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Comprehensive Evaluation of Antibiotics Emission and Fate in the River Basins of China: Source Analysis, Multimedia Modeling, and Linkage to Bacterial Resistance

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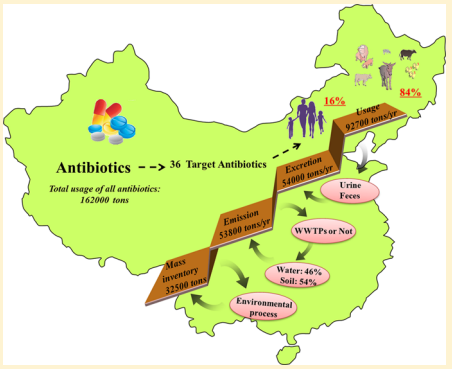
Supporting Information

ABSTRACT: Antibiotics are widely used in humans and animals, but there is a big concern about their negative impacts on ecosystem and human health after use. So far there is a lack of information on emission inventory and environmental fate of antibiotics in China. We studied national consumption, emissions, and multimedia fate of 36 frequently detected antibiotics in China by market survey, data analysis, and level III fugacity modeling tools. Based on our survey, the total usage for the 36 chemicals was 92700 tons in 2013, an estimated 54000 tons of the antibiotics was excreted by human and animals, and eventually 53800 tons of them entered into the receiving environment following various wastewater treatments. The fugacity model successfully predicted environmental concentrations (PECs) in all 58 river basins of China, which are comparable to the reported measured environmental concentrations (MECs) available in some basins. The bacterial resistance rates in the hospitals and aquatic environments were found to be related to the PECs and antibiotic usages, especially for those antibiotics used in the most recent period. This is the first comprehensive study which demonstrates an alarming usage and emission of various antibiotics in China.



INTRODUCTION

Since the advent of penicillin in 1929, antibiotics have become the boon for improving human and animal health. Veterinary antibiotics are also commonly incorporated into animal feed to improve growth rate and feed efficiency in some countries.[1,2] Consumed human and veterinary antibiotics are mainly excreted via urine and faeces,[1,3] and a significant percentage of these excretions are in unchanged and active forms.[4] The incorporation of antibiotics in the effluent and sludge from domestic wastewater treatment plants (WWTPs), hospitals, and livestock farms results in their release to the recipient environments such as surface water and soil.[1,5] Various antibiotics have been reported in different environmental compartments, such as WWTPs,[5−7] livestock farms,[8,9] river water and sediment,[10−13] soils,[14,15] and groundwater.[16] The residual antibiotics in the environment could lead to adverse effects on nontarget organisms,[17−21] contamination of food and drinking water supplies,[22,23] and increased bacterial resistance.[24,25] Therefore, it is essential to understand the environmental emission and fate as well as effects of antibiotics.

The issue of bacterial resistance due to frequent use of antibiotics attracted great attention from the general public.[9,24−28] The World Health Organization (WHO) established a worldwide monitoring network for bacterial resistance, and its global report on antimicrobial resistance surveillance 2014 showed that higher antibiotic usage may be associated with higher bacterial resistance based on the country-level research.[29] In addition, Zhang et al.[30] reported a positive correlation between the antibiotic-resistant *Escherichia coli* numbers and corresponding antibiotic levels in a Chinese river.

China is the largest producer and user of antibiotics in the world based on the market sales data.[9,31−33] After use, these antibiotics end up in various wastewaters, including municipal WWTPs. The management of antibiotics-containing domestic wastewaters and animal wastes in China faces various problems. Especially in the majority of rural areas of China, the sewage treatment rate is quite low due to the limited infrastructure.[34] As well, there are so far no specific treatment requirements for livestock wastes before discharge in China. Direct discharge into rivers or land application of livestock wastes on agricultural lands is a common practice.[13] Hence, environmental contamination of antibiotics in China would be more severe than in the developed countries like USA, where such requirements exist. In China there is no official survey report on the detailed usage of various categories of antibiotics. Thus, it becomes necessary to conduct a comprehensive research into source and emission inventories of antibiotics and their environmental fate at the national scale.

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To monitor the multimedia concentrations of antibiotics is an important step for understanding their fate and effects in the environment. However, the diversity in antibiotic categories and physicochemical properties requires specialized equipment, heavy labor, and high cost to conduct any large scale monitoring. Instead, antibiotic levels may be predicted by coupling the consumption data and wastewater treatment rate in a study area and excretion data for humans and animals as well as the environmental processes.[35−37] Fugacity-based modeling provides a promising method for estimating concentrations of chemicals in the environment.[38−40]

The objectives of this study were (1) to investigate the usages of all antibiotics for both humans and livestock animals in China in 2013 by the market survey approach; (2) to estimate the environmental emissions of 36 frequently reported antibiotics in all basins of China, predict their environmental concentrations by using a level-III fugacity model at the basin scale, and evaluate the fate of different antibiotics in the environment; and (3) to explore potential linkage of the antibiotic usages and predicted environmental concentrations (PECs) to the bacterial resistance in the hospitals and aquatic environments of China.

METHODOLOGY

Target Chemicals and Study Area. According to the reported antibiotics in livestock farms, WWTPs, and environment media in China,[2,5,10,13] 36 frequently detected antibiotics were selected as the target chemicals in this study. They cover nearly all the antibiotic categories that can be detected in China, including sulfonamides (11 chemicals), tetracyclines (5 chemicals), fluoroquinolones (8 chemicals), macrolides (5 chemicals), and β-lactams (penicillins and cephalosporins, 4 chemicals) as well as chloramphenicols (2 chemicals) and lincomycin (1 chemical). The survey was conducted for the seven regions of China (East China, North China, Central China, Northeast China, Northwest China, and Southwest China) to reflect the different usage levels. A nationwide antibiotic emission estimation and multimedia modeling were conducted at the river basin level, as described in our previous study.[40] Briefly, China is divided into 58 basins based on the Industry Standard of China,[40,41] and these basins cover all of the secondary rivers in China. The basins are composed of many administrative areas, and the parameters such as population for a basin are based on statistical data of its inclusive cities (or prefectures). Details about administrative areas and populations for human and animals included in each basin are given in the Supporting Information (SI-A).

Antibiotics Usage and Excretion. A market survey on the usage of 36 target antibiotics in China for 2013 was conducted in 2014. For the survey purpose, antibiotics are mainly classified into human and veterinary drugs. Given the huge numbers of pigs and chickens in all regions of China,[42] and the survey results of antibiotic consumptions in different livestock sectors,[2,26,43] the veterinary antibiotic usages were further classified into three subcategories: pig, chicken, and other animals. A diagram showing the methodological procedure of setting up the survey and estimating the usage of antibiotics is displayed in Figure S1. Based on the database of China Food and Drug Administration and China Institute of Veterinary Drugs Control, the registration information on human and veterinary antibiotics was collected, and the corresponding drug manufacturers were obtained. With the help of the China Pharmaceutical Industry Association, which provided a list ranking drug manufacturers based on their sales volumes, we selected the top 5−10 representative pharmaceutical companies for each of the target chemicals. Our survey was carried out in 237 drug manufacturers. The sales data and market shares of those pharmaceutical companies were carefully collected from each of the company sales managers. Then the usage data for each chemical were calculated through the sales data and market shares. In parallel to the work of the usage survey of 36 chemicals, the national total sold volumes of six categories of antibiotics (sulfonamides, tetracyclines, fluoroquinolones, macrolides, β-lactams, and others) were also collected from the Southern Medicine Economics Institute, the State Food and Drug Administration, and the China Pharmaceutical Industry Association. Those three agencies provided us with the sold volumes for five main category antibiotics (except the category of other antibiotics) in seven regions (East China, North China, Central China, South China, Northeast China, Northwest China, and Southwest China) for cross-validation purposes. Since no reliable quantitative data on the fraction of unused medication could be obtained for each target chemical, in the worst case scenario, it was assumed that the sold volume was the same as the consumed volume.

Following the survey of the target antibiotics in the seven regions of China, the average usage per person, pig, chicken, and other animals in each region was calculated based on the populations (Table S1). In our assumption, the average usage for each antibiotic of different individuals in an administrative area was given the same usage value of its locating region. As the basins are composed of cities (or prefectures), the antibiotic usage in each basin was the sum usage of their inclusive cities (or prefectures). Since many individuals (such as cattle, sheep, and fish) were included in the "Other animals" category, in order to facilitate comparison, the average usage for the "Other animals" category was obtained by the antibiotic usage divided by total annual production of the animals included in the "Other animals" category (with the unit of tons). The antibiotic usage in each basin for different individuals was the product of average usage for human, pig, chicken, and other animals and their corresponding populations for the basins (Supporting Information: SI-A).

A significant percentage of consumed human and animal pharmaceuticals may be excreted via urine and feces in its parent form.[1,3] Some studies showed that the excreted glucuronide conjugates can easily convert back to the parent form after excretion.[44,45] Considering different pharmacokinetics for individuals, we collected as many as possible the metabolism fraction data of the unchanged and glucuronide conjugates for each of the antibiotics excreted by human, pig, and chicken from published literature (Supporting Information, Table S2). The mean values generated from all of these literature values were selected in the calculation for excretions of antibiotics. Thus, the excretion amount was the product of usage and sum fraction of the unchanged and glucuronide conjugates for each chemical and each individual. The equation describing the excretion estimation is as follows

$$T_E = \sum_{i=1}^{n} P_i \times m_i \times E_i$$

where i represents the human, pig, chicken, and other animal groups; P_i is the population of the i^{th} group; m_i is the per capita antibiotic usage of the i^{th} group (ton/year); and E_i is the

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Table 1. Usage of All the Antibiotics in Seven Regions of China in 2013

	amount (tons)						
regions	sulfonamides	tetracyclines	fluoroquinolones	macrolides	β-lactams[a]	others	total[c]
East China	2270	3710	7290	14800	10700	*b*	38800
North China	1660	2520	6700	9560	7410	*b*	27900
Central China	1530	1760	5960	5790	6080	*b*	21100
South China	596	1060	1970	2870	2530	*b*	9030
Northeast China	300	679	1140	2590	1360	*b*	6070
Northwest China	180	383	419	854	519	*b*	2360
Southwest China	1390	1880	3850	5740	5450	*b*	18300
subtotal	*7920*	*12000*	*27300*	*42200*	*34100*	*38400*	***162000***

[a]Including two categories: penicillins and cephalosporins. [b]Data not available for each region but with a national total value. [c]The total amount for each region is the total of the 5 antibiotic categories.

metabolism fraction of the unchanged and glucuronide conjugates of target antibiotic chemical for the i^{th} group.

Emission Estimation. Antibiotics are disseminated into the environment from both human and agricultural sources.[1] Human emissions of antibiotics include those from urban and rural populations. WWTPs receive most of the antibiotic excretions of urban populations. The removed amount is influenced by the wastewater treatment rate of each city and the removal efficiencies of target chemicals in the WWTPs. For the human emissions from rural populations, on account of the limitations of wastewater treatment facilities,[46] a majority of wastewater in rural areas are discharged untreated in China. Thus, the antibiotic emissions from human sources consist of three parts: emission from rural populations, emission from urban populations (direct discharge without WWTPs), and emission from WWTPs. Unlike domestic wastewater, there are so far no specific treatment requirements for livestock wastes before discharge. It is a common practice to directly discharge animal wastewater into streams or dispose of solid manure onto agricultural land. While some simple treatment facilities of lagoons and sedimentation tanks are available in approximately 20% of livestock farms in China,[47] they are not very effective for removing the antibiotics.[2] Thus, it is assumed in this study that all veterinary antibiotics associated with animal wastes are discharged directly into the environment.

Wastewater discharge and land application of human and animal wastes are the two main pathways into the environment. Most of the emission from human source enters into the water compartment, and the remaining small portion of the discharged antibiotics enters into the soil compartment through sewage irrigation. The second national survey of the sewage irrigation shows that the sewage irrigation on farmland is mainly located in north China, including basins of the Haihe, Liaohe, Yellow River, and Huaihe River.[48] The reported ratio of sewage irrigation area to the whole agricultural land was 6.65%.[47] Thus, it is assumed that 6.65% of agricultural land of the cities located in the four basins were irrigated with sewage. Based on the assumption that the irrigation water amount per unit area of the agricultural land is the same, the antibiotic emission into the soil compartment via sewage irrigation can be estimated by the ratio of the sewage irrigation volume to sewage wastewater discharge volume multiplied by the total antibiotic emission from the sewage wastewater. It should be noted that the pathway of domestic sludge application on land was neglected since sludge application on agricultural land is prohibited in China. For the antibiotic emissions from animal source, excretions from chicken and other animals were assumed into the soil compartment. While for pigs, with the help of flush cleaning for the wastes,[49] all the urine and about 20% of the total feces would be discharged into the water compartment.[50]

Multimedia Model. A level-III fugacity model based on the approach of Mackay and Paterson[51] was applied to predict the multimedia fate of the 36 antibiotics in the 58 basins. The framework as well as the transfer processes and parameters of the model are similar to that reported in our previous studies,[40,52] and the details of the model and related parameters are also described in the Supporting Information (SI-B, Tables S3−S7). Briefly, air (air, particulates), water (water, suspended solids, and fish), soil (water and solids), and sediment (water and solids) are included as bulk compartments. The mass balance equations among the 4 bulk compartments are established in terms of the transfer fluxes. Antibiotic emissions to water and sediment from human and animal sources, which were calculated out by using the method listed above, are the input fluxes. Other transfer processes include advective air and water flow, degradation in air, water, soil, and sediment, accumulation in fish, diffusion between air and surface water and between water and sediment, wet and dry deposition, soil erosion, sedimentation, and resuspension between water and sediment. Then the transfer fluxes can be replaced by some parameters and corresponding calculation methods (Supporting Information: SI-B). A ready model has been built using Matlab R.2010a by the authors before.[40] With the developed level-III fugacity model, we obtained the PECs, transfer fluxes, and mass inventories for the target chemicals in the 58 basins. Uncertainty analysis was performed for the modeling results with the detailed method given in SI-B.

Bacterial Resistance Data Collection and Analysis. The antimicrobial resistance surveillance system set up by the Ministry of Health of China releases various data of bacterial resistance to antibiotics in 1427 hospitals located in six regions of China (East China, North China, Central-South China, Northeast China, Northwest China, and Southwest China) (CARSS Web site: http://narin.minke.cn/Contact). Those tested antibiotics such as ciprofloxacin, sulfamethoxazole, and tetracycline, which are frequently detected in the environment and are the target chemicals in this study, were collected to identify the relationships between the antibiotic usage and PECs and the bacterial resistance in hospitals. The latest and complete released values for hospital bacterial resistance in six regions of China were in 2011. The corresponding representative bacterial species included *Acinetobacter baumannii*, *Citrobacter freundii*, *Escherichia coli*, *Haemophilus influenzae*,

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and *Klebsiella pneumoniae*. While antibiotic susceptibility testing has been performed for the above species in the hospitals; only *Escherichia coli* (*E. coli*) strains isolated from the aquatic environment have been tested for antibiotic resistance.[53] The bacterial resistance rates for seven antibiotics (ampicillin, ceftazidime, cephazolin, ciprofloxacin, gentamicin, piperacillin, and sulfamethoxazole) for *E. coli* in the five major Chinese rivers including Pearl Rivers (ID: 43), Yellow River (ID: 18), Haihe River (IDs: 13−15, 17), Liaohe River (IDs: 7−10) and Dongjiang River (ID: 42) were investigated by our group in 2008−2009.[25,54] Combining the bacterial resistance data in the hospitals in the years of 2008−2009, the association of bacterial resistance between the hospitals and rivers was then assessed by using multivariate analysis including redundancy analysis (RDA), in advance of a detrended correspondence analysis (DCA) showing that the lengths of first ordination gradient less than 3.[55] The multivariate analyses were performed with software Canoco 4.5.

RESULTS AND DISCUSSION

Antibiotic Usage and Emission in China. Based on this survey, the total production of all antibiotics in China was estimated to be 248000 tons for 2013, and the imports and exports were 600 and 88000 tons, respectively. The total antibiotic usage in China for 2013 was estimated to be approximately 162000 tons (Table 1). Human consumption accounted for about 48% of the total antibiotics, and the rest was shared by animals. Based on the data in Table 1, sulfonamides, tetracyclines, fluoroquinolones, macrolides, β-lactams, and other antibiotics shared 5%, 7%, 17%, 26%, 21%, and 24% of the total usage, respectively. The survey in the seven regions of China for five main categories of antibiotics (except the category of other antibiotics) showed that east China consumed the largest amount of antibiotics and northwest China consumed the smallest (Table 1). As shown in Table 2, China consumed 150 times more antibiotics than the UK, and the DID (DDD: Defined daily doses/inhabitants per day; DID is for 1000 inhabitants)[61] was 6 times larger. Although the usage data pertains to different years, the DIDs of the UK, USA, Canada, and Europe are similar, with DID values approximately 6 times smaller than that for China. The consumption of veterinary antibiotics increased from 46% in 2007[9] to 52% in 2013, and this may be attributed to the human medical system reform since 2011 initiated by the Ministry of Health of China, which set some restrictions on hospitals on the numbers of varieties of antibiotics and their DDDs.[62]

Table 2. Total Usages of All Antibiotics in China and Other Developed Countries

		usage (tons)				
country	year	total	human	animals	DID[a]	ref
China	2013	162000	77760	84240	157	this study
UK	2013	1060	641	420	27.4	56, 57
USA	2011/2012	17900	3290	14600	28.8	58, 59
Canada	2011	*b*	251	*b*	20.4	60
Europe	2003	*b*	3440	*b*	20.1	32

[a]DID: Defined daily doses for 1000 inhabitants per day. Data on outpatient use of systemic antibiotics aggregated at the level of the active substance were collected and expressed in DDD.[61] The DID is DDD/1000 inhabitants. It is an index of average consumption for humans. The populations used to calculate the "Defined daily doses/1000 inhabitants per day" was available at the following: UK, http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Population+Change#tab-overview; Canada, http://www12.statcan.ca/census-recensement/index-eng.cfm; USA: http://www.census.gov/popclock/; European, http://www.census.gov/population/international/data/idb/region.php?N=%20Results%20&T=6&A=both&RT=0&Y=2003&R=130&C=. [b]No data was available.

For the selected 36 target antibiotics, their total usage was 92700 tons (Table 3). Veterinary antibiotics accounted for 84.3% (pig: 52.2%, chicken: 19.6%, and other animals: 12.5%), whereas human antibiotics only shared 15.6% (Table 3). Compared with the proportion of all the antibiotic consumption for animals, the 36 target chemicals, which are frequently detected in the environment, were contributed more by animals (52% for all antibiotics vs 84.3% for 36 antibiotics). It can be inferred that the livestock industries with low wastewater treatment rates may have major impacts on the environment.

Among the 36 antibiotics, amoxicillin, florfenicol, lincomycin, penicillin, and norfloxacin were the top 5 antibiotics used in China. Amoxicillin had the largest usage for both human and animal use. Ormetoprim had the smallest usage and was only used by chicken and other animals.

Animals consumed a larger amount of florfenicol when compared with other veterinary antibiotics. Apart from that, lincomycin, tylosin, and enrofloxacin were largely consumed by pig, with their usages all more than 3000 tons. Sulfaquinoxaline, enrofloxacin, and tylosin were consumed more than 1000 tons by chicken. In comparison with the main chemical groups of veterinary antibiotics in the USA and UK, where tetracyclines, β-lactams (including penicillin), and macrolides are the majority antibiotic active ingredients sold in veterinary medicinal products,[57,59] these three groups plus fluoroquinolones are consumed more in China. Other groups which might be the major veterinary antibiotics such as aminoglycosides and ionophores are not included in our research.

Due to their easy hydrolysis, the β-lactams are rarely measured in the environment.[5,13] In fact, it should be mentioned that more antibiotics in the β-lactams class with relatively high usages were not included in the targeted survey due to their low detection frequencies. Although only 4 chemicals were included in the β-lactams in our research, two of them ranked in the top 5 usage chemicals of all the target chemicals, while they were the top 2 for human use. It is consistent with the fact that β-lactams (cephalosporins and penicillins) are the largest category for human use in China.[31] In addition, ofloxacin, tetracycline, and norfloxacin were consumed more than 1000 tons by humans in China. It is observed that the main groups of antibiotics for human use in China are similar to other countries such as the UK,[56] USA,[58] and Canada.[60] Comparing the usage values for the specific antibiotics with those reported for other countries, China showed higher per capita consumptions of nearly all reported antibiotics. For example, the reported per capita consumption[35] of roxithromycin in Germany (in 2001), Poland (in 2000), Spain (in 2003), Sweden (in 2005), and Switzerland (in 2000) were 75.2, 53.0, 9.3, 1.6, and 20.4 mg cap^{-1} yr^{-1} respectively, while the value in China was up to 135 mg cap^{-1} yr^{-1}.

After metabolism by humans and animals, the total excretion amount for the 36 chemicals was 54000 tons, with 84.0% excreted by animals (pig: 44.4%, chicken: 18.8%, and other animals: 20.9%) and 16.0% excreted by humans. The wastewater treatment plants in China have not completely

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Table 3. Usage of Selected 36 Antibiotics in China in 2013

category	name	abbrev	CAS no.	usage (tons)				
				human	pig	chicken	others	total
sulfonamides	sulfadiazine	SDZ	68-35-9	238	648	221	148	1260
	sulfamethazine	SMZ	57-68-1	68.4	388	132	88.7	677
	sulfamethoxazole	SMX	723-46-6	2	198	67.6	45.3	313
	sulfathiazole	STZ	72-14-0	0.66	40.2	13.7	9.18	63.7
	sulfachlorpyridazine	SCP	80-32-0	*a*	329	111	77.5	518
	sulfameter	SM	651-06-9	12.6	315	107	72	507
	sulfamonomethoxine	SMM	1220-83-3	9.93	1400	477	320	2210
	sulfaquinoxaline	SQX	59-40-5	*a*	0	1250	190	1440
	sulfaguanidine	SG	57-67-0	73.6	46.9	16	10.7	147
	trimethoprim	TMP	6981-18-6	500	157	53.5	35.8	746
	ormetoprim	OMP	738-70-5	*a*	0	1.01	6.91	7.92
	total			905	3520	2450	1000	7890
tetracyclines	oxytetracycline	OTC	79-57-2	192	740	253	170	1360
	tetracycline	TC	60-54-8	1265	119	40.7	27.3	1450
	chlortetracycline	CTC	57-62-5	48.3	136	46.5	31.2	262
	doxycycline	DC	564-25-0	199	2300	786	527	3810
	methacycline	MT	914-00-1	64.2	5.45	1.92	0.85	72.4
	total			1770	3300	1130	756	6950
fluoroquinolones	norfloxacin	NFX	70458-96-7	1013	2820	961	644	5440
	ciprofloxacin	CFX	85721-33-1	455	3110	1060	712	5340
	ofloxacin	OFX	82419-36-1	1286	2440	832	557	5110
	lomefloxacin	LFX	98079-51-7	228	650	222	149	1250
	enrofloxacin	EFX	93106-60-6	*a*	3090	1150	940	5180
	fleroxacin	FL	79660-72-3	119	60.6	21.6	15.1	216
	pefloxacin	PEF	70458-92-3	200	1320	451	302	2270
	difloxacin	DIF	98106-17-3	*a*	378	172	117	667
	total			3300	13900	4870	3440	25500
macrolides	leucomycin	LCM	1392-21-8	205	941	321	215	1680
	clarithromycin	CTM	81103-11-9	65.9	114	71.5	41.4	293
	roxithromycin	RTM	80214-83-1	184	112	67.3	22.5	386
	tylosin	TYL	1401-69-0	*a*	3090	1050	706	4850
	erythromycin-H_2O	ETM-H_2O	23893-13-2	1244	1580	565	377	3770
	total			1700	5840	2070	1360	11000
β-lactams	cephalexin	CPX	15686-71-2	2542	83.4	28.3	19.2	2670
	amoxicillin	AMOX	26787-78-0	2129	6860	2340	1570	12900
	penicillin	PEN	69-57-8	917	3700	1260	846	6730
	cephazolin	KZ	25953-19-9	6.14	0.15	0.05	0.04	6.38
	total			5590	10600	3630	2440	22300
others	florfenicol	FF	73231-34-2	*a*	6370	2150	1510	10000
	chloramphenicol	CAP	154-75-2	215	552	342	119	1230
	lincomycin	LIN	154-21-2	999	4340	1480	993	7820
	total			1210	11300	3970	2620	19100
total				14500	48400	18100	11600	92700

[a]The antibiotic is a veterinary antibiotic, not for humans.

removed the antibiotics before effluent discharge into the environment.[5] The total emission for the 36 antibiotics to the environment in China was estimated to be 53800 tons, with 46% received by water and 54% by soil compartment. The emission map of China is shown in Figure 1 (A). It can be seen that there exist large differences in antibiotic emission among the basins. Dongting Lake (ID: 31) in central China received the largest discharge of the antibiotics with the total up to 3440 tons. By contrast, the Senggecangbu River basin (ID: 50) located in the west part of Tibet received the lowest antibiotics discharge of 1.18 tons. The Yellow River (ID: 18), Huaihe River (ID: 22), and Yangtze River Downstream (ID: 26) basins also received the discharge of the target antibiotics of more than 3000 tons. When the emission values were normalized by their corresponding basin area, it produced a completely different antibiotic distribution pattern, as shown in Figure 1 (B). Pearl River basin (IDs: 42, 43) located in south China showed the highest emission densities, followed by basins of Haihe River (IDs: 13−15, 17) located in north China and Taihu Lake (ID: 34) and Qiantang River (ID: 35) located in east China. The megacities of Guangzhou, Shenzhen, Beijing, and Shanghai are located in these basins. In general, the average emission densities for the basins located in east and south China were more than 6 times higher than those in west China, with the basins being separated into two different regions by the famous geographic "Hu Huanyong line", which reflects the huge impact of human activities on the distribution of antibiotics. Other emissions for personal care products,

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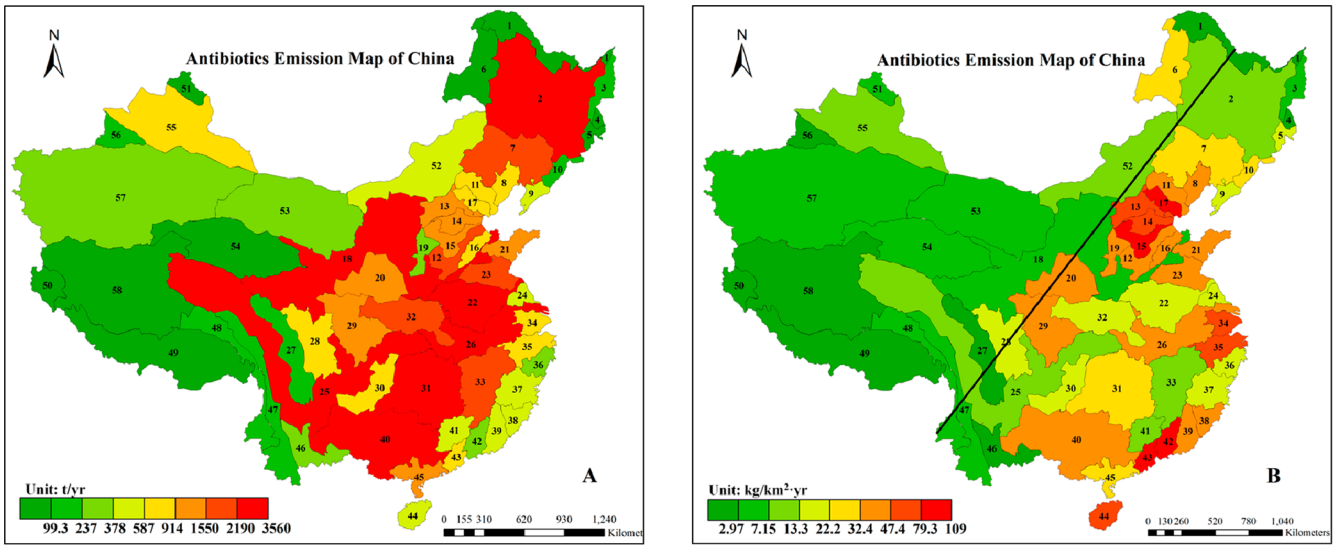

Figure 1. Map of China showing the total antibiotic emission in each river basin. (A) The total environmental emission of the antibiotics for each basin with the unit of t/yr and (B) the emission density of the antibiotics for each basin, with the unit of kg/m^2 ·yr. Basin IDs: 1. Heilongjiang; 2. Songhua River; 3. Wusuli River; 4. Suifen River; 5. Tumen River; 6. Ergun River; 7. Liao River; 8. Daling River; 9. Liaodongbandao; 10. Yalu River; 11. Luan River; 12. Zhangweinan Canal; 13. Yongding River; 14. Daqing River; 15. Ziya River; 16. Tuhai-Majia River; 17. Chaobai-Beiyun-Jiyun River; 18. Yellow River; 19. Fen River; 20. Wei River; 21. Shandong Peninsula; 22. Huai River; 23. Yishusi; 24. Lixia River; 25. Yangtze River Upstream; 26. Yangtze River Downstream; 27. Yalong River; 28. Minjiang River; 29. Jialing River; 30. Wujiang River; 31. Dongting Lake; 32. Hanjiang River; 33. Poyang Lake; 34. Taihu Lake; 35. Qiantang River; 36. Oujiang River; 37. Minjiang River; 38. Mindong-Yuedong; 39. Hanjiang River; 40. Xijiang River; 41. Beijiang River; 42. Dongjiang River; 43. Pearl River Delta; 44. Hainan; 45. Yueguiqiong; 46. Yuanjiang-Honghe; 47. Lantsang-Mekong; 48. Nujiang-Irrawaddy; 49. Brahmaputra; 50. Senggecangbu; 51. Ertix River; 52. Water system inner of Inner Mongolia; 53. Water system inner of Hexi corridor-Alxa; 54. Water system inner of Qaidam; 55. Water system inner of Junggar; 56. Water system inner of Ili-Eminhe; 57. Water system inner of Tarim; 58. Water system inner of Tibet. The black line on the map (B) is the Chinese geographic "Hu Huanyong line".

steroids, and black carbon in China were also reported to have similar distribution characters.[40,63,64]

Predicted Environmental Concentrations and Model Verification. The predicted environmental concentrations (PECs) of the 36 antibiotics in the 58 basins were simulated by the level-III fugacity model for different compartments (air, water, soil, and sediment) based on the emission data, and the detailed results are given in the Supporting Information (SI-A). Due to their low volatilities, the target antibiotics were predicted to have extremely low concentrations in air compartment (SI-A). Huge differences in concentrations for these chemicals existed among the 58 basins in China. For each of the environmental compartments, all the minimum concentrations were in basins of Brahmaputra (ID: 49) and Senggecangbu (ID: 50) located in northwest China, and the maximum values were concentrated in Haihe River of north China (IDs: 12−17). The former is in Tibet with sparse population and livestock farming, while the latter is on the gulf of Bo Hai with two of the most densely populated cities Beijing and Tianjin in China.

Figure 2 summarized the predicted median and mean concentration of the 36 target antibiotics, grouped into 7 categories. The concentrations for chloramphenicols and lincomycin were found to be higher than the other five major antibiotic categories in water. While in soil and sediment, the highest concentrations were predicted for fluoroquinolones. Among each category of sulfonamides, tetracyclines, fluoroquinolones, macrolides, and β-lactams as well as chloramphenicols, the chemicals with the maximum concentrations were sulfadiazine, doxycycline, pefloxacin, erythromycin-H_2O, florfenicol, and amoxicillin in water; sulfaquinoxaline, doxycycline, difloxacin, erythromycin-H_2O, florfenicol, and amoxicillin in soil; and trimethoprim, doxycycline, enrofloxacin, erythromycin-H_2O, florfenicol, and amoxicillin in sediment. It should be noted that other fluoroquinolones such as norfloxacin, ciprofloxacin, and ofloxacin were also predicted with relatively high concentrations in all the environmental media (water, sediment, and soil). This is consistent with the monitoring results in China as they were frequently detected either in the surface water and sediment of rivers or in the animal wastewaters and manure as well as manure-amended soils of livestock farms.[2,5,10,65] The environmental concentrations for sulfonamides and tetracyclines in China are comparable with those in USA[12,66] but higher than in some European countries such as Italy[67] and France.[68] For the macrolides, roxithromycin had a mean concentration range of ND-150 ng/L in German rivers,[4,69] while it was 0.05−378 ng/L in China. In Australia, Watkins et al.[70] reported median concentrations (ND-9 ng/L) of chloramphenicol in six river systems, but in China it was modeled up to 1081 ng/L. The measured environmental concentrations (MECs) of fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, and norfloxacin) in Italy (9 ng/L),[71] USA (up to 120 ng/L),[66] and Germany (20 ng/L)[69] are much lower than those in China with concentrations up to 7560 ng/L, with the average for all fluoroquinolones being 303 ng/L. The large difference between China and the other countries is mainly caused by the different usages of fluoroquinolones. The usage proportion for fluoroquinolones (17%) among all the antibiotics in China was higher than in other countries, such as USA (<8% for humans, <10% for animals).[58,59] In general, the aquatic environment in China has relatively higher antibiotic contamination levels when compared with other countries around the world.[72]

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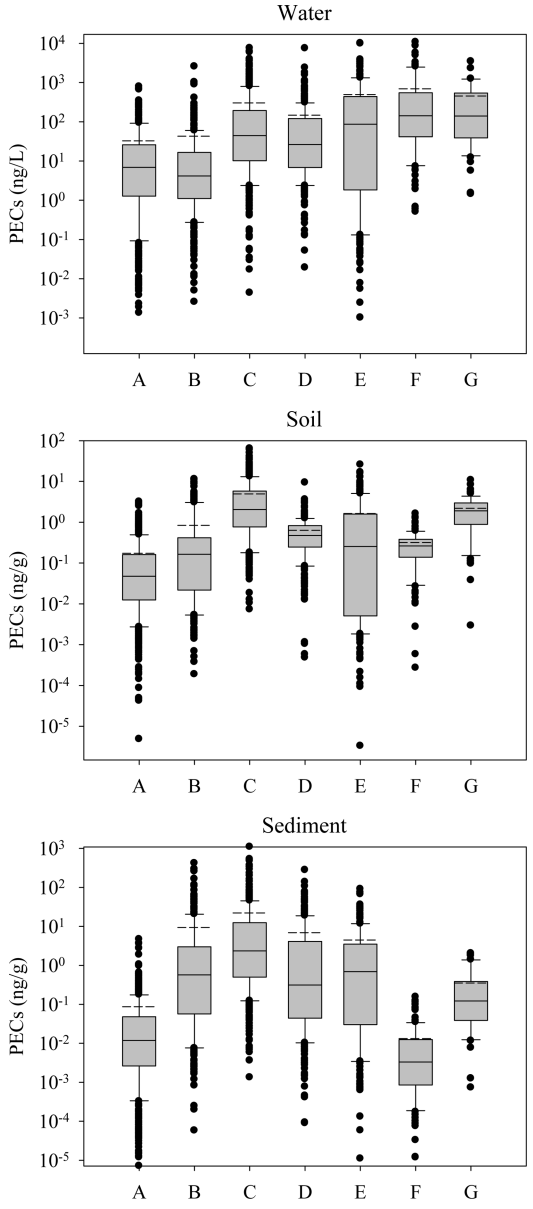

Figure 2. Box plot of the predicted concentration ranges for different categories of antibiotics (A: sulfonamides, B: tetracyclines, C: fluoroquinolones, D: macrolides, E: β-lactams F: chloramphenicols, G: lincomycin,) in water, soil, and sediment in all the basins of China. The horizontal lines represent 10th and 90th percentiles, and the boxes represent 25th and 75th percentiles, while outliers are shown as individual points. Median and mean concentrations are shown as solid and dashed horizontal lines, respectively.

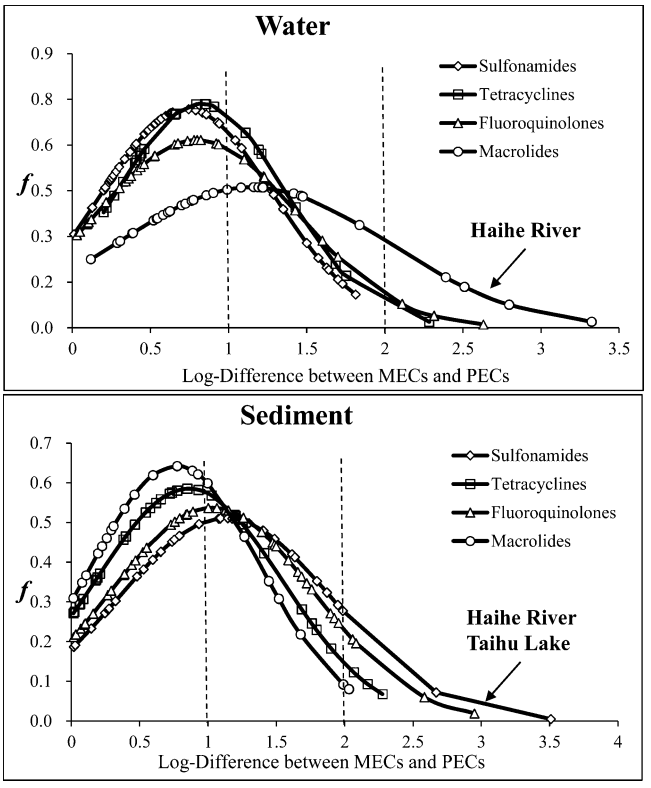

Figure 3. Normal probability distribution curves showing the logarithmic transformed differences between the measured (MECs) and modeled concentrations (PECs) of the antibiotics in water and sediment in the basins of China. The f in the diagram represents the frequency (likelihood) of the modeled concentration to take on a given value. The sulfonamides include SDZ, SMZ, SMX, STZ, SCP, SM, SMM, SQX, SG, and TMP. The tetracyclines include OTC, TC, CTC, and DC. The fluoroquinolones include NFX, CFX, OFX, LFX, EFX, and FL. The macrolides include CTM, RTM, TYL, and ERY-H_2O. Since just several MECs are available for the chloramphenicols (FF, CAP), LCM, CPX, and PEN in water and sediment in China basins, these chemicals are included in the curves of macrolides. There are no MECs for the other chemicals in the basins, so they are not included in the graphs. The two dashed vertical lines represent 1 and 2 orders of magnitude between the PECs and MECs, respectively.

In total, 332 mean MECs in water (204) and sediment (128) were collected to verify the predicted environmental concentrations (PECs) by the fugacity model (Table S8). Figure 3 shows the logarithmic transformed differences (LTDs) between the PECs and MECs and their relating frequency by means of normal distribution curve. In general, the PECs were successfully modeled for nearly all of the compounds with >50% LTDs less than 1. Only for sulfonamides lower PECs in sediment were predicted when compared to those MECs, with only 47% of the LTDs less than 1. Due to their easy hydrolysis in water, the β-lactams were modeled to give a larger difference to the MECs. Large differences (more than 2 orders of magnitude) are mostly concentrated in the basins of Haihe River, especially for the veterinary antibiotics. In this basin, all monitoring campaigns were conducted within the region of two big cities Beijing and Tianjin.[10,24,30,73,74] This may lead to a large variation in mean concentrations because the other regions in this basin are located in Hebei Province with a far less population density but many livestock farms.[42] As for the underestimation for sulfonamides in sediment of Taihu Lake, this can be explained by the limited measurements available only near the lakeside. In a word, this study demonstrated the usefulness of fugacity modeling in the prediction of environmental concentrations of antibiotics, when monitoring data are not available.

Multimedia Fate of Antibiotics. The transfer fluxes for all the 58 basins in China were predicted, and a summary for the average contribution of each transport flux to the total input or output fluxes in different compartments is displayed in Figure S2. For most of the antibiotics, the fluxes of source emission and degradation made the most contribution in various compartments. In water, the antibiotics emission from pigs contributed most for nearly all antibiotics categories, excepting for lincomycin with more contribution from erosion from soil

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to water in liquid phase (T_{32l}) as it was more consumed by animals (Table 3) and excreted more in feces than urine (Table S2). By contrast, antibiotics emission from humans contributed less than 25% of total input flux for each of the antibiotics categories, and it was extremely low for the categories of macrolides and others (chloramphenicols) which are in turn excreted more by pigs. Followed by the emissions from humans and animals, the advective input flows (T_{02t}) and diffusion from sediment to water (T_{42d}) also contributed totally about 3%−20% of the antibiotics input flux. In addition to the degradation process, the output fluxes in water were shared by sedimentation (T_{24s}) and advective flows out of the area (T_{20t}). For tetracyclines and fluoroquinolones, the T_{24s} contributed more than 62% and 39% of total output fluxes. It suggests that these two categories of antibiotics are prone to enter into the sediment as observed by other researchers.[12,75]

Mass inventories for each antibiotic in all of the 58 basins were also calculated, and the total distribution ratios for the all categories of antibiotics in different environmental media are displayed in Figure S3. For the groups of tetracyclines, fluoroquinolones, macrolides, and β-lactams, more than 50% of the total mass was distributed into the sediment compartment. Attributed to the animal waste application, there was more than 60% of the total mass for sulfonamides and lincomycin being distributed into the soil compartment. The chloramphenicols (i.e., florfenicol and chloramphenicol) were the only group with the highest distribution proportion in water. The total mass inventories for the 36 antibiotics in China were 3825 tons in water, 11516 tons in soil, and 17206 tons in sediment.

Linking Bacterial Resistance to the Usages, Emissions, and PECs of Antibiotics. The redundancy analysis (RDA) diagram (Figure 4A) showed positive relations between the hospitals and rivers for resistance of *E. coli* to three relatively old generation antibiotics (sulphamethoxazole/trimethoprim, ampicillin, and piperacillin) but negative relations for ceftazidime, cephalozin, and ciprofloxacin of the relatively new generation. Only one relatively old generation antibiotic (gentamicin) showed no relationship. The rivers 1 and 2 (Dongjiang River and Pearl River delta) lie close together, indicating that those two rivers had resembling contamination profiles in terms of the resistance of *E. coli*. In the RDA diagram (Figure 4A), the order of the site points projected to the line of antibiotic resistance inferred that the Yellow River had the highest resistance of *E. coli* to various antibiotics. For all the tested antibiotics, the antibiotic resistance rates were much higher in the hospitals than in the rivers (Table S9). It implies that antibiotic resistant bacteria in hospitals may take time to spread and disseminate in the receiving environment. In addition, river water dilution might also contribute to the difference. This result might only reflect the impact on the aquatic environment from those antibiotics of human use.

The antibiotic resistance data of the five bacterial species to three representative antibiotics (ciprofloxacin, sulfamethoxazole/trimethoprim, and tetracycline) in the hospitals of six regions of China (the official reports merged the Central and Southern China into a single region) were also used to assess the relationships among the antibiotic usage, bacterial resistance in hospitals, and the PECs in rivers (Figure 4B; Table S9). The north and central-south China are displayed to be a cluster when compared with other regions, showing similar influences of antibiotics. When compared the order of the site points projected to the lines of antibiotic resistance in the RDA

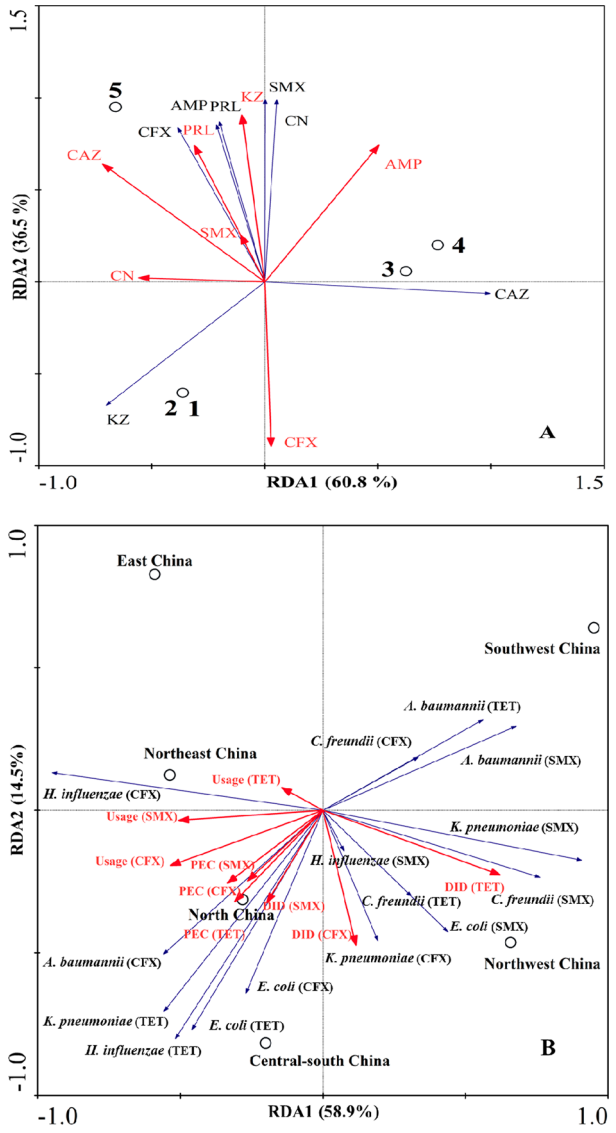

Figure 4. Redundancy analysis (RDA) ordination plots showing relations of bacterial resistance to seven respective antibiotics in hospitals and rivers (A) and the relations between hospital bacterial resistance rates and antibiotic usages (B). In graph A, the blue lines and red lines represent the resistance to *Escherichia coli* in the hospitals and rivers; empty circle symbols 1, 2, 3, 4, and 5 represent the Pear River, Dongjiang River, Haihe River, Liaohe River, and Yellow River, respectively. Accordingly, the bacterial resistance data in the hospitals are selected from the city hospitals where these rivers flow through. The RDA 1 and RDA 2 explained 61.5% and 34.4% of the total variance, respectively. In graph B, the bacterial resistance data for five bacterial species in the hospitals (blue line), antibiotics usage data including DIDs (defined daily doses per 1000 inhabitants per day) and regional total usages, and environmental concentrations (PECs) (red line) are available for three respective antibiotics (CFX: ciprofloxacin, SMX: sulfamethoxazole/trimethoprim, and TET: tetracycline). Empty circle symbols represent the six regions of China. The RDA 1 and RDA 2 explained 58.9% and 14.5% of the total variance, respectively. Abbreviations: CFX: ciprofloxacin; SMX: sulfamethoxazole/trimethoprim; CAZ: ceftazidime; AMP: ampicillin; PRL: piperacillin; CN: gentamicin; KZ: cephalozin; TET: tetracycline.

diagram (Figure 4B), it can be inferred that the central-south China had the highest bacterial resistance, while the East China had the lowest bacterial resistance. Not surprisingly, the antibiotic usage had a positive correlation with the PECs. As

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shown in Figure 4B, ciprofloxacin had the highest positive correlations (for three out of five bacterial species) between the usages, DIDs (defined daily doses per 1000 inhabitants per day), PECs, and bacterial resistances in hospitals. For tetracycline, the antibiotic resistance for *K. pneumoniae*, *H. influenzae*, and *E. coli* was positively correlated to the PECs but not to the usage and DIDs. For sulfamethoxazole, no positive correlation was observed between the bacterial resistance and the usage and PECs. Throughout the antibiotic use history, sulfonamides can be traced back to 1930s, followed by the tetracyclines in 1940s, and then the latest fluoroquinolones in 1980s. The time sequence of these three representative antibiotics highly reflects the degree of correlation between the bacterial resistance and the chemical usage and PECs. The longer an antibiotic has been used, the less the correlation of bacterial resistance to its current usage and environmental concentrations due to the long-term resistome dissemination and cross resistance against other antibiotics.[4] Therefore, the bacterial resistance for an antibiotic in a region is linked to its use history, current usage, and environmental concentrations.

Uncertainty Analysis and Model Implications. Monte Carlo simulation was employed to propagate collective variance of the inputs through the model for assessment of the overall uncertainty in the predictions, and this method has been successfully performed in our previous study.[40] Briefly, probability distributions for input parameters were used to replace discrete values, by randomly selecting values from each input parameter distribution. The simulation was run for 500 times using a build-in function of "randn" in Matlab. Difference between the third and the first quartiles (abbreviated as SQR) was used to quantify the uncertainties. Detailed description on the uncertainty analysis and related parameters are listed in the Supporting Information (SI-B, Table S10). As shown in Figure S4 of the Supporting Information (SI-B), for the fluoroquinolones and β-lactams, larger uncertainty existed when compared with other chemicals. Because of little reported values for their parameters, we assumed the maximum coefficient of variation (100%) for those parameters and thus devised the largest uncertainty. This means that the uncertainty analysis was conducted in the worst case scenario. However, most of the SQRs fell into 2 (Figure S4), showing that the difference between the third and first quartiles were within 2 orders of magnitude for most of the chemicals. In all, despite large uncertainties which can be found for some chemicals modeling, considering the comparable predicted concentrations and generally reasonable uncertainties, the model can provide a general consistency with the contamination of the antibiotics.

Uncertainty on the linkage of antibiotic usage to bacterial resistance largely depends on the data quality collected from the hospitals. So the uncertainty involved in the RDA results was assessed by collecting bacteria resistance data in hospitals reported for different years, and the result from this uncertainty analysis showed that the relationships between hospital bacterial resistance and river bacterial resistance as well as the antibiotic usage were not much affected by time to some extent (Figure S5). According to the global report from World Health Organization on higher antibiotic usage associated with higher bacterial resistance at the country-level,[29] it is believed that the antibiotic usage data is an effective tool to predict the spread of antibiotic resistance.

The results from the present study found an alarming nationwide overuse and emission of various antibiotics in China. This has resulted in the relatively high environmental concentrations and increased antibiotic resistance in hospitals and receiving environments. In addition, animal use of various antibiotics has also been a serious concern as increased bacterial resistance and widespread presence of ARBs and ARGs were reported in livestock farms and surrounding environments.[9,24,26] This could pose a great threat to human health when bacteria causing infections are no longer susceptible to antibiotic treatment;[76] therefore, tight management measures are urgently needed to control the overuse of antibiotics in China. This could also be a reminder for other developing countries with similar situations. Rational use of antibiotics in humans and animals should be promoted around the world.

■ ASSOCIATED CONTENT

Supporting Information

Detailed description of the model framework and parameters, tables of modeling data, and additional figures. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.5b00729.

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Notes

The authors declare no competing financial interest.

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