

# Source Apportionment, Hydrodynamic Influence, and Environmental Stress of Pharmaceuticals in a Microtidal Estuary with Multiple Outlets in South China

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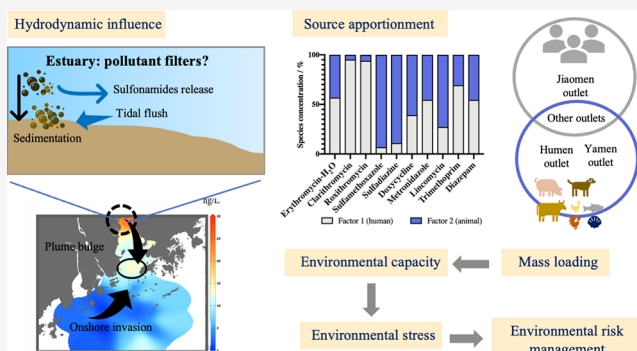
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**ABSTRACT:** Pharmaceutical residues in the environment are of great concern as ubiquitous emerging contaminants. This study investigated the presence of 40 pharmaceuticals in water and sediment of the Pearl River Estuary (PRE) in the wet season of 2020. Among psychiatric drugs, only diazepam was found in water samples while six of them were detected in the sediment. The  $\Sigma$ antibiotics levels ranged from 6.18 to 35.9 ng/L and 2.63 to 140 ng/g dry weight in water and sediment samples, respectively. Fluoroquinolones and tetracyclines were found well settling in the outlet sediment, while sulfonamides could be released from disturbed sediment under stronger tidal wash-out conditions. After entering the marine waters, pharmaceuticals tended to deposit at the PRE mouth by the influence of the plume bulge and onshore invasion of deep shelf waters. Low ecological risks to the aquatic organisms and of causing antimicrobial resistance were identified. Likewise, hydrological modeling results revealed insignificant risks: erythromycin-H<sub>2</sub>O and sulfamethoxazole discharged through the outlets constituted 30.8% and 6.74% of their environmental capacity, respectively. Source apportionment revealed that pharmaceutical discharges through the Humen and Yamen outlets were predominantly of animal origin. Overall, our findings provide strategic insights on environmental regulations to further minimize the environmental stress of pharmaceuticals in the PRE.

**KEYWORDS:** antibiotic, psychiatric pharmaceutical, tidal event, environmental capacity, positive matrix factorization, hydrological modeling, Pearl River Estuary



## INTRODUCTION

In recent decades, pharmaceuticals in the environment have been regarded as emerging chemicals of concern (ECCs).<sup>1</sup> In particular, antibiotics and psychiatric pharmaceuticals are receiving special attention, as antibiotics are capable of causing antimicrobial resistance (AMR) and psychiatric pharmaceuticals show rapid toxic effects on non-target organisms largely at the ng/mL levels.<sup>2,3</sup>

Estuaries have been regarded as pollutant filters,<sup>4</sup> and with the pollution in these ecosystems being recently highlighted, a global estuaries monitoring program was launched in the United Nations Decade of Ocean Science for Sustainable Development (2021–2030).<sup>5</sup> In estuaries, tidal currents can significantly influence water quality parameters. However, existing field data is insufficient for an assessment of the impact of tidal events and the subsequent changes in water quality parameters on the geochemical processes and transport of pollutants, especially ECCs.

With its high population and industrial density and numerous animal husbandry and aquaculture facilities, the

Great Bay Area (GBA) is a hotspot for contamination by ECCs such as pharmaceuticals, especially in the aquatic environment of the Pearl River Estuary (PRE).<sup>6</sup> Several studies have reported the seasonal occurrence of antibiotics in the PRE;<sup>7–9</sup> however, despite the use of over 14 therapeutic classes of antibiotics, these studies only analyzed four classes. Two studies in particular investigated the occurrence of antibiotics at all eight outlets; however, these studies were conducted at different sampling times and did not consider the influence of tidal events, resulting in increased bias in the instant mass loading estimation.<sup>8,9</sup> With regard to psychiatric pharmaceuticals, no studies have reported their occurrence in PRE waters to the best of our knowledge.

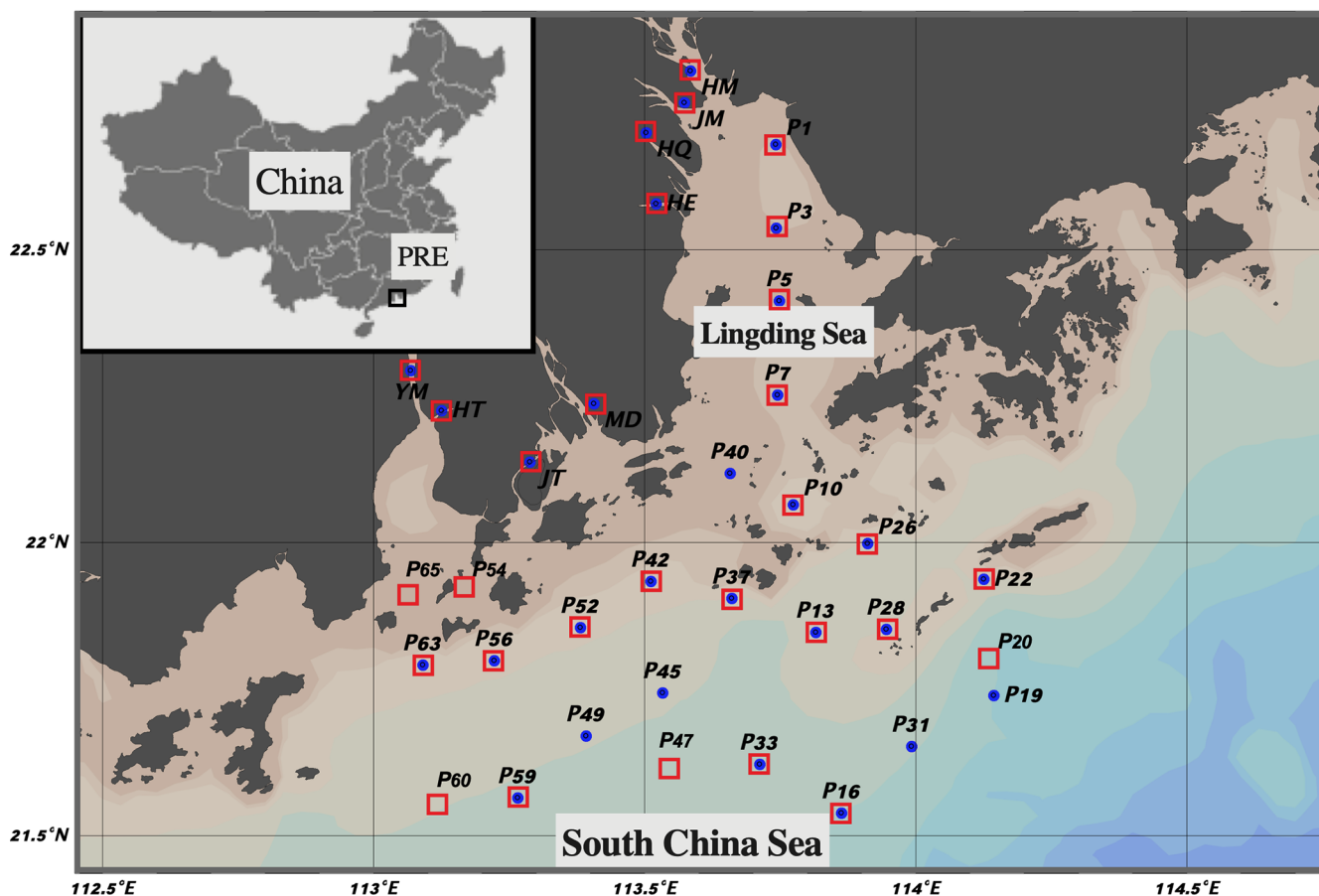
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**Figure 1.** Sampling sites at the eight major Pearl River outlets ( $n = 8$ ) and the adjacent areas of the northern South China Sea (SCS) ( $n = 22$ ); the blue dots and red squares represent water and sediment sampling sites, respectively; PRE refers to the outlets and the receiving marine water body (i.e., northern SCS) of the Pearl River in the present study, and the Lingding Sea (LDS) refers to the estuarine embayment influenced by the four eastern outlets and belongs to northern SCS.

Regulations aimed at protecting marine environments from the impacts of ECCs, including those of pharmaceuticals in the GBA, have been inadequate. Until recently, interim marine water quality criteria for ECCs in the GBA were developed, of which 0.04–12 ng/L was set for six pharmaceuticals with higher priority.<sup>6</sup> However, environmental monitoring of a marine area alone may prove to be time-consuming and expensive. Hydrological modeling with the integration of environmental analysis and water quality criteria can be a useful tool for predicting the distribution and fate of environmental pollutants, estimating the environmental capacities of pollutants, and evaluating the saturation situation in a specific area.<sup>10</sup> Positive matrix factorization (PMF), a source apportionment analysis tool, is considered to be a useful tool for factor analysis and has been successfully applied to surface water quality data with unique advantages.<sup>11</sup> It considers data uncertainty and explains only one feature or process in one factor, thereby making the results more interpretable.<sup>11</sup> The application of source apportionment analysis can provide useful information for policymakers to take prompt actions on the main contributors following an environmental health status assessment.

Under the policy intervention on pharmaceutical prescription and the continuous increase of pharmaceutical expenditure in the PRE, it is of concern whether the updated presence of pharmaceuticals can pose significant risks to the marine environment of the PRE. Thus, in the present study, we

comprehensively investigated the occurrence of antibiotics and psychiatric pharmaceuticals in the PRE, examined the influence of tidal events at the eight major Pearl River outlets and hydrodynamic conditions on the fates of pharmaceuticals, and estimated the environmental capacities and stress of pharmaceuticals at the eight outlets by modeling. The application of hydrological modeling integrated with environmental analysis enables straightforward environmental stress estimation and avoids large-scale marine sampling. It is applicable to estuaries/bays worldwide. Our findings also offer strategic insights on environmental regulations through source apportionment evaluation and can provide a reference for the formulation of strategies to minimize the environmental stress inflicted upon the PRE by various pharmaceuticals.

## MATERIALS AND METHODS

**Chemicals and Materials.** A total of 40 pharmaceuticals were analyzed, of which 29 were antibiotics and 11 were psychiatric pharmaceuticals. The studied antibiotics were further classified into 11 groups according to their chemical structures: five penicillins, three cephalosporins, five macrolides, three sulfonamides, one sulfonamide-related (trimethoprim), four tetracyclines, four fluoroquinolones, one nitroimidazole, one lincosamide, one carbapenem, and one amphenicol (Table S1). A total of 20 mass-labeled pharmaceuticals were used as internal standards, of which nine were for antibiotics and 11 were for psychiatric

pharmaceuticals.<sup>13</sup> <sup>13</sup>C<sub>3</sub>-caffeine was used as the surrogate standard.

Details regarding the standards, solvents, and the preparation of individual stock solutions of the chemical standards are described in the SI.

**Sample Collection.** The sampling sites of the eight major outlets of the Pearl River are shown in Figure 1: Humen (HM), Jiaomen (JM), Hongqili (HQ), Hengmen (HE), Modaomen (MD), Jitimen (JT), Yamen (YM), and Hutiaomen (HT). Three sampling rounds were conducted simultaneously during maximum river discharge at the eight outlets during the ebb tide on June 18th, 20th, and 23rd, 2020, featuring a neap, medium, and spring tide, respectively.<sup>12</sup> The sampling region was further extended from the Pearl River outlets to the tidal-dominated estuarine embayment, Lingding Sea (LDS), and outer areas, from July 6th to 12th, 2020 (Figure 1). Surface and bottom water samples (1 L, *n* = 2 each) and surface sediment samples (depth of 0–10 cm) were collected. The sampling details are described in the SI.

**Sample Extraction and Cleanup.** The water samples were filtered through a 0.5 μm glass fiber membrane (47 mm, Advantec Toyo Roshi Kaisha Ltd., Japan). The pH of the filtered sample was adjusted to ~3 using formic acid, after which 0.2 g of Na<sub>2</sub>EDTA was added to chelate metals. Subsequently, 20 ng of surrogate <sup>13</sup>C<sub>3</sub>-caffeine was added to the sample, and the mixture was shaken and allowed to stand for 30 min. The following solid-phase extraction procedures using the OASIS HLB SPE cartridge (200 mg, 6 cc; Waters Corporation, MA, USA) were similar to those of Leung et al.<sup>13</sup> and are provided in the SI.

A sediment sample [1 g dry weight (dw), *n* = 2] was weighed in a 50 mL PP tube. Sample was spiked with 20 ng of the surrogate <sup>13</sup>C<sub>3</sub>-caffeine, then shaken, and left to stand for 30 min. Then, the sediment was extracted by three rounds of 10 mL citric buffer (pH = 4)/acetonitrile mixture (*v/v* = 1:1) with the aid of sonication. The extract was diluted and further extracted by an HLB cartridge (200 mg) coupled with a Bond Elut SAX cartridge (500 mg, 6 mL; Agilent Technologies, CA, USA) in the front as the cleanup cartridge. Extraction and cleanup procedures of suspended solids in water samples with filter papers were exactly the same as those of the sediment. Details on the procedures are provided in the SI.

**Instrumental Analysis.** The target pharmaceuticals were identified using an Agilent 1290 Infinity liquid chromatograph (LC) (Palo Alto, CA, USA) coupled with a SCIEX QTRAP 5500 tandem mass spectrometer (Woodlands, Singapore) with an electrospray ionization (ESI) interface operated in multiple reaction monitoring (MRM) mode. An Agilent Zorbax Eclipse Plus C18 (2.1 mm i.d. × 50 mm L, 1.8 μm; Palo Alto, CA, USA) was used as the analytical column. Mobile phase A consisted of Milli-Q water (0.02% formic acid, *v/v*) and phase B of methanol (0.02% formic acid, *v/v*). The LC gradient program is presented in Table S2. All analytes were determined under positive MRM mode, except chloramphenicol and cloxacillin under negative mode (Table S3). The details of the ESI parameters are provided in the SI.

**Quality Assurance and Quality Control.** An eight-point standard calibration curve, with concentrations ranging from 0.005 to 50 ng/mL, was used for the quantification of each target analyte. The regression coefficient of the analyte standard curve was ≥0.999.

Matrix-spiked recovery experiments were performed using filtered seawater and freeze-dried sediment samples. The

instrumental detection limit (IDL) was defined as an instrumental signal-to-noise ratio of ≥3:1. The method detection limit (MDL) was calculated as follows:

$$\text{MDL} = \frac{\text{IDL}}{\text{method recovery} \times \text{concentration factor}}$$

where MQL is defined as 10/3 MDL.

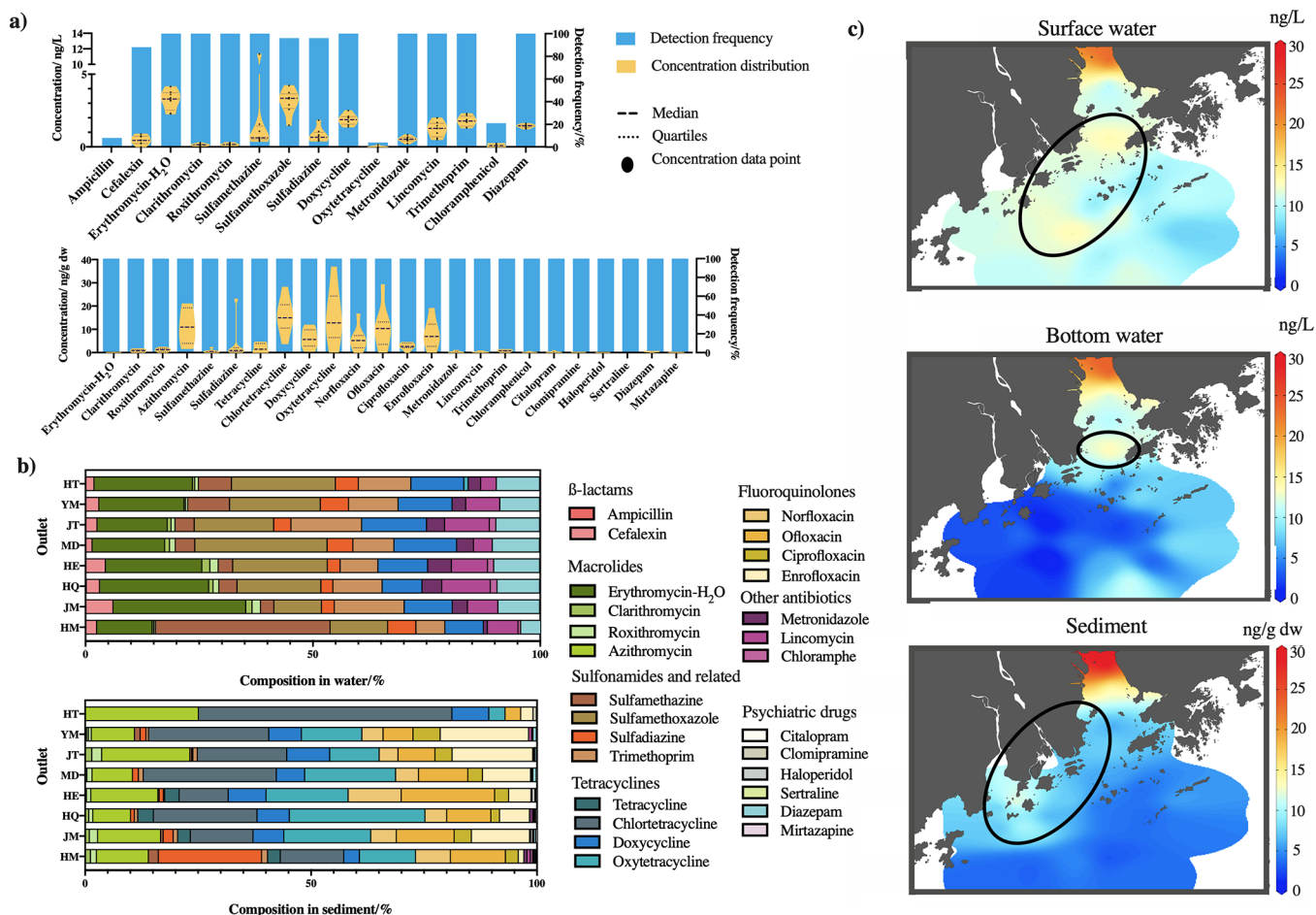
Method recoveries, IDLs, MDLs, and MQLs for dissolved water, suspended solids, and sediment samples are listed in Table S4. Some target pharmaceuticals were excluded in data analysis for sediments due to poor recoveries (e.g., β-lactams and meropenem).

Field and procedural blanks were used during the sampling campaign and in every batch of experiments. All the target analytes in the blanks were found to be below the MDLs. Procedural recovery experiments were also performed for every batch of experiments, with recoveries ranging from 58% to 127% for water and from 31% to 102% for sediment samples (Table S4). Surrogate recoveries ranged from 65% to 84%.

**Analysis of Water Quality Parameters.** Total nitrogen (TN), total phosphorus (TP), permanganate index (COD<sub>Mn</sub>), salinity, dissolved oxygen (DO), and water temperature were measured in water samples collected from the eight major outlets following the Chinese national guidelines (Table S5). Depth, water temperature, DO, turbidity, and chlorophyll *a* were measured using an EXO1 multiparameter sonde (YSI Inc., OH, USA) in water samples collected from the northern South China Sea (SCS), whereas salinity was measured using RBRduo (RBR Ltd., Canada). All values of the water quality parameters are listed in Tables S6 and S7.

**Modeling.** Environmental capacity estimation of erythromycin-H<sub>2</sub>O and sulfamethoxazole, which were detected consistently in the present study, was performed using the water quality module of a semi-implicit Eulerian–Lagrangian finite-element (SELFE) numerical model. The model has been successfully validated and applied to the Columbia River Estuary, USA, and subsequently globally.<sup>14</sup> The parameters of the SELFE model used in this study were modified from a validated 2-D PRE model, which was calibrated using multiple sets of measured hydrological data.<sup>15</sup> The measured and modeled mass loads of erythromycin-H<sub>2</sub>O and sulfamethoxazole at HM and MD, the two major outlets of the PRE, were compared to examine the reliability of the model (Figure S1). The average relative errors for erythromycin-H<sub>2</sub>O and sulfamethoxazole were 2.9% and 2.1% at HM and 5.2% and 3.9% at MD, respectively. The results generated by the model were, therefore, considered well corroborated by the measured values. The modeling time covered the period from June 1st 2020 to June 30th 2020, which represented the typical hydrological conditions of the PRE in the wet season. The modeling scales are shown in Figure S2. The upper boundaries included dynamic boundary and mass loading boundary. The dynamic boundary was set as the monitored flow of the eight outlets during three tidal events. The mass loading boundary was input by multiplying the instant flowrates of the outlets and the instant measured concentrations of the antibiotics. Most treated wastewater in Hong Kong was discharged into the sea. Considering the high density of population and different medical systems from other PRE cities, the discharge of antibiotics from sewage treatment plants (STPs) in Hong Kong in the wet season of 2020 was also included (unpublished data). All the input values from the major point sources (outlets and STPs in Hong Kong) are presented





**Figure 2.** (a) Levels (left scale, violin box) and detection frequencies (right scale, bar) of pharmaceuticals detected in the dissolved water (up) and sediment (down) of the eight outlets (dot, dashed line, and dotted line represent levels of the pharmaceutical at one outlet, median value, and quartile, respectively; level < MQL was regarded as not detected). (b) Composition profile of the detected pharmaceuticals in dissolved water (up) and sediment (down) among the eight outlets. (c) Distribution of  $\Sigma$ antibiotics in the surface water (up), bottom water (middle), and surface sediment (down) from the adjacent northern SCS. Deposition zones of pharmaceutical contamination (apart from the sites near HM, the largest outlet of the Pearl River) are circled.

in Table S8. Other possible sources such as marine aquaculture were not considered in the modeling, as aquaculture only accounted for 5.7% of the global antibiotic usage.<sup>16</sup> Downstream of the receiving marine environment, tidal harmonic constants were adopted for water circulation simulation for 30 days. The half-life values of erythromycin-H<sub>2</sub>O and sulfamethoxazole were input to account for the environmental attenuation processes during diffusion from the outlets to the marine waters and were set as 42 and 20.3 days, respectively, with photodegradation, sorption, and biodegradation taken into consideration.<sup>17,18</sup> We divided the domain into two areas, brackish and saltwater, using an isosalinity line of 20 psu.<sup>19</sup> Water quality thresholds of erythromycin-H<sub>2</sub>O and sulfamethoxazole were set as 10.6 and 40 ng/L, respectively, for the saltwater area,<sup>6,20</sup> whereas those for the brackish water area were 31.8 and 120 ng/L with an additional applying factor of three due to the lower species abundance in the brackish area.<sup>21</sup> After modeling the hydrodynamics for 30 days, the quality control points within the modeling domain with the highest levels of antibiotics were identified, and the environmental capacity at the eight outlets was determined as the mass load by linearly maximizing the loading values until the quality control points reached the thresholds.

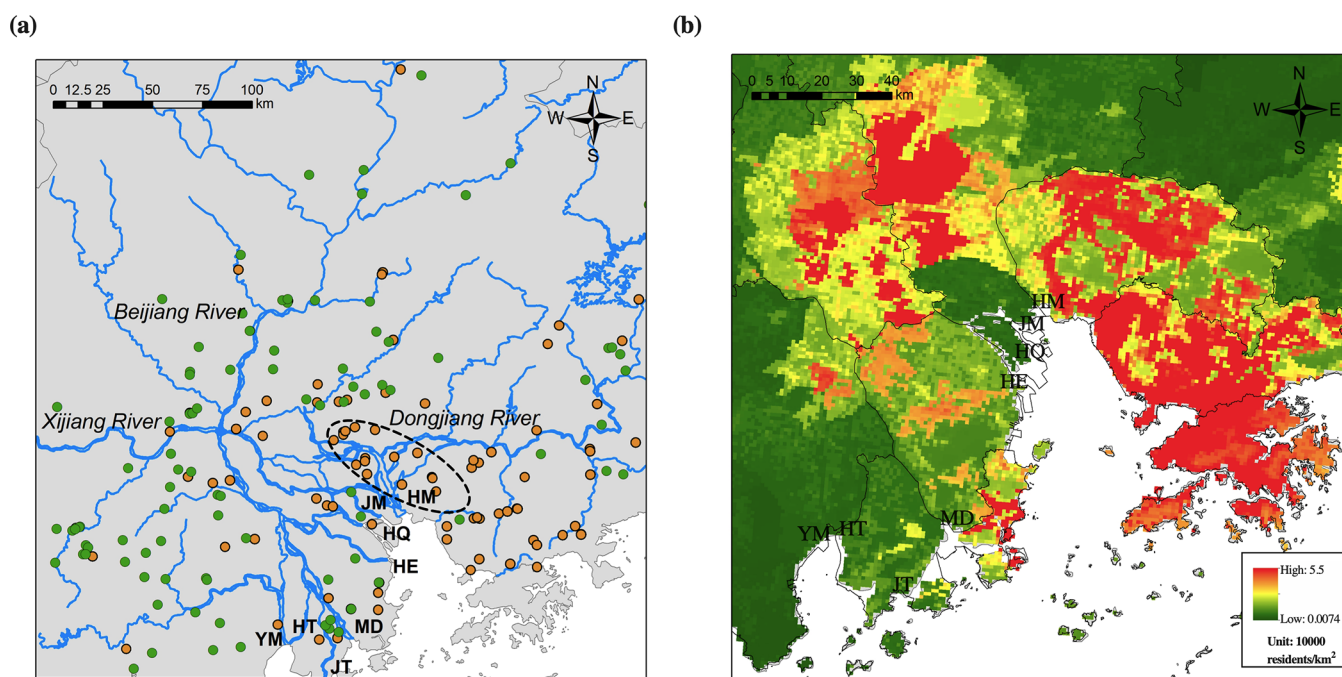
Source apportionment of the detected pharmaceuticals was performed using PMF (EPA Positive Matrix Factorization 5.0, USEPA), following standard procedures. The operation flow of positive matrix factorization (PMF) modeling is shown in Figure S3. Briefly, after data input and base model runs, three error estimation methods were performed to evaluate the variability and validity of the PMF solutions: displacement (DISP), bootstrap (BS), and BS-DISP (a hybrid approach). Only analytes with detection frequencies >80% were included in the analysis. For analytes that were not detected or had levels less than the method quantification limits (MQLs), 1/2 MQLs were adopted. The data uncertainties (Unc) were determined using the following equation:

$$\text{Unc} = \frac{5}{6} \times \text{MQL}$$

where the values were <MQLs and determined as

$$\text{Unc} = \sqrt{(\text{error fraction} \times \text{concentration})^2 + (0.5 \times \text{MQL})^2}$$

where the values were  $\geq$ MQLs and the error fraction refers to the relative standard deviation of pharmaceutical concentrations in the same sample.



**Figure 3.** (a) Location of swine farms ( $n = 116$ ) (orange dots) and poultry farms ( $n = 189$ ) (green dots) across Guangdong Province. Some of the farms were not located within the investigated catchment and therefore are not shown in the map. The list of the farms was obtained from the Department of Agriculture and Rural Affairs of Guangdong Province ([http://dara.gd.gov.cn/tzgg2272/content/post\\_1557168.html](http://dara.gd.gov.cn/tzgg2272/content/post_1557168.html)) and an open-access contribution to Baidu Wenku (<https://wenku.baidu.com/view/05bf240c3b3567ec112d8a43.html>). (b) Population density in the PRE catchments, shown as 10,000 residents/ $\text{km}^2$ . The population data (2019) was adopted from <https://www.resdc.cn/data.aspx?DATAID=251>.

**Data Analysis.** The mass load of the target pharmaceuticals through the eight major outlets of the Pearl River was calculated using the following equation:

$$M_i = C_i \times Q_i \times 60 \times 60 \times 24 \times 10^{-9}$$

where  $M_i$  and  $C_i$  are the instant mass load (kg/d) and the average concentration (ng/L) of each analyte in the water samples, respectively,  $Q_i$  is the instant flow ( $\text{m}^3/\text{s}$ ), and the numerical values represent the unit conversion factors. The flow rates at the outlets are presented in Table S6.

The risk assessment of the target pharmaceuticals was performed by calculating the risk quotient (RQ) using the following equation:

$$\text{RQ} = \frac{\text{MEC}}{\text{PNEC}}$$

where MEC is the measured environmental concentration (ng/L) and PNEC is the predicted no-effect concentration (ng/L).

The ecological risks to the aquatic environment and AMR were evaluated. The maximum level of each detected pharmaceutical in the water samples was adopted as the MEC to evaluate the worst-case scenario. Details of the derivation of the PNEC values are described in the SI in Tables S9–S11.

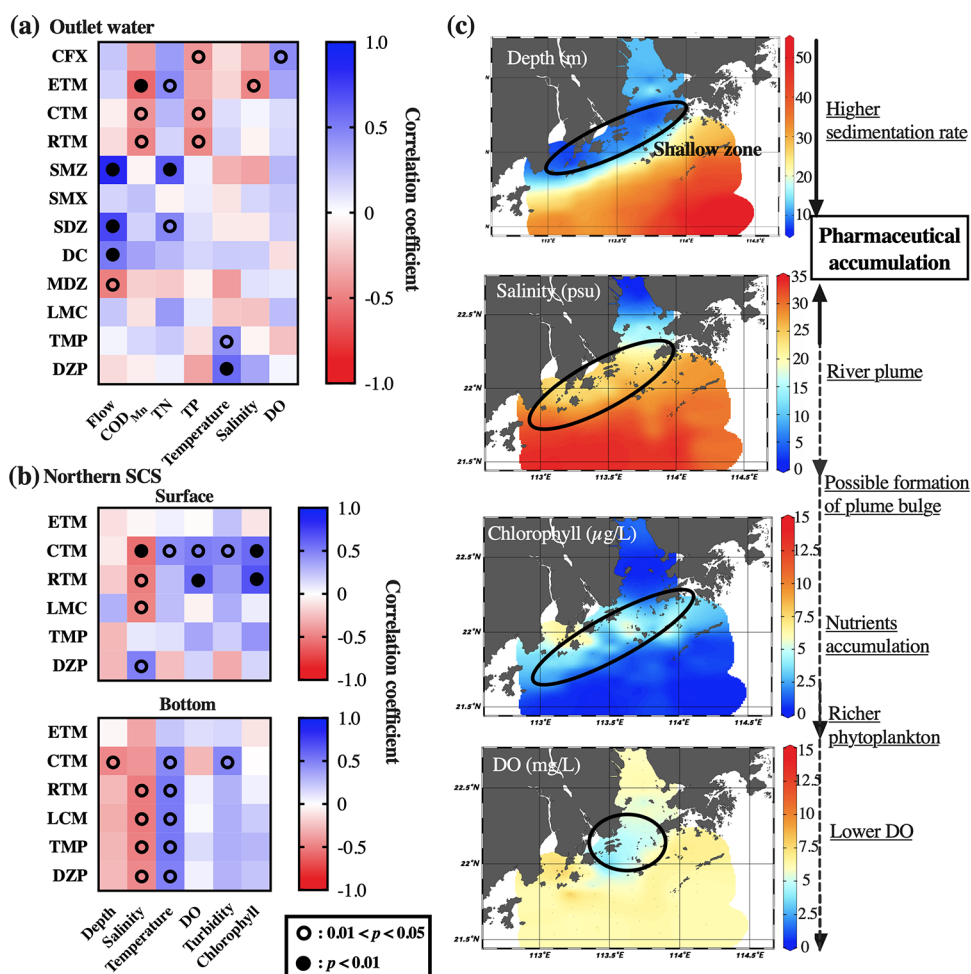
The Kolmogorov–Smirnov test was conducted to examine the data distribution. Student–Newman–Keuls parametric tests and Kruskal–Wallis non-parametric tests were conducted to evaluate the between-group differences for normally distributed and non-normally distributed data, respectively. A paired Wilcoxon signed-rank test was used to examine the differences between surface and bottom waters. Nonparametric correlation analysis was conducted using Pearson’s correlation

coefficient. Only analytes with detection frequencies of  $>40\%$  were included in the statistical analysis. The significance level ( $p$ ) was set at 0.05. Statistical analyses were performed using SPSS (version 26.0, IBM Corporation, NY, USA). Other data were processed using Prism (version 8.0, GraphPad Software, CA, USA) and Ocean Data View software (version 5.4.0).

## RESULTS AND DISCUSSION

**Levels and Distribution. Dissolved Water.** Overall, 15 out of the 40 target pharmaceuticals, including 14 antibiotics and 1 psychiatric pharmaceutical, were detected in water samples collected from the eight major Pearl River outlets during the three tidal events featuring neap, medium, and spring tides. No significant difference in the concentrations of individual pharmaceuticals was found between the surface and bottom water samples from the outlets (Wilcoxon test,  $p < 0.05$ ); thus, the samples were pooled ( $n = 4$ ) to estimate the average values per sampling site.

Concentrations of  $\Sigma$ antibiotics ranged from 9.32 to 35.9 ng/L in all the outlet water samples (Table S12). The concentrations of the individual pharmaceuticals among the eight outlets were comparable, except for sulfamethazine (Figure 2a). Higher concentrations of sulfamethazine were detected in water samples at HM (from 6.04 to 16.5 ng/L) in the three tidal events compared with the other seven outlets ( $<\text{MQL}$  to 2.33 ng/L). Sulfamethazine was the most abundant pharmaceutical, accounting for 38.4% at HM but only 2.92–9.21% at other outlets (Figure 2b and Table S13). This observation suggests the presence of major contamination sources downstream near HM, likely originating from swine farms as swine husbandry alone accounts for nearly 60% of the sulfamethazine used in China.<sup>22</sup> Furthermore, swine farms across Guangdong Province were densely located on the



**Figure 4.** Correlations of the detected pharmaceuticals and the monitored water quality parameters in (a) outlet water and (b) surface layer water (up) and bottom layer water (down) in the northern SCS. (c) Distribution of depth, salinity, chlorophyll *a*, and DO in the surface layer of the northern SCS. Relationships between these water quality parameters and pharmaceutical contamination are also shown. The deposition zones are circled. Abbreviations: CFX (cefalexin); ETM (erythromycin-H<sub>2</sub>O); CTM (clarithromycin); RTM (roxithromycin); SMZ (sulfamethazine); SMX (sulfamethoxazole); SDZ (sulfadiazine); MDZ (metronidazole); LMC (lincomycin); TMP (trimethoprim); DC (doxycycline); DZP (diazepam); COD<sub>Mn</sub> (permanganate index); TN (total nitrogen); TP (total phosphorus); DO (dissolved oxygen).

eastern side of HM, whereas the distribution of poultry farms was more even (Figure 3a).

In the northern SCS, fewer target pharmaceuticals (nine antibiotics and one psychiatric pharmaceutical) were detected in the collected seawater samples (Table S14). The highest concentration of  $\Sigma$ antibiotics was observed at the sampling site named Point 1 (P1), which was closest to the HM outlet, at 23.6 ng/L (average of surface and bottom waters) (Figure 2c and Table S14). For other sampling sites, concentrations of  $\Sigma$ antibiotics in the surface layer were comparable, ranging between 6.18 and 12.3 ng/L, whereas those in the bottom layer ranged from not detected to 13.0 ng/L. Diazepam was evenly distributed in the surface layer at an average level of 1.41 ng/L, possibly implying its relatively high persistence and transport capacity in the aquatic environment.<sup>23,24</sup>

**Sediment.** Overall, 24 out of 31 target pharmaceuticals (18 antibiotics and 6 psychiatric pharmaceuticals) were detected in the surface sediment at the eight outlets and 22 northern SCS sites, with the concentrations of  $\Sigma$ antibiotics ranging from 6.74 to 140 ng/g dw and from 2.63 to 31.7 ng/g dw, respectively, while those of  $\Sigma$ psychiatric pharmaceuticals ranging from 0.0521 to 1.38 ng/g dw and from n.d. to 0.410 ng/g dw, respectively (Figure 2c and Table S15). Several antibiotics

were detected at higher concentrations (up to 36.8 ng/g dw for oxytetracycline) and accounted for a higher proportion of  $\Sigma$ antibiotics, such as fluoroquinolones, tetracyclines, and macrolides. Many of these antibiotics were not detected in water samples (i.e., chlortetracycline, azithromycin, and all fluoroquinolones). Several studies have reported the stronger sorption capacities of fluoroquinolones, tetracyclines, and macrolides, related to either their higher hydrophobicity or more binding sites with the metal ions, compared with other classes of antibiotics (e.g., sulfonamides).<sup>25–27</sup> Psychiatric pharmaceuticals contributed little to the proportion of  $\Sigma$ pharmaceuticals in the sediment, probably because they were relatively less consumed while extensively metabolized before excretion, compared with antibiotics.<sup>28,29</sup> Overall, the higher abundances in the species of fluoroquinolones, tetracyclines, macrolides, and psychiatric pharmaceuticals found in sediment samples indicate their preferential partitioning to sediments. Their accumulation potential and thereby their deposition in sediment served as a direct or indirect source of exposure for the benthos.

More detailed discussion on the levels and distribution of pharmaceuticals in the PRE is described in Section 1.6 in the SI.



**Comparison with Other Studies.** Levels of the antibiotics detected in the water and sediment of our study were compared with studies globally. Detailed discussion is described in Section 1.7 and Table S16 in the SI. Overall, the levels of antibiotics found in the PRE in the present study were historically low compared to those in other coastal areas from studies conducted in the same region, nationwide, and on a global scale. This could be ascribed to stricter regulations on antibiotic prescription and the ban on the use of some antibiotics (e.g., fluoroquinolones) for veterinary use.<sup>30,31</sup> The COVID-19 pandemic could be another possible reason as reduced consumption of antibiotics has been observed in China; for example, the antibiotic consumption dropped by 27.38% in 2020 as compared with 2019 in eastern regions; a significant reduction of antibiotic supplies was also observed between 2019 and 2020 in Hong Kong.<sup>32,33</sup>

### Influencing Factors and Environmental Implications on the Distribution of Pharmaceuticals. Tidal Events.

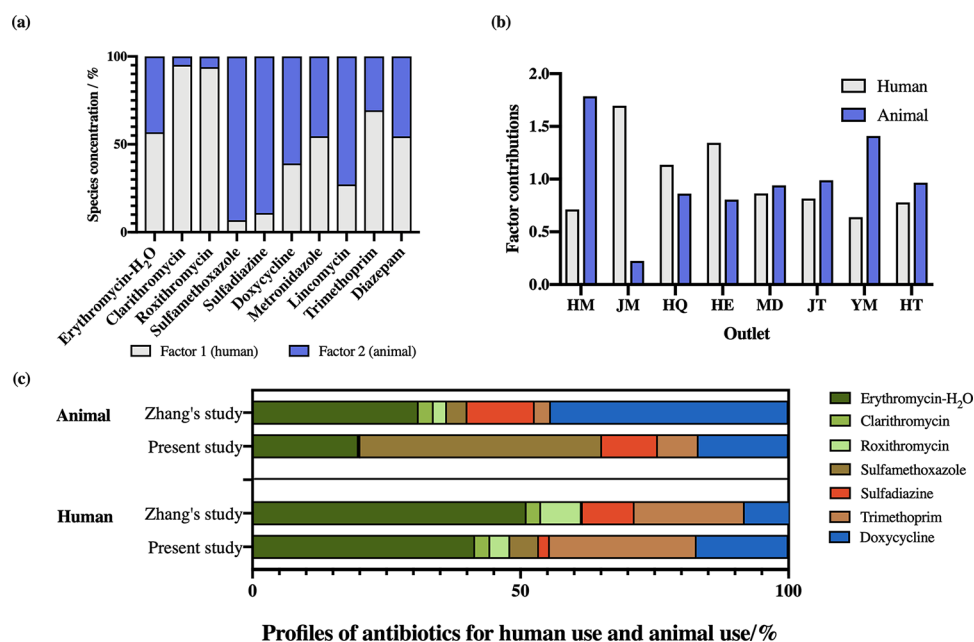
Some correlations were observed between the antibiotic levels and water parameters. Sulfonamides, including sulfamethazine, sulfadiazine, and doxycycline, were positively correlated with flow rate (Pearson,  $p < 0.05$ ) (Figure 4a and Table S17). This was not likely caused by additional land runoff as no significant differences were observed for the water quality parameters (DO, TN, TP, and  $\text{COD}_{\text{Mn}}$ ) among the three tidal events (Newman–Keuls,  $p < 0.05$ ), and the PRE was considered as a microtidal estuary with an average tidal range of 0.85–1.62 m among the outlets.<sup>34</sup> This could be explained by the release of pharmaceuticals from the sediment under the condition of higher suspended sediment content caused by a higher flow rate.<sup>35</sup> It has been suggested that the desorption rate increases at high suspended sediment concentrations due to more frequent interactions between the water and particles and higher colloid content produced under such conditions.<sup>35</sup> Levels of the aforementioned sulfonamides and erythromycin- $\text{H}_2\text{O}$  (a degradation product of erythromycin with higher hydrophilicity) were found to be positively correlated with TN. Several studies have revealed that tidal disturbance promotes the release of sulfonamides,  $\text{NH}_4^+-\text{N}$ , and  $\text{NO}_3^--\text{N}$  from sediments, which could be attributed to either of the following: [1] higher suspended sediment after tidal disturbance as in the case of flow rate<sup>35</sup> or [2] sharply decreased salinity at ebb tides, which enhances the re-dissolution derived from the salting-out effect for pharmaceuticals and ion pairing with seawater anions for  $\text{NH}_4^+-\text{N}$  during flood tides.<sup>36,37</sup> Notably, such correlations with TN and flow rate were mainly found for sulfonamides, which showed relatively low sorption capacities compared with other groups of antibiotics (i.e., tetracyclines, fluoroquinolones, and macrolides). A possible reason might be the lower molecular weight of sulfonamides (<300 Da) as a previous study reported that the organic carbon normalized partition coefficients of pharmaceuticals were positively correlated with their molecular weights.<sup>35</sup> The release of sulfonamides from estuarine sediments observed in our study was also evidenced by our results that levels of sulfamethazine and sulfadiazine ranged <0.195–2.23 ng/g dw and <0.0557–23.0 ng/g dw, respectively, in the outlet sediment while neither were detected in the suspended particles in water samples from the bottom layer (Table S15). The release from estuarine sediments during tidal events explained the markedly increased levels and mass loads of sulfonamides during the spring tide, especially at HM and JM, which contributed the most to the mass loads through the eight outlets (see Section Mass Loads and Environmental

Capacity Estimation). Estuaries have been regarded as filters where some environmental pollutant types settle (e.g., fluoroquinolones and tetracyclines as discussed in Sub-section Sediment); however, our results suggest that redissolution of certain pharmaceuticals (i.e., sulfonamides) from estuarine-suspended sediment under strong tidal wash-out can be an important source of certain pharmaceutical contamination conveyed from freshwater to the marine environment.

**Hydrodynamic Conditions.** The distribution of pharmaceuticals is strongly influenced by complex hydrodynamics and bottom topography in the northern SCS. The distribution patterns of the water quality parameters in the surface and bottom layers are presented in Figure 4c and Figure S4. Horizontally, in the surface layer, higher levels of  $\Sigma$ pharmaceuticals were observed at stations near the outlets and mouth of the PRE. Levels of  $\Sigma$ pharmaceuticals at the mouth of the PRE from sites near Macau northeastward to southern Hong Kong were higher than those in the inner area of the PRE. Water samples in this area, together with the area near the four western outlets (circled in Figure 4c, hereafter referred to as the deposition zone), feature shallower and brackish water with salinity generally ranging from 20 to 25 psu, revealing that this deposition zone was strongly influenced by the estuarine plume. Higher values of chlorophyll *a* and lower values of DO were observed in this zone than in the surrounding sites (Figure 4c), which implied the possible formation of a plume bulge.<sup>38</sup> Several studies have reported the occurrence of hypoxia and plume bulges in this deposition zone, implying that the distribution pattern observed in our study was representative of the wet season in the northern SCS.<sup>39,40</sup> Plume bulges can be relatively stable for several days, which allows the accumulation of nutrients from freshwater runoff, favoring the growth of phytoplankton and thus accounting for higher chlorophyll *a* and lower DO as well as higher levels of pharmaceuticals.<sup>38</sup> Nearby aquaculture can also contribute to pharmaceutical contamination.<sup>41</sup> Sewage effluent input from Hong Kong STPs may be another possible source,<sup>42</sup> although no major STPs are located near this deposition zone. In the bottom layer, a significant negative correlation was found between the salinity and water temperature (Pearson,  $p < 0.05$ ). Most of the detected pharmaceuticals were positively correlated with water temperature and negatively correlated with salinity (Figure 4b). Among the 22 sampling sites in the northern SCS, the salinity and water temperature within the mouth of the PRE were significantly lower and higher than those in the outer sea, respectively (Kruskal–Wallis,  $p < 0.05$ ). Higher levels of  $\Sigma$ pharmaceuticals were also observed within the mouth of the PRE, implying that this area is directly influenced by freshwater runoff in the bottom layer. This observation could be further explained by the onshore invasion of the deep shelf waters, hindering the diffusion of offshore freshwater from the PRE outlets in the wet season.<sup>43</sup>

**Risk Assessment for the Aquatic Environment and AMR Potential.** According to the calculated RQs (Figure S5), high environmental risk was not observed for any detected pharmaceutical. The highest RQ was observed for diazepam, which might pose a low to medium risk to the aquatic environment. For antibiotics, the risks posed to both the aquatic environment and AMR were low.

Our results preliminarily reveal that as one of the main sources of AMR, the concentrations of antibiotics in the PRE outlets and their receiving marine environment were probably not high enough to cause AMR. However, the actual AMR



**Figure 5.** (a) Source apportionment by PMF verified two sources of pharmaceuticals in the outlet waters, where gray bar represents human origin and purple bar represents animal origin. (b) Contribution of the two factors verified by PMF at the outlets of the PRE. (c) Profiles of detected pharmaceuticals for human use and animal use in the present study and Zhang's study.<sup>22</sup>

situation is complicated and could be more severe, considering that antibiotic resistance genes (ARGs) could originate from other contamination sources (i.e., presence at the upstream sites) and routes (i.e., horizontal gene transfer).<sup>44</sup> Therefore, further investigation, including the analysis of ARGs, should be performed to evaluate the actual AMR situation in the PRE.

**Source Apportionment.** PMF is a trial-and-error approach. The number of factors was determined based on the results of DISP, BS, and BS-DISP. Two-factor solution was validated by the error estimate methods (see more details in Section 1.8 and Table S18 in the SI). Also, solutions of factors more than two were also tried but invalidated. Results of DISP, BS, and BS-DISP when using both two-factor and three-factor solutions are listed in Table S18. The uncertainty-scaled residuals of the species in our study are presented in Table S19. The residual factors that may infrequently exist in the samples were excluded during the PMF algorithm. Except lincomycin, other species were well fitted. Over 80% of the data points had absolute scaled residuals values <4, indicating the existence of stable and consistent sources.

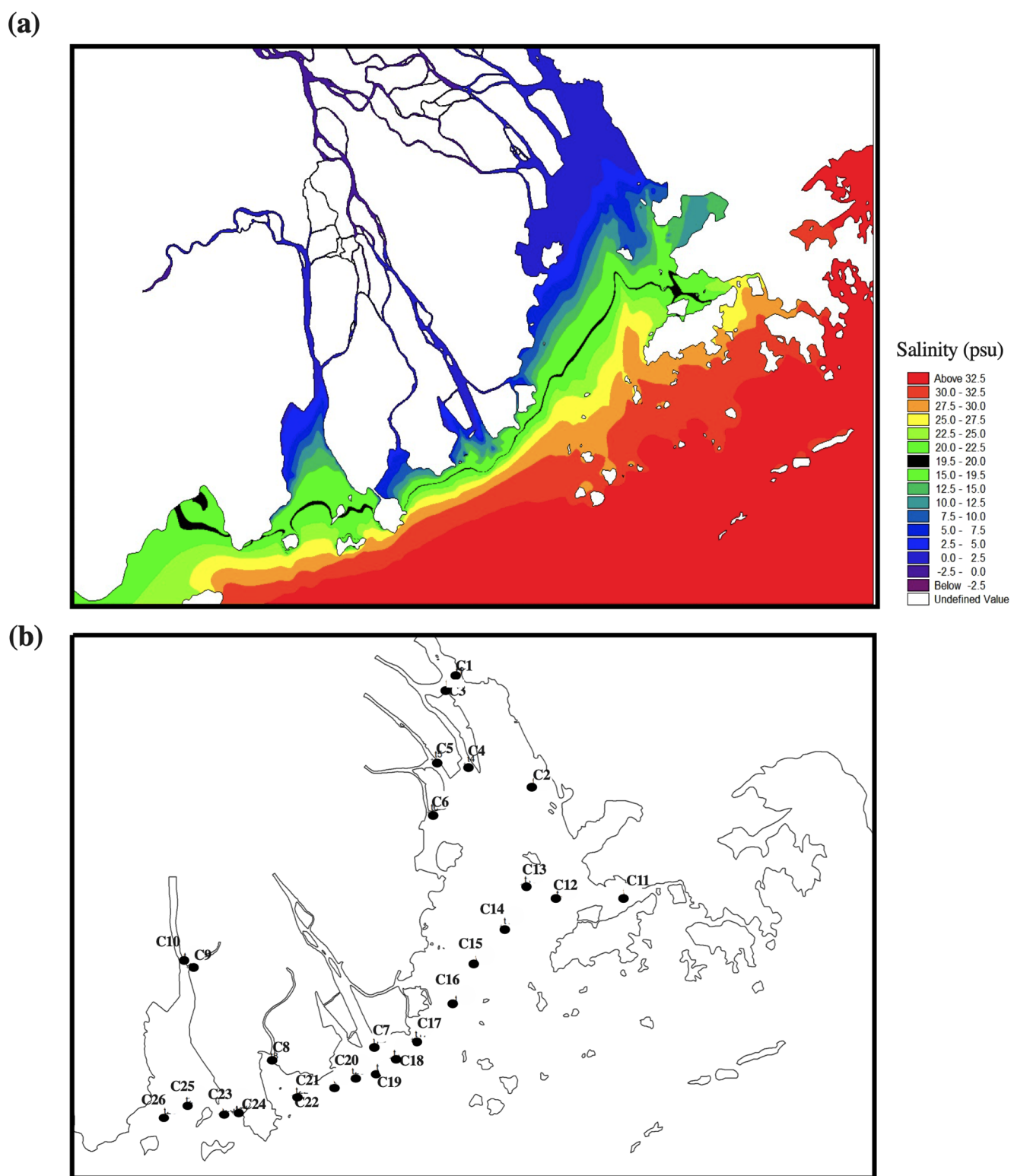
Profiles of sulfonamides and their commonly used potentiator trimethoprim were used for factor verification as the consumption profile of this class of antibiotics in humans and animals was less regulated in China. Trimethoprim was consumed more by humans (67.0%) in China.<sup>22</sup> The first factor (gray bar) accounted for 69.4% of the trimethoprim profile, indicating that the first factor should be “human use” (Figure 5a). Sulfamethoxazole and sulfadiazine were mainly characterized by the second factor (purple bar in Figure 5a). Compared with human consumption, 99.4% of the sulfamethoxazole and 81.1% of the sulfadiazine were used in veterinary practice in China.<sup>22</sup> Despite several regulations on antibiotic usage having successively taken effect in recent years, the use of sulfonamides in animal husbandry is still permitted. Therefore, the second factor was verified as “animal use”. The proportion of other detected antibiotics for animal use in our study was markedly lower than that reported in 2013 in China, possibly

due to much stricter and integrative regulations on the use of antibiotics for veterinary use<sup>30,45</sup> and regional and nationwide differences in usage patterns. Diazepam is prescribed as an anxiolytic agent for both humans and animals. Notably, our results showed that 45.5% of the diazepam originated from animal use. This implies the possible occurrence of diazepam in food of animal origin from the PRE, considering the pharmaceutical's environmental persistence.<sup>46</sup>

Factor contribution results revealed that pharmaceuticals found in HM was mainly of animal origin (Figure 5b). As discussed in the above section, the presence of large numbers of swine farms in the HM catchment could partly explain the high levels of sulfamethazine observed (Figure 3a). Meanwhile, HM catchment was more densely populated than other outlet catchments (Figure 3b). This is possibly because only around 15.6% of the antibiotics in China were prescribed for human use.<sup>22</sup> Daily dose of antibiotics applied to livestock was much higher than that to humans. Pharmaceuticals found in YM with animal origin was also prevalent, whereas those in JM were predominantly of human origin. Pharmaceuticals of human and animal origin shared a relatively even contribution in the rest of the outlets. Region-specific management measures could potentially be implemented to effectively mitigate environmental stress. For example, surveillance authorities may inspect local farms located within the HM and YM catchments and improve the coverage of wastewater collection and equipped treatments within the JM catchment as the first priority.

Compositions of the detected pharmaceuticals consumed for human and animal use were also presented and compared with 2013 data in Figure 5c.<sup>22</sup> Diazepam, metronidazole, and lincomycin were excluded from comparison because they were relatively less well fitted to the PMF solution or unavailable in the compared reference. Composition of the detected pharmaceuticals for human use was relatively stable between the two studies, compared with that for animal use. A decrease in the consumption of macrolides and sulfadiazine by human was observed, whereas the usage of sulfamethoxazole,





**Figure 6.** (a) Salinity distribution of the surface water in the PRE. The black band represents the areas where salinity was 20 psu, which divided the domain into two areas, brackish water area (upper the black band) and saltwater area (lower the black band). Values of salinity were averaged by the SELFE model using long-term modeling data. (b) Water quality control stations with higher levels of antibiotics identified by the SELFE model after 1 month simulation of antibiotic discharges through the eight outlets of the Pearl River in the wet season of 2020.

trimethoprim, and doxycycline increased. Regarding pharmaceuticals for animal use, a decrease in the consumption of macrolides and doxycycline was observed, while usage of sulfonamides and its potentiator, trimethoprim, increased. The shift generally reflected the influence of national regulations on

the prescription of antibiotics in China. Specifically, the three detected macrolides were not authorized for use in aquaculture and not allowed to be used as animal feed additives.<sup>30,45</sup> In contrast, usage of sulfonamides in animal husbandry remained authorized.<sup>30</sup> This shift was environmentally positive since

Table 1. Environmental Capacity, Mass Loads, and Current Environmental Stress in the PRE

		erythromycin-H <sub>2</sub> O			sulfamethoxazole		
		mass load (kg/d)	capacity (kg/d)	stress	mass load (kg/d)	capacity (kg/d)	stress
eastern	HM	6.57	19.5	33.6%	6.64	113	5.90%
	JM	2.28	6.77	33.7%	0.873	14.7	5.94%
	HQ	0.519	1.54	33.6%	0.346	5.86	5.90%
	HE	1.02	3.03	33.5%	0.935	15.9	5.89%
western	MD	1.66	7.12	23.3%	3.07	28.7	10.7%
	JT	0.358	1.79	20.0%	0.391	4.21	9.28%
	YM	1.32	4.57	28.8%	1.50	22.3	6.74%
	HT	0.393	1.37	28.8%	0.436	6.46	6.75%
	All	14.1	45.7	30.8%	14.2	211	6.74%

sulfonamides generally had higher or comparable PNEC values to the aquatic organisms and of causing AMR as suggested by Tell et al. (2019).<sup>47</sup>

#### Mass Loads and Environmental Capacity Estimation.

The total mass loads of  $\Sigma$ antibiotics from the Pearl River, calculated based on the eight outlet outflows, reached 115 kg/d during the spring tide, which was nearly twice as high as those seen in the other two tidal events (Table S20). A substantial increase in mass loads during the spring tide was observed at HM, JM, and YM, whereas the mass loads at the other outlets were much less variable. Among the eight outlets, HM predominated and accounted for over 50% of the total mass load of  $\Sigma$ antibiotics, whereas HT contributed the least. HM is the largest outlet of the Pearl River, and the predominance of HM in the mass loads of antibiotics was also found in two previous studies, both of which, however, reported a <30% contribution from HM.<sup>8,9</sup>

The isosalinity line at 20 psu is shown in Figure 6a. To represent the wet season, the average values of the estimated environmental capacity of each outlet from the three tidal scenarios were adopted. Based on pre-set water criteria, environmental capacities of the eight outlets ranged from 1.37 kg/d (HT) to 19.5 kg/d (HM) for erythromycin-H<sub>2</sub>O and 4.21 kg/d (JT) to 112 kg/d (HM) for sulfamethoxazole (Table 1). The mass loads of these antibiotics accounted for 20.0%–33.7% (erythromycin-H<sub>2</sub>O) and 5.89%–10.7% (sulfamethoxazole) of their environmental capacities. Thus, the stress caused by current discharges of these antibiotics through the input from the outlets to the northern SCS on the PRE in the sampling season was insignificant, indicating a low risk to the marine environment of the PRE, and that no immediate measures were necessary. This conclusion derived from hydrological modeling was consistent with our evaluated environmental risks based on the measured concentrations. Higher stress posed by erythromycin-H<sub>2</sub>O was observed in the eastern outlets, whereas that posed by sulfamethoxazole was observed on the western side. Regardless of the sampling points located within or near the outlets (C1–C10 in Figure 6b), C11–C26 were predicted as control points that reached the water quality criteria once the mass loads of the selected antibiotics at the outlets exceeded their estimated environmental capacities by the hydrological model. The control points within the LDS overlapped well with the deposition zone observed from the measured results, as discussed in the above section. This suggests that continuous pharmaceutical monitoring, especially for heavily used antibiotics such as erythromycin-H<sub>2</sub>O and sulfamethoxazole, should be conducted to obtain real-time updates on the ecological health status in the PRE, especially LDS.

Regarding study limitations, dry season data were lacking in this work. More sampling campaigns are recommended to explicate a more comprehensive evaluation of the environmental health status of the PRE. Overall, our study provided an informative reference for effective monitoring and risk management of pharmaceuticals in the PRE waters.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.est.2c02384>.

Additional information about standard preparation, sample pretreatment, analysis procedures; Table S1: List of the target analytes and their internal standards; Table S2: LC elution program; Table S3: MRM transitions used in MS/MS; Table S4: Method recoveries, IDLs, MDLs, MQLs, and procedural recoveries of the target analytes; Table S5: National guidelines adopted for the analysis of water quality parameters; Table S6: Values of the water quality parameters detected in samples collected from the eight major outlets of the Pearl River; Table S7: Values of the water quality parameters detected in the northern South China Sea of PRE; Table S8: Input concentrations (ng/L) from the major point sources; Table S9: Derivation of PNEC-ENV of antibiotics that were not available from AMR Industry Alliance Antibiotic Discharge Targets; Table S10: Values of PNEC-ENV ( $\mu\text{g/L}$ ) and PNEC-AMR ( $\mu\text{g/L}$ ) for the target antibiotics adopted from AMR Industry Alliance Antibiotic Discharge Targets; Table S11: Selected ecotoxicity information of diazepam with calculated PNECs; Table S12: Concentrations (ng/L) and detection frequencies (DFs) of individual pharmaceuticals detected at the eight riverine outlets during three tidal events; Table S13: Composition profile of target pharmaceuticals in the water samples among the 8 riverine outlets; Table S14: Concentrations (ng/L) of the detected pharmaceuticals in surface (S) and bottom (B) seawater from the Lingding Sea; Table S15: Concentrations (ng/g dw) of the target pharmaceuticals in sediments; Table S16: Comparison of the concentrations of antibiotics in sediment (ng/g dw) in this study with those from other estuaries nationwide; Table S17: Pearson correlation coefficients of pharmaceuticals and water quality parameters; Table S18: Error estimates results when two factors and three factors were requested; Table S19: Uncertainty-scaled residuals of the species from the base

run result; Table S20: Mass loads (kg/d) of the target pharmaceuticals in the eight outlets in three different tidal events; Figure S1: Comparison on the mass loads (g/s) of erythromycin-H<sub>2</sub>O and sulfamethoxazole at Humen (HM) and Modaomen (MD) outlets between measured and modeled values; Figure S2: Modeling domain by the semi-implicit Eulerian-Lagrangian finite-element (SELFE) numerical model; Figure S3: Flow of positive matrix factorization modeling by using EPA Positive Matrix Factorization 5.0 (USEPA); Figure S4: Water quality parameters in surface and bottom layers in the Lingding Sea; Figure S5: Risk quotients (RQs) of the detected individual and mixture of target pharmaceuticals in the worst-case scenario (PDF)

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### Notes

The authors declare no competing financial interest.

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