) and the French Seine (<10 ng/L) [17]. The detection rate of SAs was 100%, the average concentration ranged from 5.39 ng/L (sulfisoxazole (SIZ)) -15.41 ng/L (SCT). All four types of TCs were detected, 100% (ROX), 92% (spiramycin (SPI)), and 83% (ERY and TYL), respectively. The average concentration of TCs ranged from 0.45 ng/L (TC)-2.99 ng/L (OTC). The detection frequency of the four major cyclic esters were greater than 80%, with an average concentration ranging from 0.28 ng/L (TYL)-2.47 ng/L (ROX) [35]. The average concentration of QNs found in the Bosten Lake sediments ranged 8.6-76.51μg/kg. The mean concentrations of SAs in the regional sediment sample were detected in concentrations as high as 3.81 μg/kg (SCT). The four types of TCs had a detection rate of 100%, with an average concentration ranging 4.23 μg/kg (CDC)-10.41 μg/kg (CTC). The ML target compounds were 100% detected in sediment samples, except for TYL, with a detection rate of 92%. The average concentration of MLs ranged from 0.65μg/kg (TYL)-9.69 μg/kg (ROX). In CAPs, FF was 100% detected and the detection rate of CAP was 91.7%.

17 antibiotics were detected in the surface water samples of Ulungur Lake. The highest average concentration within the target antibiotics for the water samples was 20.78 ng/L (CIP) (shown in Figs 11 and 12), while the average concentration in sediment samples was 118.17 g/kg (CIP). The maximum concentrations detected from the water samples and sediments were 53.85 ng/L (LOM) and 364.39μg/kg (CIP), respectively.

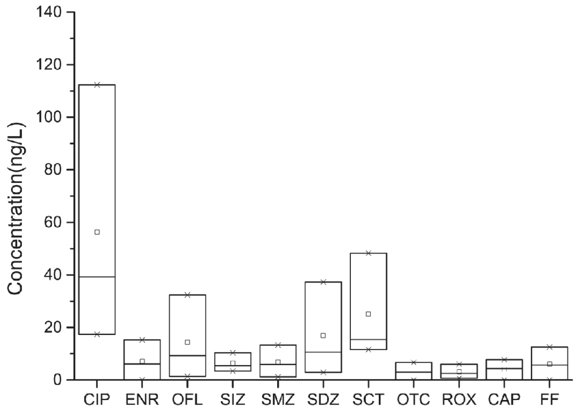

Fig. 11. Range of antibiotic concentrations in water samples from Bosten Lake.

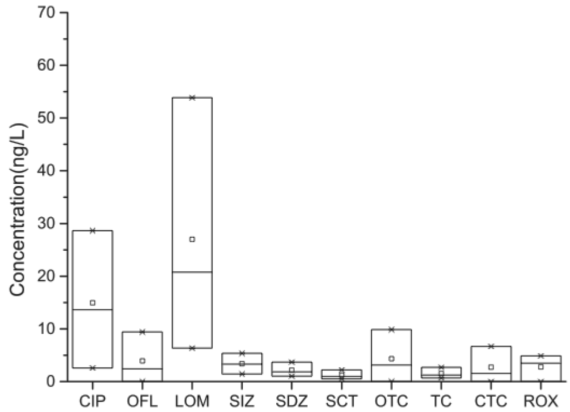

Fig. 12. Range of antibiotic concentrations in water samples from Ulungur Lake.

Evaluation the Comparability of Results

As shown in Table 3, sample features of the 7 investigated watersheds are summarized and compared below:

1) Number of samples: The number of samples in each investigated watershed ranged from 16 to 152, with an average of 56 and standard deviation of 47.
2) Date of sampling: The sampling years mostly ranged from 2010 to 2016, except for the samples collected in the Yellow River in 2006. Some watersheds collected samples in both summer and winter (i.e., the Songhua, Yangtze and Pearl rivers), while others took samples from May to September (i.e., Haihe River, Liaohe River, Yellow River, and Northwest Flow Area).
3) Types of samples: Water samples were compared for the 7 watersheds in this paper. The sample volume and analysis methods are also listed in Table 3.

Table 3. Sampling situation of major Chinese watersheds.

Watershed	Number of samples	Sample volume	Sampling date	Sample analysis method
Haihe River	29	500 mL	September 2010	HPLC-MS/MS
Songhua River	152	1L	January, May, July, and October 2016	UPLC-MS/MS
Liaohe River	50	1L	May 2012	N/A
Yangtze River	93 (Three gorges reservoir area)	1L	May and June 2016	LC-MC/MS
	7 (Yangtze estuary)	2L	July and October 2011, January and May 2012	UPLC-MS/MS
Yellow River	24	1L	June 2006	HPLC-ESI-MS/MS
Northwest Flow Area	12(Bosten Lake)	1L	July 2012	HPLC-MS/MS
	12(Ulungur Lake)			
Pearl River	16	1L	June and October 2009, January 2010	LC-MS/MS

Conclusions

This paper reviewed a series of papers on antibiotics in the natural aquatic environment in China. In recent decades, China has consumed a great deal of antibiotics, resulting in higher levels in the environment – especially waterways. The primary antibiotic pollutants for each watershed are: ERY in the Liaohe River, SIA in the Haihe River, NOR in Yellow River and Pearl River, and OTC in Ulungur Lake. Economic and demographic factors have severely affected the distribution of antibiotics. Based on these watersheds, the temporal and spatial distribution of antibiotic pollution displays the eastern watersheds (i.e., Haihe River and Liaohe river) to be higher than the rest of China. In this paper, the current level of antibiotics detected in the Yellow River and the southeastern Liaohe River are alarming, resulting in seriously polluted watersheds. Specifically, in the east region of the Heihe-Tengchong line of China, the concentration of antibiotics detected is very high. At present, there are few studies for western and southwestern China, indicating that people's attention to antibiotics should urgently be improved. There needs to be more community awareness and education on the concentration of antibiotics found in the environment. Increasing levels of antibiotics in the environment, especially in the waterways, is a major public health concern. On the other hand, in water treatment, there are very few indicators of high antibiotic levels in final effluent. More needs to be done to determine and control the concentration of antibiotics discharged into the environment.

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Conflict of Interest

The authors declare no conflict of interest.

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