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Review

Spatio-Temporal Distribution and Risk Assessment of Antibiotic in the Aquatic Environment in China Nationwide, A Review

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Abstract: Antibiotics have been an emerging concern due to the potential adverse threat on the environment and human health. Studies on the presence and fate of antibiotics in Chinese aqueous environments have increased in the past few years. Nevertheless, the distribution of antibiotics contributing to the development and dissemination of antibiotic resistance in China nationwide remains unclear. This review summarizes the temporal and spatial distribution of antibiotics in different aqueous environmental systems across the China in the last decade. In all, 79 antibiotics with the concentration range of 0.04 ng/L~6.54 μg/L have been detected in the aquatic environment in China. The Bohai Sea had the highest annual average concentration of total antibiotics ranging from 5.66 to 1552.59 ng/L. The peak of antibiotics in four typical water systems occurred in different years. Antibiotics in the surface water of Northern China accounted for 47.0% of the total annual average concentrations in four regions. Sulfonamides, tetracyclines and fluoroquinolones were the dominant compounds both for seawater and surface water. In contrast, β-lactams, sulfonamides and fluoroquinolones were the most abundant for the wastewater treatment plants. That indicated that β-lactams were from human medicine and tetracyclines were from veterinary antibiotics. The risk assessment demonstrated ofloxacin, norfloxacin and enrofloxacin had posed the higher risk than other antibiotics. The review provides an improved understanding on aquatic antibiotics pollution to outline the Chinese scenario and addresses the prospects for future research relating to the issues requiring urgent attention.

Keywords: antibiotics; seawater; surface water; WWTPs; risk assessment

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1. Introduction

Antibiotics as emerging contaminants have been a topic of increasing concern and research due to their massive use in the human, veterinary and agricultural environment, as anti-infection agents and growth promoters [1–5]. China is one of the largest producers and consumers of antibiotics [6,7]. It is estimated that there were more than 162,000 tons consumed annually by 2013, 48% of which were used for humans and the rest were for animals [6,8]. This indicated that the consumption of antibiotics was almost 119g per capita annually, which was much higher than the average in America [9,10]. Traditional wastewater treatment plants (WWTPs) were designed without the consideration of antibiotics removal and many studies have confirmed that there were antibiotic residues in the treated effluent [11–14]. Thus, these contaminants can directly enter the aquatic environment through wastewater systems [15–19]. The diffusion of antibiotics in the environment, especially in water systems, is believed to increase antibiotic resistance and pose a potential threat on the ecosystem and human health [5,20–23]. At present, there have been more than 10 categories of antibiotics detected in multiple water medium, including aminoglycosides, chloramphenicols (CPs), β-lactams, macrolides

(MCs), polypeptides, fluoroquinolones (QNs), sulfonamides (SAs), tetracyclines (TCs) and streptogramins [24–34]. However, differences in the occurrence of these various antibiotics in water bodies nationwide are still unclear. Meanwhile, previous studies on the occurrence, distribution and fate of antibiotics are mostly concentrated on a relatively small scale, mainly on one or several rivers [35–40]. Little is currently known about antibiotic pollution in China on a national scale.

China has more than 23,000 rivers with a basin area of about 100 km^2, and rapid development has greatly expanded the industry, agriculture and aquaculture of these basins, which inevitably causes a large number of antibiotics to be used. These antibiotics cannot be fully metabolized and are often excreted into the environment through urine and feces [41–45]. Therefore, antibiotics in the aquatic environment could originate from a variety of sources, such as human and animal waste, fertilizer, hospital and domestic sewage, pharmaceutical wastewater and agriculture runoff [46–51]. Owing to the various sources of antibiotics and the imbalance of regional development, the types and distribution pattern of antibiotics vary from one region to another. Megacities such as Beijing, with a high population density and developed medical level, are accompanied by the persistent discharge of antibiotic contamination, hence the highest concentration was up to 2722.00 ng/L for ofloxacin (OFL) [52]. Comparatively, the highest antibiotic concentration was 32.24 ng/L for OFL in Bosten Lake, Xinjiang [53]. In consequence, it is essential to further investigate the comprehensive regional distribution of antibiotics across the country in order that competent authorities establish effective and appropriate regulations and monitoring strategies for these substances in the aqueous environment.

Antibiotics could lead to a selective burden on water microorganisms, even at a low concentration, and induce the formation of antibiotic resistance, which is deemed to be the most important challenge to human health in the 21st century [54–56]. Antibiotics have pseudo persisted in the environment because of their continuous input [57–60]. More importantly, chronic exposure to trace levels of antibiotics may accelerate the horizontal transfer of antibiotic resistance genes and contribute to the creation of drug-resistant strains, which poses increasing risk to the global ecosystem and human health [61–66]. Therefore, it is crucial to evaluate the environmental risk of antibiotics to provide insights to the understanding of the ecotoxicity.

To our best knowledge, all published research of the occurrence of antibiotics in the aqueous environment were collected in this study from Elsevier Science Direct, Wiley Online Library, American Chemical Society and Springer-Verlag, during 2008~2019. This review aims to provide an up to date comprehensive overview on the occurrence and distribution of antibiotics in the different aqueous environmental systems across China. Antibiotic risk assessment, sources and their dynamic relating to this topic have been focused on to provide reliable information for the establishment of the supervision legal framework and water quality criteria of antibiotics. Some issues, which should be considered in the future to better understand the risks of antibiotics in the aquatic environment and offer preventive measures, are also addressed.

2. Materials and Methods

2.1. Literature Retrieval and Data Source

In order to reflect the distribution level of antibiotics in the aquatic environment in China thoroughly, Elsevier Science Direct, Wiley Online Library, American Chemical Society and Springer-Verlag were used as the search sources in this study. Considering the impact of COVID-19 on antibiotic consumption, the data from 2020 to 2022 were excluded [67,68], and a total of 1033 open peer-reviewed literature from 2008 to 2019 (publishing time) were retrieved with the keywords of antibiotic, PPCPs, occurrence, water, wastewater, etc. In these publications, only antibiotics in the water media were concerned, and the data about sediments and other medium was excluded. Quantitative data on antibiotics was collated based on geographic region and only data with a clear research area in China was selected. In order to ensure the accuracy of the data, references which failed to specify the antibiotic concentration, sample sites and/or sample time were excluded. Some articles on antibiotics in WWTPs, in which the concentration of antibiotics in the influents and effluents was not both reported, were also excluded. A few articles that studied both treated wastewater and the receiving water body were compiled separately during the data processing. Therefore, the datum in this paper was collected from 114 articles, including 95 reported on the concentration of antibiotics in seawater and surface water, and 27 in WWTPs.

Among the diverse antibiotics, 76 antibiotics, including 13 β-lactams, 10 macrolides (MCs), 23 sulfonamides (SAs), 23 fluroquinolones (QNs), 4 tetracyclines (TCs) and 3 chloramphenicol (CPs) with the amount of usage in the forefront were focused on to better discuss the nationwide distribution and assess the environmental risk of antibiotics. The detailed information about these antibiotics is listed in Table S1. In addition, other types of antibiotics, including lincomycin, metronidazole and vancomycin, were also involved in investigating the concentration of antibiotics in the WWTPs. All abbreviations and corresponding full names of all antibiotics involved in this study are listed in Table S2.

2.2. Data Processing and Statistical Analysis

The regional distribution of antibiotics was determined using the mean or median measured environmental concentrations of antibiotics calculated by one or several data sources in the Appendix SA. As there were only the maximum and minimum concentrations provided, the geometric average substitution would be adopted as the average concentration. While "below method detection level" (<MDL) or "not detected" (n.d.) was reported in articles, half of the method detection level or limit of quantification was adopted to calculate risk quotients [69].

2.3. Study Area Division

There were 38 cities investigated and distributed in the Northeast (4 locations), North (7 locations), Northwest (4 locations), East (12 locations), Central (1 location), Southwest (5 locations), and South of China (5 locations). The study area was divided into seven regions in Figure 1, namely Northeastern China (NEC), Northern China (NC), Northwestern China (NWC), Eastern China (EC), Central China (CC), Southern China (SC) and Southwestern China (SWC). All abbreviations and corresponding full names of regions are listed in Table S2. According to the number of literatures in the study area, research hotspots were concentrated below the Hu Huanyong line. EC is the hottest research focus, followed by the SC and NC. The number of publications among these three regions was much higher than that in the northwestern and southwestern regions. That might be related to economy, population density, antibiotics usage and other factors, which were consistent with the basis determined by Hu Huanyong Line.

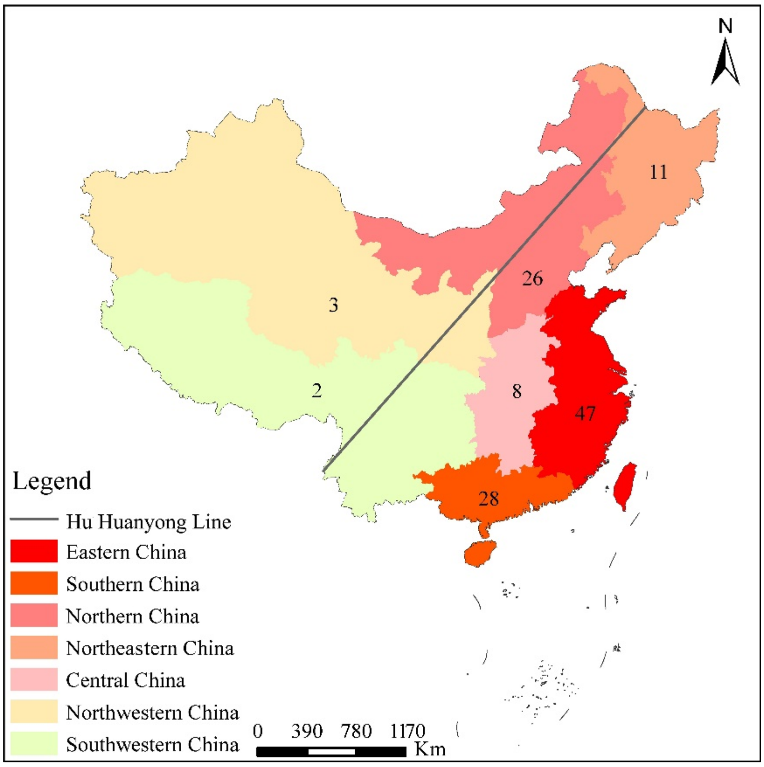

Figure 1. The number of articles about antibiotics in aquatic environment and wastewater treatment plants in investigational areas. A few articles involve antibiotics pollution of multiple research areas, so the total number of publications in each region (125) exceed the total number of valid articles (114).

3. Results and Discussion

3.1. Temporal Dynamic of Antibiotics in the Typical Water Body

Four representative water systems, including the Bohai Sea (BS), the Yellow Sea (YS), the Yangtze River Basin (YRB) and the Pearl River Basin (PRB) were selected for distribution difference analysis of antibiotics in North and South of China. The BS and YS not only have intensive aquaculture [70,71], but also receive large amounts of municipal sewage from coastal cities [72,73]. The YRB and PRB have the largest runoff in China [74]. These four basins are typical of water systems and can reflect the antibiotics pollution in aquatic environment from multiple sources. Meanwhile, studies on the occurrence of antibiotics in their individual systems are the most universal, but lack of comparative analysis. Therefore, the distribution of antibiotics in these four areas was analyzed and discussed, firstly based on the collected data.

The concentration of antibiotics in the seawater of China in the past decade is shown in Figure 2. There were five categories of QNs, MCs, SAs, TCs and β-lactams containing 35 antibiotics detected in the BS and no available data in 2011, 2012 and 2013 (Figure 2a). The highest and lowest antibiotics pollution occurred in 2009 and 2016 at the total concentration of 2281.68 and 63.00 ng/L, respectively. The total concentration ranges of QNs, MCs, SAs and TCs were 8.26~488.04 ng/L, 0.80~557.05 ng/L, 4.86~1,877.00 ng/L and 17.91~80.76 ng/L, respectively. The β-lactams were only detected in 2016 with the total concentration of 4.37 ng/L. SAs were the dominant antibiotics in the BS with annual average concentration of 490.49 ng/L. Trimethoprim (TMP) had the highest concentration of 924.79 ng/L in 2009. Sulfamethoxazole (SMX) and sulfadiazine (SD) were extensively detected in all the years except 2014 with the concentration range of 1.72~224.27 ng/L and 0.05~81.47 ng/L, respectively. The high detection rate, concentration and types of SAs might be attributed to their widespread use as human and veterinary medicine [39,75]. Moreover, SAs were so hydrophilic and persistent that they had high detection frequency in water column [76]. QNs were the second highest antibiotics in BS with the annual average concentration of 252.41 ng/L, although there were only five kinds of QNs detected in the BS. The highest concentration of total QNs was 493.42 ng/L in 2017, followed by 488.04 ng/L in 2009. Norfloxacin (NOR) was the most abundant QNs, contributing 29.75~52.33% to QNs burden, and OFL was the most frequently detected QNs (not detected only in 2016) with the average annual concentrations of up to 124.86 ng/L. The annual average concentrations of MCs and TCs were 122.94 and 39.06 ng/L, respectively. The most serious pollution of MCs and TCs also appeared in 2017. However, the lowest concentration of MCs was 0.80 ng/L in 2010, and that for TCs was 17.91 ng/L in 2008.

Compared with the BS, there were 5 years of available data and 49 antibiotics compounds detected in the YS belong to six families (Figure 2b). A total of 17 varieties of QNs were detected in the YS, far more abundant than the five in the BS. However, the annual total concentration range of QNs was 94.45~185.41 ng/L, much lower than that in the BS. The overall antibiotics levels were highest in 2012 and lowest in 2011 with the total concentration of 433.23 and 12 ng/L, respectively. QNs were the superior contaminants with annual average concentration of 146.74 ng/L, followed by MCs (107.52 ng/L), SAs (64.84 ng/L), TCs (61.46 ng/L), β-lactams (9.90 ng/L) and CPs (7.43 ng/L). The detection frequencies of SAs and TCs were 80%, higher than that of others (40%~60%). SAs are not easy to degrade and hydrophilic enough to be transferred into the aquatic environment, which can explain their high present rate in aquatic environment [16,52]. In general, QNs and SAs were the most abundant antibiotics detected both in the BS and the YS, which may have resulted from their heavy use in marine aquaculture [77]. Moreover, the concentration of antibiotics in the BS was significantly higher than that in the YS ($p < 0.05$). On the one hand, Bohai is a closed inland sea with poor water exchange ability, which makes the pollutants difficult to diffuse. On the other hand, a larger amount of sewage was discharged into the BS due to its adjacence to 157 cities [70]. It is also indicated that the n anthropogenic activities play a notable impact on distribution of antibiotics in the coastal aquatic environment [78,79].

In all, 39 antibiotics of six categories were detected in the YRB and antibiotic contamination data was available in all the years except for in 2008 and 2017 (Figure 2c). In contrast, the PRB had only 5 years of data available in the past decade and there were 32 antibiotics of six categories detected in the PRB (Figure 2d). In the YRB, the peak antibiotic pollution emerged in 2015 with the total concentration of all antibiotics of 540.32 ng/L, and the lowest total concentration of all antibiotics was 28.26 ng/L in 2016. The highest total concentration of all antibiotics in the PRB was 617.29 in 2016 ng/L. There was a great difference in the temporal distribution of antibiotics between the YRB and the PRB. However, both in the YRB and PRB, SAs and QNs were the dominant antibiotics and their concentrations were higher than other types of antibiotics. In the YRB, the annual average concentrations of SAs and QNs were 135.11 and 115.73 ng/L, respectively, while in the PRB, the two figures were 60.23 and 86.33 ng/L.

MCs, TCs, β-lactams and CPs were reported at least once in the literatures in the four selected basins except in the BS. CPs antibiotics were detected in the YS, YRB and PRB, with the average annual concentration of 7.43, 37.41 and 46.26 ng/L, respectively. Although many countries have prohibited the use of chloramphenicol (CAP) in animal husbandry and aquaculture [71,80], CAP has been reported to be widely used in aquaculture in China due to the low price and steady effectiveness [71,81]. Aquaculture may be the main source of CAP contamination. The annual average concentrations of β-lactams antibiotics were largely lower than that of other antibiotics (4.37 ng/L for BS, 9.90 ng/L for YS, 4.02 ng/L for YRB), mainly because β-lactams antibiotics are prone to hydrolyze and difficult to detect [82,83]. However, the annual average concentrations of β-lactams antibiotics detected in the PRB reached 70.48 ng/L, which may be due to randomness and uncertainty of sampling considering the low detection rate. The annual average concentrations of MCs antibiotics in the BS were the highest and up to 122.94 ng/L, followed by 107.52 ng/L in the YS, 31.90 ng/L in the PRB, and 16.75 ng/L in the YRB. The average annual concentration of TCs in the BS, the YS, the YRB and the PRB was 39.06 ng/L, 61.46 ng/L, 63.05 ng/L and 24.49 ng/L, respectively. Due to the inconspicuous treatment effect for humans and animals, TCs were gradually replaced by other antibiotics, such as β-lactam and MCs in the last 20 years.

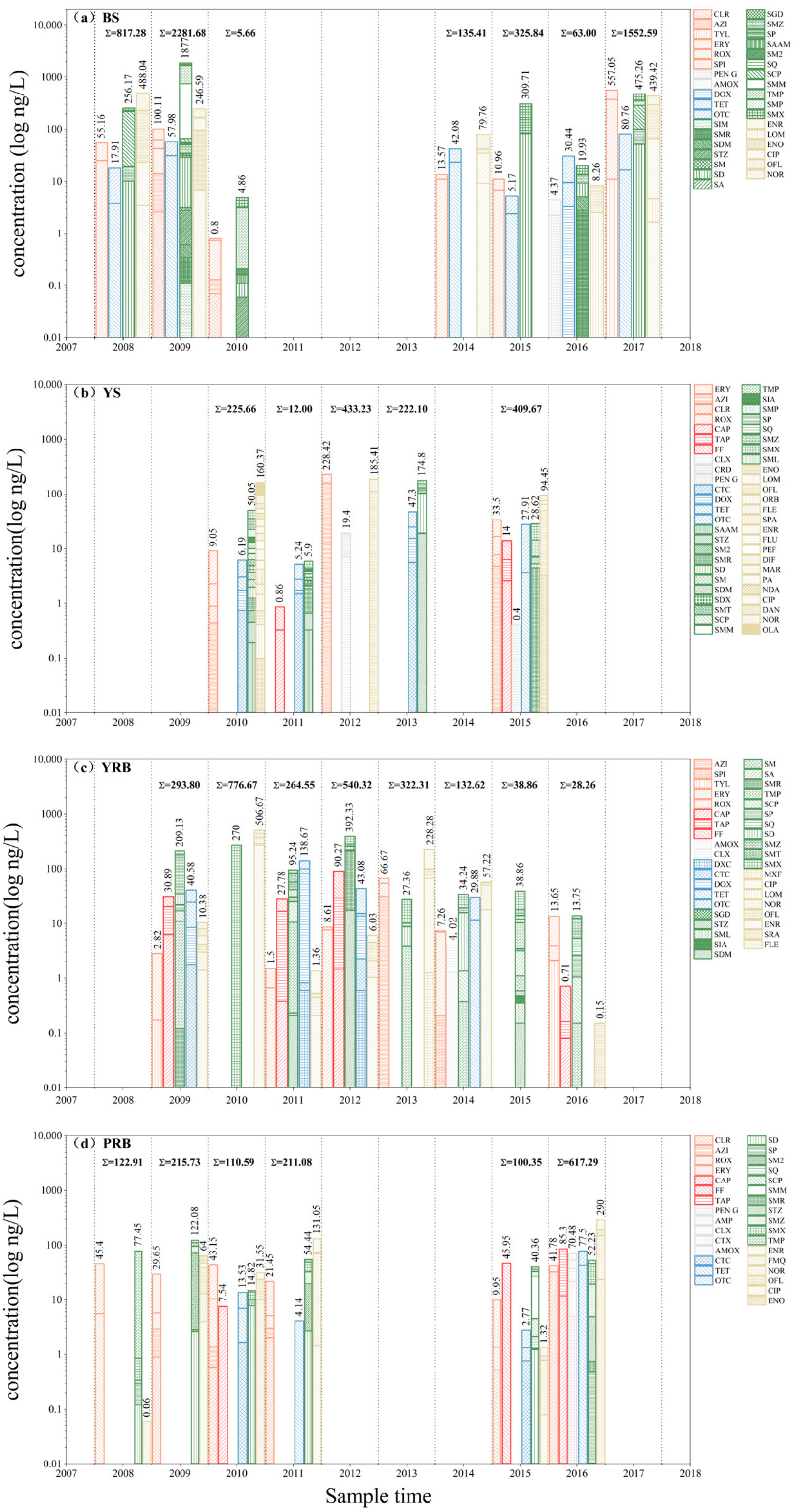

Figure 2. Temporal distribution of antibiotics in four typical water systems in China. (**a**–**d**) represent antibiotics in the he BS, YS, YRB and PRB, respectively. ∑ represents the total average concentration of all antibiotics in that year (unit: ng/L). The number above the stack histogram represents the total concentration of this type of antibiotics (unit: ng/L).

3.2. Spatial Distribution of Antibiotics in the Surface Water

As shown in Figure 1, the literatures above the Hu Huanyong Line are rare and effective statistical analysis is difficult to carry out. Therefore, four regions, including NC, EC, SC and CC below the Hu Huanyong Line were selected as typical regions to analyze the dynamic of antibiotics from 2007 to 2018(sample time)according to the number of open peer-reviewed literatures. NC includes Beijing, Tianjin and Hebei Provinces. SC includes Guangdong, Hainan Provinces, Guangxi Zhuang autonomous region, and the Hong Kong special administrative region. There are eight provinces in EC, containing Shanghai, Jiangsu, Zhejiang, Anhui, Fujian, Jiangxi, Shandong and Taiwan. Henan Province, Hubei Province, and Hunan Province are included in CC.

The concentration of all antibiotics detected in the surface water of four regions is shown in Figure 3. The total annual average concentrations of the antibiotics in surface water were in the order of NC > EC > CC> SC. Among the four regions of China, NC had the highest concentrations of antibiotics, accounting for 47.0% of the total annual average concentrations. In fact, there was a sampling river receiving water discharged from a pharmaceutical factory, which lead to an extensive increase of the annual concentration of antibiotics in the NC. It was suggested that the level of antibiotics pollution was greatly affected by the sample locations. The most plentiful antibiotics contamination had arisen in 2008 with the total concentration of up to 6569.64 ng/L and β-lactams were the predominant antibiotics with the total concentration of 5886.67 ng/L in the NC (Figure 3a). The concentration of individual β-lactams antibiotics ranged from 170.00 to 3810.00 ng/L, detected in receiving water at the drainage outlet of pharmaceutical plants [84]. There was no available data about antibiotics in surface water in 2012, 2014, 2015 and 2016 in the NC. The EC had valid data in all years in past decades, due to abundant surface water resources and the developed economy. The total concentration of all antibiotics in the EC increased in the first 5 years and decreased in the next 5 years (Figure 3b). The overall antibiotics levels were highest in 2012 and lowest in 2015 with the total average concentration of 3720.84 and 37.94 ng/L, respectively. SAs and TCs had the highest concentration of 2234.64 and 1706.6 ng/L in the EC. The wastewater samples collected from a poultry farm in 2012 in the EC resulted in the tetracycline (TET) concentration of up to 3437.50 ng/L in surface water in Table A11 [85]. The concentration of oxytetracycline (OTC) was up to 2260.00 ng/L in 2013 in Taihu Lake [86]. Nevertheless, there was another reason for the high concentration of TCs in Taihu Lake. It is reported that TCs are the second widely used veterinary medicine and food additives in aquaculture and livestock industries in the world [87]. Taihu Lake is an important base for aquaculture in China, which might be responsible for the high TCs in this area. The total average concentration of antibiotics in surface water in SC was basically decreasing year by year (Figure 3c). However, in 2015, the concentration of SAs antibiotics increased sharply up to 722.38 ng/L, due to the water samples collected from aquaculture farms in Guangdong Province [83]. It is remarkable that MCs had the maximum average concentration of 759.13 ng/L in the SC. Six classes of the selected antibiotics were detected in four regions except the CC. There was no information about CPs and β-lactams antibiotics in the CC in the articles reviewed. In the limited data about antibiotics in the CC, the levels of antibiotics contamination were higher than that in other three regions in 2015 and 2016 (Figure 3d). TCs had the highest annual average concentration of 1305.55 ng/L, mainly due to the pollution of Honghu Lake [88]. The total concentration of MCs was 598.38 in 2014, contributing 69.56% of all the antibiotics.

At the beginning of 2013, the Ministry of Environmental Protection launched the twelfth five-year plan for control and prevention of environmental risks of chemical substances and pharmaceuticals was included. In general, antibiotic contamination has gradually been improved in the past five years, which is closely related to the efforts of managers and the cognition of the people. SAs and TCs as the most abundant antibiotics in the four regions mainly originated from aquaculture and livestock industries and the variation of their occurrence and distribution was deeply dependent on the discharge of wastewater from these industries. Therefore, priority control of use and discharge of antibiotic in the aquaculture and livestock are the significant avenue in order to reduce the antibiotic pollution.

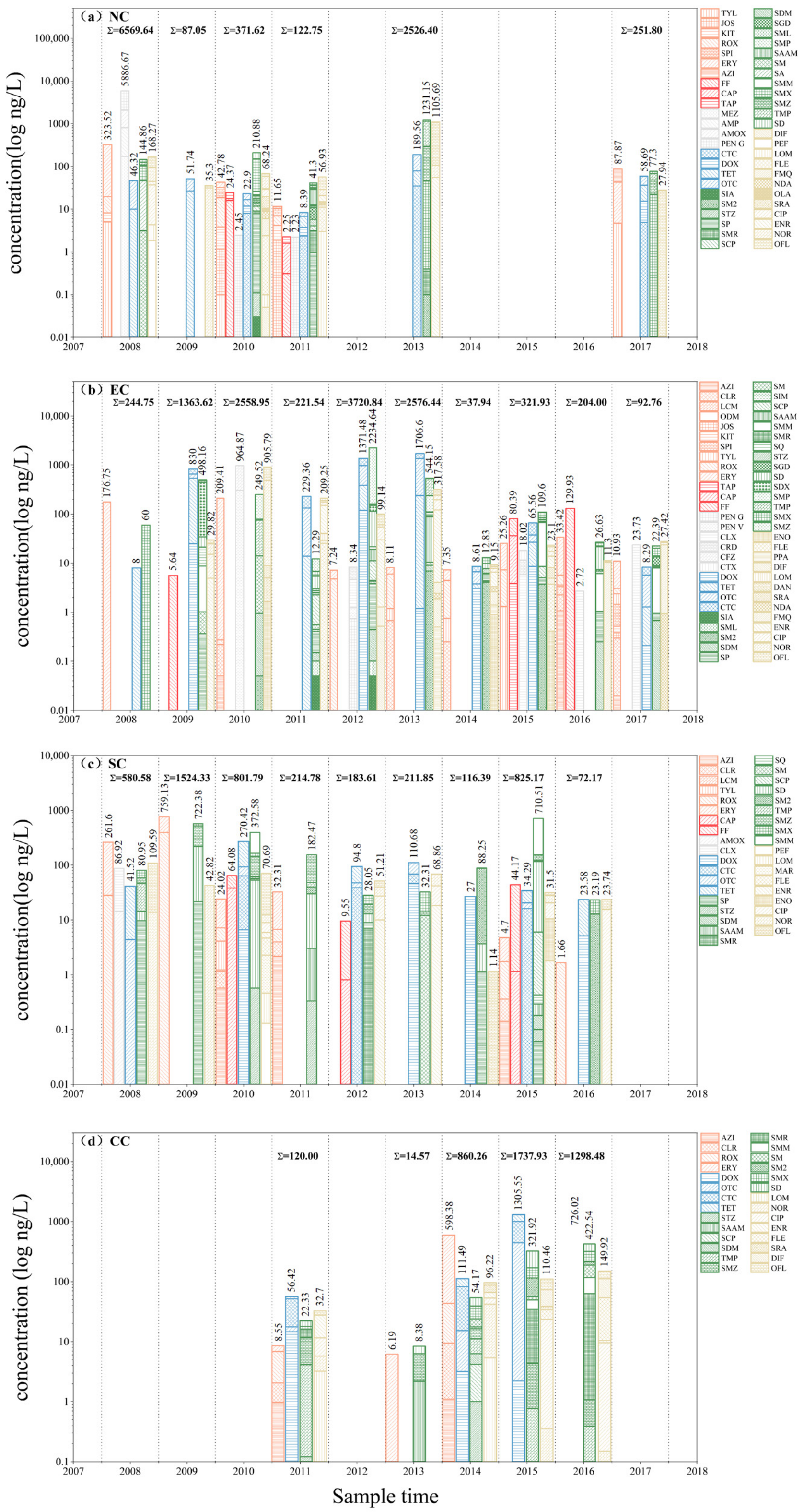

Figure 3. Concentration of antibiotics in the surface water in four regions of China. (**a**–**d**) represent antibiotics in the NC, EC, SC and CC, respectively. ∑ represents the total average concentration of all antibiotics in that year (unit: ng/L). The number above the stack histogram represents the total concentration of this type of antibiotics (unit: ng/L).

3.3. Antibiotics Pollution in the WWTPs

Conventional WWTPs cannot eliminate all antibiotics completely [89,90], which results in the occurrence of these contaminations even in the treated effluents [6,91]. Previous reports have documented that WWTPs effluent is one of the main sources of antibiotics in the aquatic environment [1,92], which is consistent with the previous analysis results. However, little information is available the distribution characteristics of antibiotic in the WWTPs nationwide. Antibiotics in the influent and effluent of WWTPs in seven regions over the past decade are presented in Figure 4. In all, 64 antibiotics, including 10 β-lactams, nine MCs, 17 SAs, 16 QNs, six TCs, three CPs, one lincosamides, one glycopeptides, and one imidazoles, were discovered in the WWTPs all over the country. The data on antibiotics of the EC was collected for 6 years, and the SC and the NC were for 5 and 4 years, which is related to infrastructure construction, economic and social development. The highest total antibiotic concentration in the influent and the effluent appeared in the SC in 2016, which were 16,577.22 and 2625.25 ng/L. The second highest total antibiotic concentration of 14,124.91 and 1988.88 ng/L for the influent and the effluent occurred in the NC in 2009. Antibiotics pollution in the WWTPs of the CC was lightest with the highest concentration of 530.47 ng/L for the influent and 27.21 ng/L for the effluent in 2014. The concentration of antibiotics in the WWTPs was much higher than that in the seawater and surface water, elucidating that WWTPs are considerable sources and sinks of antibiotics pollution.

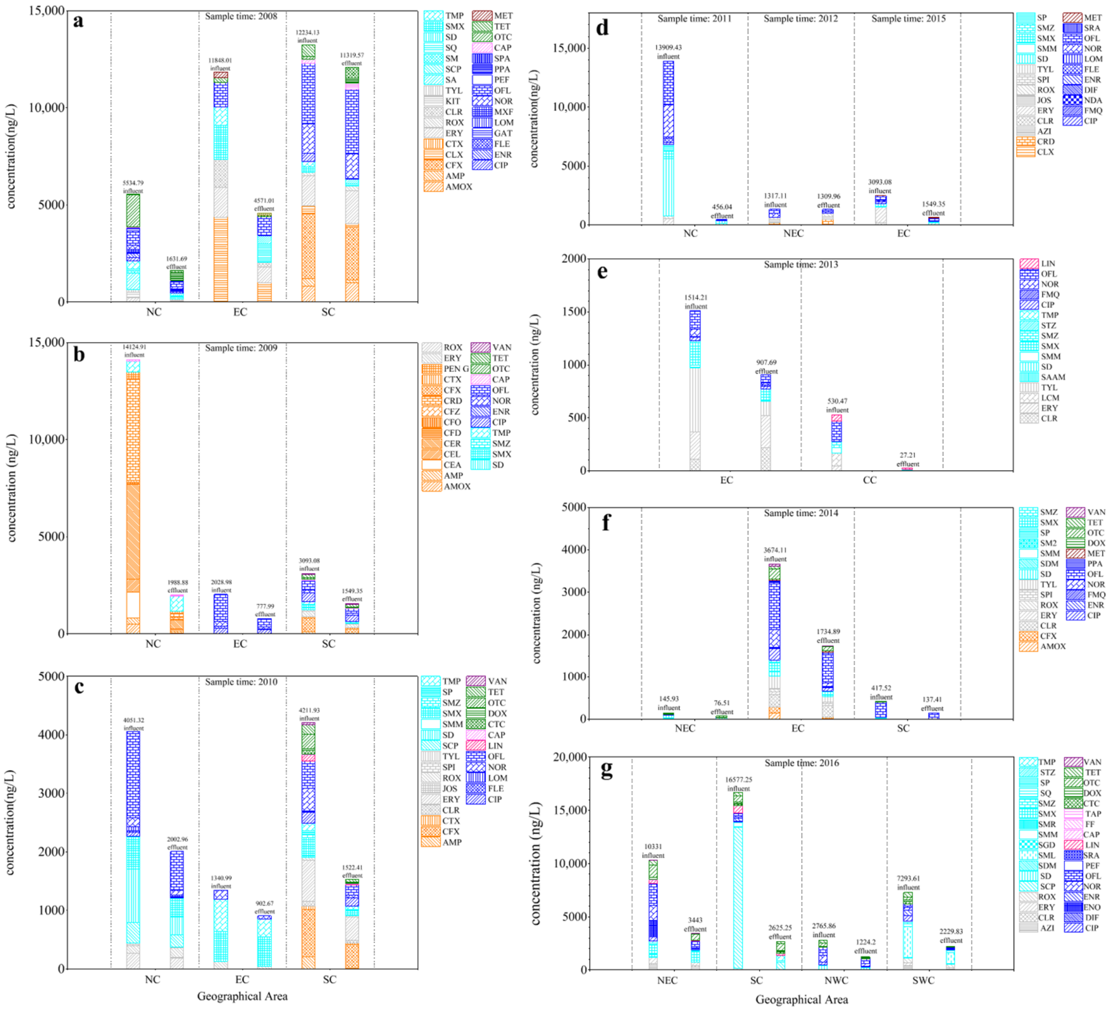

Figure 4. Concentrations of antibiotics in the wastewater of China. (**a**–**g**) represent antibiotics in the different sample year during 2008~2016. The number above the stack histogram represents the total concentration of this type of antibiotics (unit: ng/L).

It was found that β-lactams in the influents of WWTPs had the highest average concentration of up to 10,577.37 ng/L, followed by SAs with the average concentration of 9050.32 ng/L and QNs with the average concentration of 4039.01 ng/L. The domestic sewage is the main source of urban WWTPs in China [93]. Combined with the fact that β-lactams were rarely detected in seawater and surface water, it can be asserted that β-lactams are the most commonly used human antibiotics in China [6]. Compared with that in seawater and surface water, the concentration and detection rate of TCs in the WWTPs were lower, further indicating that TCs stemmed from veterinary antibiotics rather than human antibiotics. The removal rate of β-lactams was 80.51%, perhaps due to the characteristics of easy degradation of β-lactam antibiotics [17]. However, the highest concentration of β-lactams in the effluents still reached up to 2061.19 ng/L. The highest concentrations of SAs and QNs in the effluents were 2129.77 ng/L and 1054.80 ng/L, respectively. The removal rate of SAs was 76.47%, and the rate for QNs was slightly lower and recorded as 73.88%. For MCs, TCs and CPs, the removal efficiency were 53.61%, 56.81%, and 43.47%, respectively. In addition to the characteristics of antibiotics, there are many reasons for the low removal rate of antibiotic pollutants in WWTPs. First of all, it is difficult to achieve the desired removal rate for antibiotics especially at the trace initial concentration [94]. Secondly, multiple substances exist in the treating water at the same time, which may cause the precursor substances to be recombined into antibiotics [95]. Finally, returned sludge and membrane fouling may be potential sources of antibiotics in effluent [96]. Among the 64 antibiotics, cefalexin (CLX), OFL, amoxicillin (AMOX), erythromycin (ERY), and trimethoprim (TMP) were the top five antibiotic residues in the effluents. It is notable that antibiotics with extremely low detection frequencies were not considered in the sorting in order to reduce the uncertainty. The mean concentrations of antibiotics in the effluents of the NWC in 2016 were lower than that in coastal areas, demonstrating the huge impact of human activities and socioeconomic status on the distribution of antibiotics [6].

3.4. Environmental Risk Assessment of Antibiotics Nationwide

A major concern with regard to ubiquitous antibiotics in the aquatic environment is the uncertainty about their adverse potential ecological effects on the aquatic organisms due to long-term exposure. As mentioned above, six categories of 79 antibiotics were discovered in seawater, surface water and WWTPs, with relatively high concentrations in some water systems. Thus, the environmental risk of antibiotics needs to be estimated. Algae is sensitive to antibiotics and always used as a risk indicator in the aquatic environment [97,98]. After data analysis and preliminary evaluation, the environmental risk on aquatic organisms (algae) of 12 antibiotics, which were the most commonly presence and used in aquatic environment, was assessed by risk quotients (RQs) according to the European Technical Guidance Document on Risk Assessment [99]. The RQs to aquatic organisms were calculated through the measured environmental concentration (MEC) divided by the predicted no effect concentration (PNEC) as follows:

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

The PNEC in water was calculated as the following the equation:

$$PNEC = \frac{LC_{50} or EC_{50}}{AF} \quad (2)$$

where LC_{50} is the half maximal lethal concentration, EC_{50} is the concentration for 50% of maximal effect, and AF is an appropriate standard assessment factor of 1000 [100]. The MEC values for each water system or region were calculated by the method mentioned in data processing section. The PNEC was estimated based on available acute and chronic toxicity data from the open peer-reviewed literatures (Table 1). The RQs are classified into the following three risk levels: $RQ < 0.1$ means low risk, $0.1 \leq RQ < 1.0$ means medium risk, and $RQ \geq 1.0$ means high ecological risk [101].

Table 1. Aquatic toxicity data of antibiotics to the most sensitive aquatic species.

Antibiotics	Abbreviation	Sensitive Aquatic Species	Toxicity Types	AF	Toxicity Data (mg L^{-1})		PNEC (ng L^{-1})	References
					EC50	NOEC [a]		
Roxithromycin	ROX	*P. subcapitata*	Chronic	1000	0.047		47	[102]
Sulfamethazine	SMZ	*Lemna minor*	Acute	1000	1.74		1740	[103]
Sulfamethoxazole	SMX	*S. vacuolatus*	Acute	1000	1.54		1540	[103]
Sulfadiazine	SD	*S. vacuolatus*	Acute	1000	2.22		2220	[103]
Trimethoprim	TMP	*R. salina*	Acute	1000	16.40		16,400	[104]
Norfloxacin	NOR	*V. fischeri*	Chronic	100		0.01038	103.8	[105]
Ofloxacin	OFL	*P. subcapitata*	Chronic	100		0.00113	11.3	[106]
Enrofloxacin	ENR	*M. aeruginosa*	Acute	1000	0.05		49	[107]
Chlortetracycline	CTC	*C. pyrenoidosa*	Acute	1000	9.31		9310	[87]
Doxycycline	DOX	*S. leopolensis*	Acute	1000	0.32		316	[108]
Tetracycline	TET	*P. subcapitata*	Acute	1000	3.31		3310	[109]
Oxytetracycline	OTC	*P. subcapitata*	Acute	1000	1.04		1040	[110]

[a] No Observed Effect Concentration

The risk levels of the selected antibiotics for algae in seawater and surface water are presented in Figures 5 and 6. Detailed RQs and MEC values are listed in Tables S3 and S4. In general, a majority of RQs were less than 0.1 by a range of 0.001 to 0.098, indicating low risk related to the current relatively low concentrations of antibiotics in aquatic environment. The risk of antibiotics in the seawater was slightly higher than that in surface water, which was inseparable from numerous studies on these typical seawater systems. It is inspiring that the risk of antibiotics tended to decrease gradually and medium and high risks in 2017 were less than those in previous years, although the influence of samples uncertainty cannot be ruled out. Both in seawater and surface water, QNs possessed highest ecological risk for algae with a great many of RQs greater than 1.0. In 2013, OFL in the NC with the RQ of 88.355 had the highest risk to algae in surface water. The main reason is that the sampling river at the outlet of the WWTPs received the effluent, resulting in the OFL concentration of up to 2722.00 ng/L [48]. It is demonstrated that WWTPs are the main source of antibiotics risk especially in their receiving water body. NOR and enrofloxacin (ENR) exhibited high risk with the RQ values of 4.540 and 2.633, respectively. Four selected SAs except SMZ showed low to medium risks. The RQ of SMZ was 1.191 at a high risk level in the EC in 2012. ROX had experienced medium to high risks in both surface water and seawater, suggesting non-negligible potential harm on aquatic ecosystem. Among TCs, only OTC caused high risk in surface water of the EC in 2013, and other TCs presented low risk to algae. However, algae is the basis of trophic level; even slight change in the algal population may affect the balance in an aquatic system [1]. In addition, combined risks of antibiotics need further investigations considering the co-existence of multiple antibiotics in the water body.

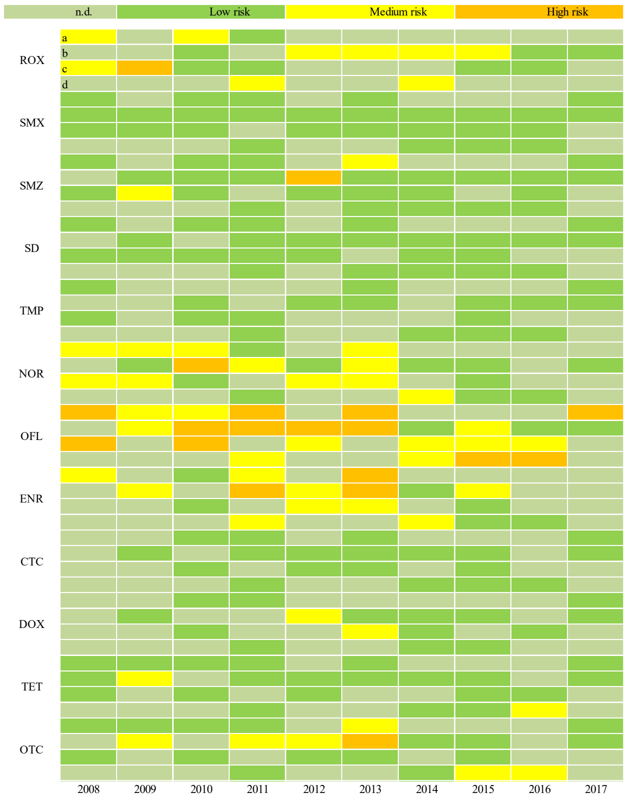

Figure 5. Risk figure based on the calculated RQs for the antibiotics in the seawater of China. (a). BS; (b). YS; (c) YRB; (d) PRB.

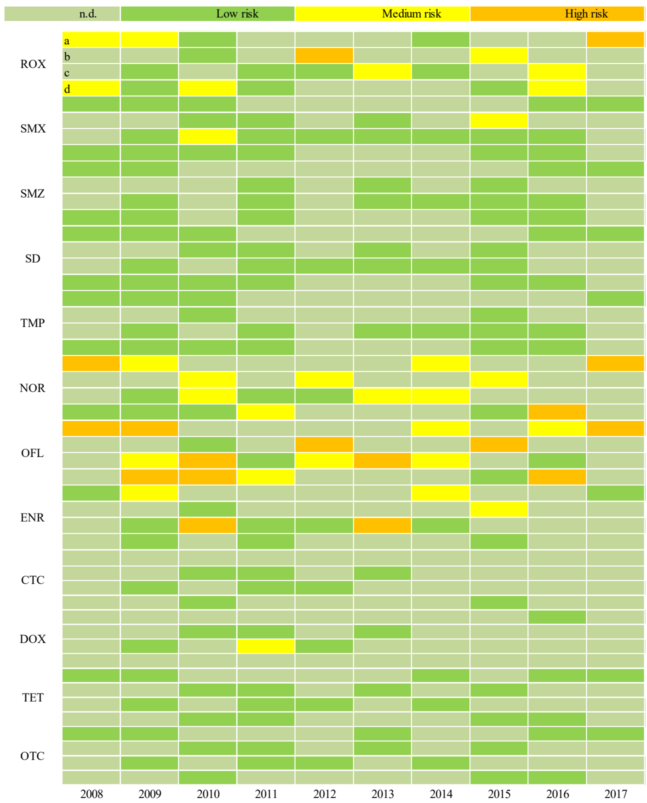

Figure 6. Risk figure based on the calculated RQs for the antibiotics in the surface water in four regions of China. (a). NC; (b). SC; (c). EC; (d). CC.

4. Conclusions and Future Research Prospects

An abundance of open peer-reviewed literatures about antibiotics in the natural aquatic environment and WWTPs throughout China were reviewed in this study. A total of 79 antibiotics were discovered at least once in aquatic environment with the mean concentration ranging from 0.04 ng/L to 6.54 μg/L. In the four typical water systems, the BS had the highest annual average concentration of total antibiotics ranging from 5.66 to 1552.59 ng/L, while the YS had the most abundant types of antibiotics detected. The dominant antibiotics were SAs in the BS with annual average concentration of 490.49 ng/L and QNs in the YS with annual average concentration of 146.74 ng/L, whereas SAs and QNs were the predominant compounds in the YRB and PRB. The temporal distribution in these four water compartments varied greatly and the peak of antibiotics occurred in different years. In terms of spatial distribution, NC had the highest concentrations of antibiotics in the surface water of four regions, contributing 47.0% of the total annual average concentrations. β-lactams were the dominant antibiotics with the total concentration of 5886.67 ng/L in the NC, while β-lactams had low detection frequency and concentration in other regions. There were so many studies on antibiotics of surface water in the EC that EC was the only region with available antibiotic data in all years. The total average concentration of antibiotics in the SC surface water showed a decreasing trend gradually. SAs and TCs had the highest annual average concentration of 1706.6 ng/L in the EC and 1305.55 ng/L in the CC. At the same time, SAs were another superior contaminant in the EC with the highest annual average concentration of 2234.64 ng/L. These pollutants mainly originated from the aquaculture and livestock industries according to the data source. Nine categories of 64 antibiotics were detected in the WWTPs all over the China and the concentration was much higher than that in the seawater and surface water, indicating that WWTPs are significant sources and sinks of antibiotics pollution. β-lactams, SAs and QNs were the most abundant antibiotics both in the influent and effluent of WWTPs. It can be inferred that β-lactams were from human medicine and TCs were from veterinary antibiotics. The removal rate of antibiotics ranged from 43.47% to 80.51%, which may influence the occurrence of antibiotics in the environment. Risk assessment showed that OFL, NOR and ENR had posed the higher risk than other antibiotics. OTC caused high risk in surface water of the EC in 2013, while SMZ posed a high risk in the EC in 2012. ROX had undergone medium to high risks in both surface water and seawater. On the whole, most antibiotics were at the low risk level and the risk of antibiotics in the seawater was slightly higher than that in surface water. However, research on the antibiotics in aquatic environments is just the tip of the iceberg. Studies concentrated on Southwest and Northwest China are still lacking and long-term spatio-temporal characteristics of antibiotics have not been involved. In addition, there are lack of effective combined risk assessment methods and systematic toxicological database for antibiotics.

Therefore, the following future research prospects are proposed.

1. Previous studies on antibiotics are mainly concentrated in developed areas. Further investigation on the occurrence and distribution of antibiotics in the aquatic environment, especially in the underdeveloped or developing areas (above the Hu Huanyong Line), should be carried out to make clear the level and fate of antibiotics in China and draw a map of antibiotic distribution in the water body.
2. Antibiotics used in the aquaculture and livestock husbandry have resulted in their higher concentration in the water environment. Practical standards and regulations about the permissible limits and types of antibiotics in aquaculture and livestock industries should be formulated and established to control the levels of TCs, SAs and QNs in surface water and seawater.
3. WWTPs are significant sources and sinks of antibiotics pollution. The removal efficiency of traditional wastewater treatment processes should be improved and the new wastewater treatment processes should be developed to cut off one of the most important pathways of antibiotics and restrict the dispreading of β-lactams, SAs and QNs in the aquatic environment.

4. Combined antibiotics risk at trace level of antibiotics chronic exposure needs to be explored and the toxic effects and mechanisms of antibiotics on organisms should be paid more attention. Furthermore, the diffusion and ecological/health effect of ARGs relating to antibiotics have become another research hotspot.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/su15010386/s1, Table S1: Physico-chemical properties of antibiotics investigated in this study; Table S2: Abbreviation and full name index; Table S3: Risk quotients of antibiotics in seawater of China; Table S4: Risk quotients of antibiotics in surface water of China. Appendix SA. Detailed data including the maximum, mean, and minimum concentration of antibiotics, sample location, sample time and corresponding reference was listed in the Supplementary Materials.

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