# Spatially explicit large-scale environmental risk assessment of pharmaceuticals in surface water in China

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## Abstract

With improving health care and an aging population, the consumption of human pharmaceuticals in China has been increasing dramatically. Environmental risks posed by many active pharmaceutical ingredients (APIs) are still unknown. This study used a spatially-explicit dilution-factor methodology to model predicted environmental concentrations (PECs) of 11 human-use APIs in surface water for a preliminary environmental risk assessment (ERA). Median PECs in surface water across China range between 0.01-8.0×$10^3$ ng/L for the different APIs, under a moderate patient use scenario. Higher environmental risks of APIs in surface water are in regions with high water stress, e.g. northern China. Levonorgestrel, estradiol, ethinyl estradiol and abiraterone acetate were predicted to potentially pose a high or moderate environmental risk in China if consumption levels reach those in Europe. Relative risks of these four APIs have the potential to be amongst those chemicals with the highest impact on surface water in China when compared to the risks associated with other regulated chemicals, including triclosan and some standard water quality parameters including $BOD_5$ (5-day biological oxygen demand), COD (chemical oxygen demand), Cu, Zn and Hg and linear alkylbenzene sulphonate. This method could support the regulation of this category of chemicals and risk mitigation strategies in China.


## Introduction

Pharmaceuticals are a class of chemicals used in prevention or treatment of human and animal diseases. As a middle-income country with a very large population, China represents a market with a large potential in human-use pharmaceutical consumption due to improving health care and an aging population.[1] China has already become the second largest pharmaceutical market in the world with a forecasted market growth of ca. 55% from US $108 billion in 2015 to $167 billion by 2020.[2] After drug administration, many active pharmaceutical ingredients (APIs) are excreted in an unaltered form in urine or faeces of treated patients with relatively high rates ≥ 40%.[3] Pharmaceutical residues then enter the environment directly without treatment, or in effluents from wastewater treatment plants (WWTPs) after partial removal.[4, 5] The population weighted national average wastewater treatment rate is estimated to be only ca. 57% in 2016 in China based on the reported urban and rural data.[6] Therefore, the release of human-use APIs to aquatic environment could be high in China, especially as patient access to healthcare grows in future years. Some APIs have been ubiquitously detected in the environment and wastewater treatment effluents across China.[1, 7, 8]

Given that many drug targets are conserved across taxa,[9-11] it is reasonable to expect that some APIs could exhibit unintended post-therapeutic effects to non-target organisms in the environment, if the exposure concentration is high enough. Adverse effects of APIs on non-

target organisms have already been observed at environmentally relevant concentrations. For example, natural or synthetic hormones can act as endocrine disruptors in the environment and impact wild animals, plants and humans.[12, 13] Environmental exposure to β-blockers could possibly cause morphological abnormalities or growth inhibition in fish.[14, 15] And concerns have been raised on cytotoxicity and genotoxicity of some anti-cancer APIs in the environment.[16]

However, despite such concerns about their ecotoxicity, the environmental occurrence, distribution and risks of many APIs are rarely investigated and assessed in China, especially on a national scale. There are nearly 1600 new molecular entities that are currently approved by US FDA (Food and Drug Administration in the United States) for therapeutic use, of which most are being used in China.[17] More therapies are expected to emerge in the future, and an assessment of environmental risk is needed to protect the natural environment. It is very resource intensive to conduct nationwide monitoring programmes for each API in China. Current national studies are limited and are mostly conducted at a catchment scale, and with a limited range of APIs under investigation.[18-23] So, the environmental risk of some APIs has largely been neglected, and developing appropriate environmental regulation on such APIs takes time. It is imperative, therefore, to seek efficient solutions to perform a nationwide assessment and prioritisation of the potential environmental risk of APIs across China, to identify the geographic variation and the relative risk that this class of compounds poses compared to other chemicals and ultimately to identify the APIs and locations with the highest risks. Such an approach is a key priority to provide a rapid assessment of environmental risk from pharmaceuticals which can be used to develop future environmental management plans.[24]

This study provides a modelling approach, using a gridded dilution-factor methodology, to conduct a nationwide ERA of 11 representative human medicines in surface water across China to provide a rank of relative risk. The selection of APIs selected for study covers a range of pharmaceutical classes that have concerned scientists and policy makers for their ecotoxicity, such as hormone drugs, β-blockers, antiarrhythmic medication, opioid antagonists, diabetes medicines, anti-cancer drugs and nonsteroidal anti-inflammatories. It also covers APIs with a wide range of consumption rates and ecotoxicological effects with predicted no effect concentrations (PNECs) in the range $10^{-5}$-$10^{2}$ µg/L. Most of the selected APIs have not been extensively studied in China. European per capita usage levels have been applied in this study for a conservative risk assessment, but mainly due to the lack of usage data for China and the expected increasing per capita usage. It is highly likely that usage in China will reach levels in Europe for some therapies. Spatially explicitly deterministic ERAs were used to predict the spatial variation in different exposure scenarios to provide a comprehensive evaluation of risk; including best and worst case exposure scenarios with respect to waste water treatment removal. The ultimate objective is to raise the attention to those APIs and modes of action that may pose

the highest risk to surface waters in China, especially those with a higher ranking than chemicals already subject to environmental regulation and surveillance.

## Methods and materials

**Target chemicals** To consider a wide range of pharmaceutical categories, usage and toxic potency (defined as PNECs in Table 1), the following 11 human-use-only APIs were selected for study with abbreviations in brackets, estradiol (E2), ethinyl estradiol (EE2), levonorgestrel (LNG), atenolol (ATE), naloxegol (NAL), abiraterone acetate (ABI), amiodarone (AMI), metformin (MET), everolimus (EVE), diclofenac (DCF) and ibuprofen (IBPF). E2 and EE2 are estrogens. LNG is a pharmaceutical progestin used for hormonal contraception and in ovarian cancer therapy. ATE is a β-blocker for cardiovascular diseases. AMI is an antiarrhythmic medication for treatments or prevention irregular heartbeats. DCF and IBPF are nonsteroidal anti-inflammatory drugs (NSAIDs). NAL is a commonly used opioid antagonist drug. ABI is an androgen synthesis inhibitor (enzyme CYP17A1 inhibitor). EVE is an anti-cancer drug and currently used to prevent rejection of organ transplants. Few studies have been published that describe the ecotoxicity and environmental risks of NAL, ABI and EVE. E2, EE2, LNG and ABI are all hormonal drugs. They are generally widely used and their human excretion rates are high (>60%, Table 1) compared with many other APIs,[3] which may potentially lead to high emissions to the aquatic environment. More information on ecotoxicity and environmental risks of each of the above APIs are described in SI.

**Emission and modelling approach** Release via domestic sewage discharge after patient use and excretion, to surface water was considered in the modelling, which generally is the major emission and exposure pathways of human-use APIs in environment. Emission data related to manufacturing operations and associated process effluents were not available and thus not considered within this assessment, which may result in underestimation of risk and a failure to identify certain hotspots, i.e. production sites. A crude method for Predicted Environmental Concentration (PEC) determination in surface water was applied in a previous study on "Down-the-drain" chemicals[25] and in reports for preliminary ERA of APIs,[26] which assumed that 100% patient use of the API with no return to pharmacy, and 100% of the population was connected to WWTPs. In this study, spatially varied wastewater treatment connection rates (the percentage of population connected to WWTPs) have been considered for calculating PECs with a spatial resolution of 0.5º in China for a more realistic situation using Eq. 1.

$$PEC\ (ug/L) = (A \times 10^9/P) \times E \times (1 - WWTP_{CR} \times R)/(365 \times V)/D \quad (1)$$

Where A (kg/year) is the total patient consumption of APIs and P indicates the population treated by APIs. A/P (kg/cap/year) is the per capita use of specific APIs. Due to the lack of

publicly available consumption data for the selected APIs in China, per capita usage from 15-22 different European countries were adopted as a proxy data for individual APIs (shown in Table 1). This acts as a reasonable proxy as the usage of APIs and access to medicines in China is expected to increase and could reach or surpass European levels. However, this is an approximation as for some APIs there may be differences in disease prevalence, susceptibility and cultural that will affect drug usage between Europe and China. E refers to excretion rates of APIs by humans. The values were collected from literature data, and 100% was assumed for AMI (Table 1), as no excretion rate was reported. WWTP_CR refers to average wastewater treatment connection rate for rural area and urban areas (calculated by Eq. 2). R is the removal efficiency of APIs in the WWTPs. Attempts were made to collect measured R values from the literature where they existed. The SimpleTreat 3.2 model[27] was used to predict R values with different degradation rates to supplement data for APIs without any measurements available and to consider the possible range and variation of R in different scenarios for each API (from worst case to rapidly degraded). The physicochemical properties of APIs (molecular weight, logKow, vapour pressure, water solubility, Henry's law constant and pKa) as model inputs are given in Table S2. More details are explained below. V (L/day/cap) refers to the daily volume of wastewater released per capita which was estimated by the total wastewater released divided by population (resolution, ~1 km) for each city in China in 2013.[6] The gridded V (resolution, 0.5°) was calculated with ArcGIS 10.4 by taking the average V in areas covered by each grid cell. D is the dilution factor calculated using Eq. 3.

$$\text{WWTP\_CR} = WWTP\_CR_u \times Urban\_R + WWTP\_CR_r \times (1 - Urban\_R) \quad (2)$$

$$D = (Q+q)/q \quad (3)$$

Where in Eq. 2 $WWTP\_CR_u$ and $WWTP\_CR_r$ refer to wastewater treatment connection rates in urban and rural areas, respectively, which were estimated by the volume of wastewater treated by WWTPs divided by the total volume of wastewater released in urban and rural areas, respectively, in China.[6] $Urban\_R$ indicates urbanization rates. These data were taken from a projection in a previous study for 2010.[28] Briefly, the Chinese population projected by Landscan for 2010 was utilized (spatial resolution, 1km),[29] and a population density > 1000 capita/km$^2$ was used as the threshold to identify urban population across China. This population dataset is the most reliable high spatial resolution available. In Eq. 3, Q is the discharge flow of the receiving water body (m$^3$/s) and q is the discharge flow of the wastewater (m$^3$/s). Q for China was extracted from a globally modelled surface water discharge dataset with a resolution of 0.5°;[30] and q was aggregated to 0.5° by city level wastewater discharge flow per capita (projected to ~1 km) multiplied by population.[6, 29]

Existing PNEC values of the selected APIs have been compiled in SI Table S1. To maintain consistency, the values for most APIs were chosen from the Vestel et al. study,[31] as many are derived from OECD studies used as part of a regulatory marketing application and are lower than those reported in other studies. For the APIs not included in the Vestel et al. study, the lowest value from other literature sources or databases were used in this study (Table 1). The risk quotient (RQ) PEC/PNEC was subsequently calculated to assess environmental risks of APIs in China. A nominal classification of RQ values < 0.1, between 0.1–1, 1–10 and > 10 predicts insignificant environmental risk, low environmental risk, moderate environmental risk and high environmental risk, respectively.[32, 33]

**Deterministic study of environmental risks and scenario description** Both deterministic and probabilistic assessments were used to provide information on different aspects of environmental concentrations and risks.[34, 35] Deterministic approaches are widely used in environmental modelling with prescribed values for each parameter. The approach was used to predict the geographic distribution of environmental concentrations and risks in surface waters across China for different scenarios. In contrast, Monte Carlo simulation was conducted in the probabilistic method, which shows the probabilistic environmental occurrence and risks in China considering the range, frequency and all possible combinations of parameters, including per capita usage, excretion rates and removal efficiencies in WWTPs of individual APIs. The probabilistic assessment does not reflect spatial information but reveals the probability of risk across China.

Table 1 Statistical data of APIs' daily usage per capita, human excretion rates and PNEC of individual APIs

| Chemicals | PNEC (μg/L) | per capita use of APIs (ug/cap/day)[d] | | | | | Excretion rates |
|---|---|---|---|---|---|---|---|
| | | Mean | STD | Median | Max | Min | |
| Abiraterone Acetate | 0.0013[a] | 38.1 | 23.6 | 38.4 | 80.1 | 0.76 | 93%[e] |
| Amiodarone | 0.12[b] | 454.7 | 271.1 | 416.2 | 1038 | 26.3 | 100% |
| Estradiol | 0.0003[b] | 9.6 | 8.5 | 7.1 | 32.6 | 0.76 | 60%[f] |
| Ethinylestradiol | 0.000031[a] | 1.5 | 0.94 | 1.5 | 4.4 | 0.25 | 100%[f] |
| Levonorgestrel | 0.00001[b] | 2.2 | 2.1 | 1.6 | 8.9 | 0.27 | 77%[g] |
| Atenolol | 148[a, c] | 392.8 | 261.8 | 369.3 | 999.5 | 47.4 | 90%[h] |
| Naloxegol | 200[c] | 0.066 | - | 0.066 | 0.066 | 0.066 | 84%[g] |
| Metformin | 100[a] | 53117 | 11761 | 53935 | 75872 | 33370 | 90%[g] |
| Everolimus | 0.0014[a] | 0.31 | 0.12 | 0.32 | 0.53 | 0.072 | 85%[g] |
| Diclofenac | 32[a] | 1579.3 | 679.6 | 1411 | 3134 | 411 | 100%[i] |
| Ibuprofen | 68[b] | 21673 | 13994 | 17896 | 53907 | 4335 | 95%[g] |

Notes: a, Vestel et al. (2016),[31]
b, the Swedish Environmental Classification System, fass.se (access date: 30 November 2017);
c, Pharmaceuticals in the Environment, AstraZeneca.[37]
d, the per capita use of APIs was from IMS Health;[38]

e, Sternberg et al. 2014;[39]
f, Stanczyk et al. 2013 ;[40]
g, DrugBank;[41]
h, Haro et al. 2017;[42]
i, Williams and Buvanendran;[43]

Four scenarios were defined for the deterministic study to consider the full range of input parameters (summarized in Table 2). Scenario 1 (Sc1) was the worst case, in which the APIs taken by humans were assumed to be completely excreted (E = 100%) and no API was removed by WWTPs (R = 0). Maximum per capita usage was applied in Sc1. Scenarios 2-4 (Sc2-4) considered reduced excretion rates by humans, different per capita usage for each API and different R values for WWTPs. Three first-order biodegradation rate constants (k) were considered to predict R for each API by using SimpleTreat 3.2. The k of 0.1, 0.3 and 1 $hr^{-1}$ represents the chemical being "inherently biodegradable but fulfilling specific criteria", "readily biodegradable but failing 10-day window" and "readily biodegradable" respectively, which indicate low, moderate and high R values in WWTPs and were adopted by scenarios 2, 3 and 4 (Table S3).[44] More details on model input data for SimpleTreat and biodegradation rates are provided in SI. When available, an average measured R value from the literature would be used instead of the predicted value if it was beyond the range of prediction or closer to the moderate predicted R for individual chemicals (as shown in bold in Table S4). The maximum and minimum European per capita use levels of individual APIs (Table 1) were applied in Sc1 and Sc4 respectively. The median per capita use was applied in Sc 2 and 3. Identical excretion rates were used in Sc 2, 3 and 4 as shown in Table 1.

Table 2 The summary of the assumptions for the four scenarios

| Scenarios | Usage | Removal efficiency | Excretion rate |
|---|---|---|---|
| Sc1 | Maximum | 0 | 100% for all APIs |
| Sc2 | Median | Low (predictions when k = 0.1) | as shown in Table 1 |
| Sc3 | Median | Moderate (Predictions when k = 0.3) | as shown in Table 1 |
| Sc4 | Minimum | High (predictions when k = 1) | as shown in Table 1 |

Notes: k is the first-order biodegradation rate (Details are in the SI and Table S4.)

**Probabilistic study of environmental risks.** The uncertainty associated with the parameters described above, were considered in the probabilistic approach. Monte Carlo simulation was applied to Eq. 1 and run 10,000 times to generate probabilistic PECs for each API. These PECs were then divided by the PNEC for individual APIs to obtain RQs. Values of $WWTP\_CR$, V and D were randomly taken from the original datasets of these parameters projected for China by Eq. 2-3 and the methods stated above. Lognormal distribution for R and API per capita use per day and normal distribution for E were used to generate random values for the three parameters for use the Monte Carlo simulation.[34, 45] The mean and standard derivation (STD) for generating random values that align to the corresponding statistical distributions are contained in Tables 1 and S4. For R, measurements were used as the mean in the probabilistic

study and if not available, the predicted value based on the moderate removal efficiency (Table 2) was applied. An STD of 30% and 20% was assumed for R when one R value (either measured or predicted) and two measured R values were available, respectively.[46, 47] STD of human excretion rates was assumed to be 30% for all chemicals, as only a single value was found in the literature (Table 1).

**Comparing API risks with other regulated chemicals** To determine the relative environmental risk of pharmaceutical exposure to that of other chemicals of concern, the median RQs derived from Sc3 in the deterministic study were compared with those of some regulated chemicals. The regulated chemicals include triclosan (TCS)[48] and standard water quality parameters, such as $BOD_5$ (5-day biochemical oxygen demand), COD (chemical oxygen demand), linear alkylbenzene sulphonate (LAS) and heavy metals including Cu, Zn and Hg. PECs of TCS estimated using the present method with the usage from a previous study for 2012[49] were used in the comparison. Measured environmental concentrations (MECs) of the standard water quality parameters collected from over 5000 gauging stations across China for 2013 were acquired from Ministry of Environmental Protection China. The median RQ of these chemicals was estimated by dividing median MECs (or PECs) by their PNECs (or guideline values for COD and $BOD_5$) in China. The lowest value of available PNECs was taken if more than one PNEC values was found from literature for these chemicals (Table S5).

## Results and discussion

**Dilution factors, wastewater discharge flows and wastewater treatment connection rates** The distribution of dilution factors can be indicative of the spatial pattern of water abundance. The default dilution factor is set at 10 by EMA (European Medicines Agency) for carrying out ERAs in Europe.[36] Keller et al. calculated dilution factors for each catchment in China, which range from <10 to over $10^4$.[50] In this study, a spatially explicit dilution factor was calculated (Eq. 3) which ranged from 1 to $5.7\times10^7$ with a median of 96 across China. The range is broader than that estimated by Keller et al., as dilution factors were averaged across each catchment in the Keller et al. study but the 0.5˚-grid resolution ensured a spatially refined dilution factor in this study. There are higher dilution factors in the south and northeast of China and the Yellow River catchment, where there are more abundant water resources and higher discharge flow rates than in other regions (Fig. 1A). The regions with a dilution factor of 1 are displayed in red, as it potentially indicates a high exposure level with zero dilution. However, western China and regions in western Inner Mongolia displayed in red are sparsely populated compared to many other regions in China, therefore, the release of APIs might be low. For the volume of wastewater released, a default value is set to be 200 L/cap/day by the EMA for Europe. In this study, the volume of waste water per person per day was estimated to range from 0.01 to 439

L with a median of 38 L. In ca. 0.6% grid cells, the estimated wastewater released is below 0.8 L/cap/day, which is the lowest estimated 24-hour urine volume if taking 2 L of fluid daily.[51] These regions are around Gansu, west Xinjiang, west Sichuan and Tibet, which are all dry and economically deprived areas. Pit toilets are usually used in these rural or dry areas, so excreta of many people may neither enter the aquatic environment directly in these areas nor be accounted for in the yearbooks. From Fig. 1B, most regions in China have a daily volume of wastewater per capita below the European default level. Figure S1 shows the average wastewater treatment connection rate for each 0.5° grid cell across China, which ranges 0.001%-99% with a median of ca. 20%.

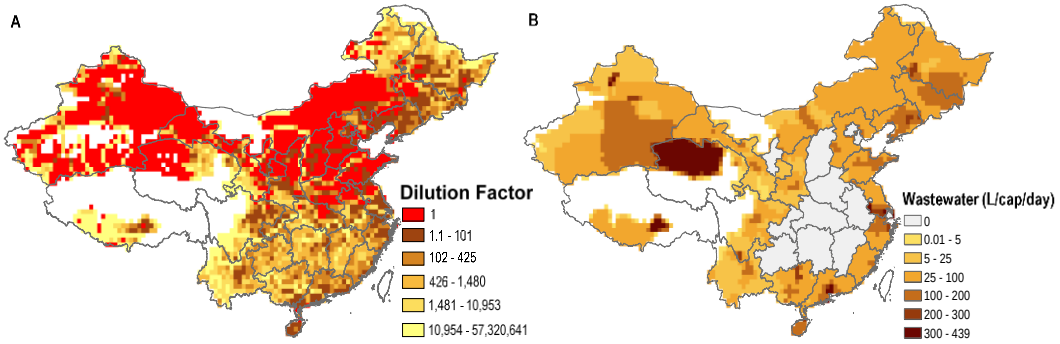


Fig. 1 Distribution of the dilution factor (A) and daily wastewater released per capita (B) in China (0.5°); the white area indicates no wastewater released.

**PECs of APIs in deterministic study** The spatial distribution patterns of PECs are similar under the four scenarios, as they are all determined by the combination of the spatial distribution patterns of dilution factors, wastewater treatment connection rates and population density. These parameters are identical for the four scenarios. The focus here will be on Sc3 as it is a moderate scenario and might be more reasonable than other extreme scenarios. The spatial variation of PECs across China is high as shown by the STDs and ranges in Table S6. Northern China, apart from the northeast, has higher PECs than other areas (Fig. 2 and Fig. S2), such as river basins in North China Plain (NCP), Shanxi, northern Shaanxi, Gansu, middle of Inner Mongolia and northwest Xinjiang. This generally aligns with the spatial distribution of dilution factors across China (Fig. 1A). These regions are mostly dry regions with water stress and limited water resources. Nationally, an estimated 80% of the 11 APIs in the aquatic environment in China will be derived from freshly discharged untreated wastewater. This proportion will decrease with the urbanization and construction of WWTPs in China. Urban populations may contribute ca. 34% of the 11 APIs in aquatic environment. However, this was estimated by assuming a constant per capita usage across China, and per capita consumption of APIs is probably lower in rural areas than in urban areas. Substantial differences in PECs exist between Sc1 (worst case) and Sc4 (best case) with up to two orders of magnitude for some APIs

such as ABI and E2. The difference between low (Sc2) and high (Sc4) removal efficiency scenarios is small. The difference between scenarios varies among chemicals and spatial areas, as detailed in SI and Fig. S2 and S4 and Table S7.

Many of the selected APIs are rarely included in measurement campaigns, especially as part of large-scale monitoring programmes in China, and limited existing studies exist that can be compared to validate the predictions within this study. Yao et al. (2018) detected high concentrations of pharmaceuticals in regions with extreme water stress, such as northern and eastern coastal areas.[8, 52] The spatial distribution pattern is similar with that described in this study. They measured four of the APIs modelled in this study, which exhibited 0-3 orders of magnitude lower median concentrations compared to Sc3 in this study, i.e. E2 (median, 0.26 ng/L), MET (170 ng/L), DCF (3.1 ng/L) and IBPF (7.9 ng/L).[8, 52] The most likely reason for this would be that expected higher future consumption levels were applied in this study. Additionally, field campaigns providing measurement data do not have widespread coverage and may not have included more areas with extremely high water stressed in the north but those areas with higher dilution factors or high wastewater treatment connectivity in developed areas. The PEC distribution of MET in Sc3 (Fig. S3) illustrates this clearly with similar spatial distribution to that measured by Yao et al. but a wider coverage.[8] Meanwhile, Yao et al. estimated that 54% of two groups of pharmaceuticals in surface waters originated from untreated sewage. They may have overestimated the percentage by using principal component analysis with multiple linear regression. Based on a future projection of urbanization rates and WWTP construction,[28] the average proportion might reach about 54% for these APIs around the year 2025, although it may moderately vary for different APIs. Zhang et al. reported a PEC range of $4.8\times10^{-3}$ - 0.96 ng/L for E2 across China at river-basin scale,[22] which is within the range of Sc3 in this study (Table S6). More comparisons with other studies are in the SI. These comparisons prove that the predictive performance of this modelling approach appears to be adequate for a preliminary assessment and the availability of further monitoring data will enable model refinements to be made to improve the predictive power further.

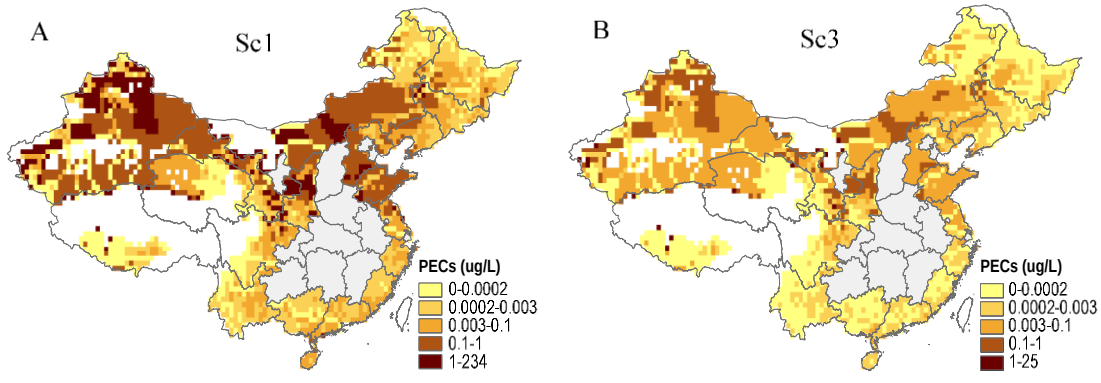


Fig. 2 PEC spatial distribution of estradiol in Sc1 (A) and Sc3 (B)

**Environmental risks of APIs from deterministic study** The level of environmental risk is distinct to individual APIs, however, the spatial distribution patterns are identical which aligns to the PECs. Higher RQs are found in north China (except the Northeast) than in other areas, which is the same with the distribution pattern of PECs. Fig. S5 shows that most regions in north China (except the Northeast) have extremely high environmental risk with RQs > 10 for ABI, AMI, E2, EE2 and LNG in Sc1-3 and even in Sc4 for LNG, EE2 and E2. According to the median RQs of APIs across China, the sequence of environmental risks of chemicals in the four scenarios is generally the same albeit with slight differences. LNG, EE2, E2 and ABI are the top four APIs with the highest environmental risks under all four scenarios (Table S8-S9). Median RQs of the four APIs are greater than 10 in Sc1, greater than 1 in scenarios 1-3 and greater than 0.1 in all four scenarios across China. They will probably lead to high environmental risks (RQ > 1) in > 50% of areas in China under all four exposure scenarios (Fig. 4 and Table S10).

LNG is ranked at the top with median RQs > 10 in scenarios 1-3. There are 98% of areas with RQs > 0.1 for LNG across China, of which ca. 78% have high environmental risk, 13% have moderate environmental risk and 6.6% have low environmental risks (Fig. 4). Only some regions along the Yangtze River and Yellow River may have insignificant environmental risk caused by LNG. These findings suggest that LNG should be a priority for further investigation. The median RQ of AMI is greater than 0.1 in scenarios 1-3. With the exception of ATE and NAL, a high environmental risk might be presented by the other APIs to a varying extent in China under the four scenarios, as shown in SI Table S10. More details on differences among scenarios are contained in SI and Tables S7-S8. The difference among scenarios illustrates the significance of value selection for parameters in assessment of environmental exposure levels and risks for chemicals. Scenario studies can provide useful perspectives for a range of situations that will be of interest to decision makers.

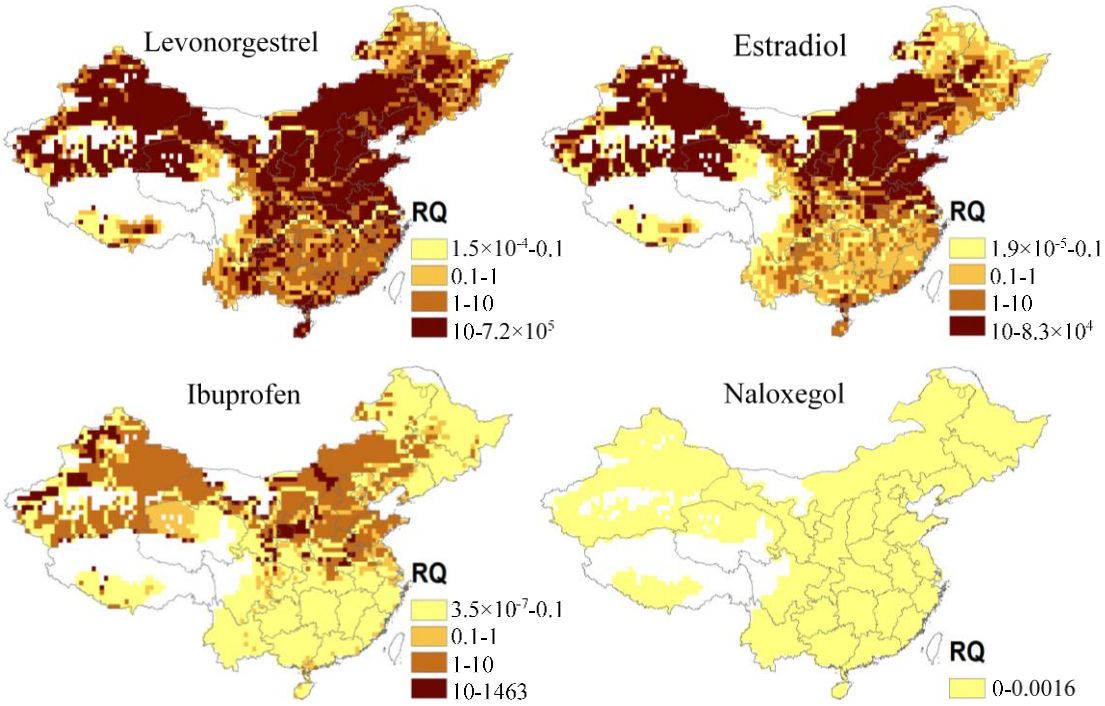


Fig. 3 Spatial distribution of RQ of APIs in Sc3

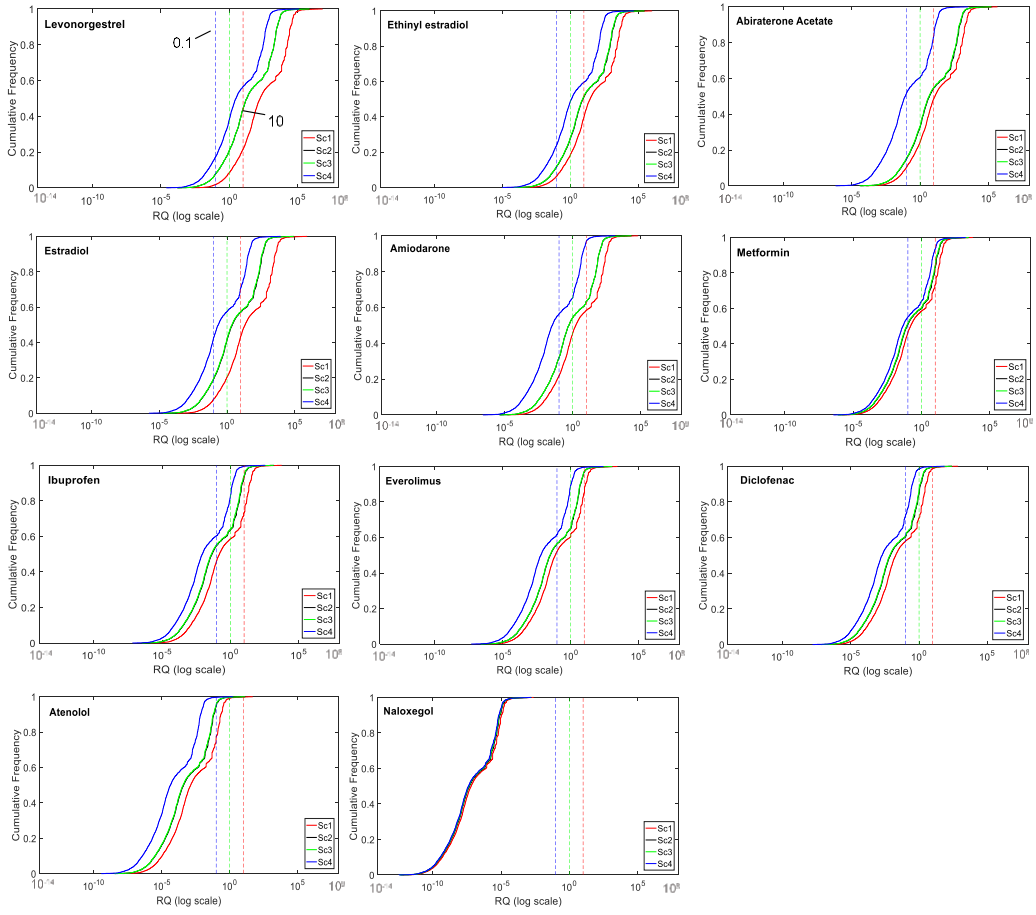


Fig 4. Cumulative frequency of RQ for each API under different scenarios with varied per capita use; the threshold values of RQ were shown as vertical dash line in different colours, i.e. 0.1, 1 and 10 in blue, green and red

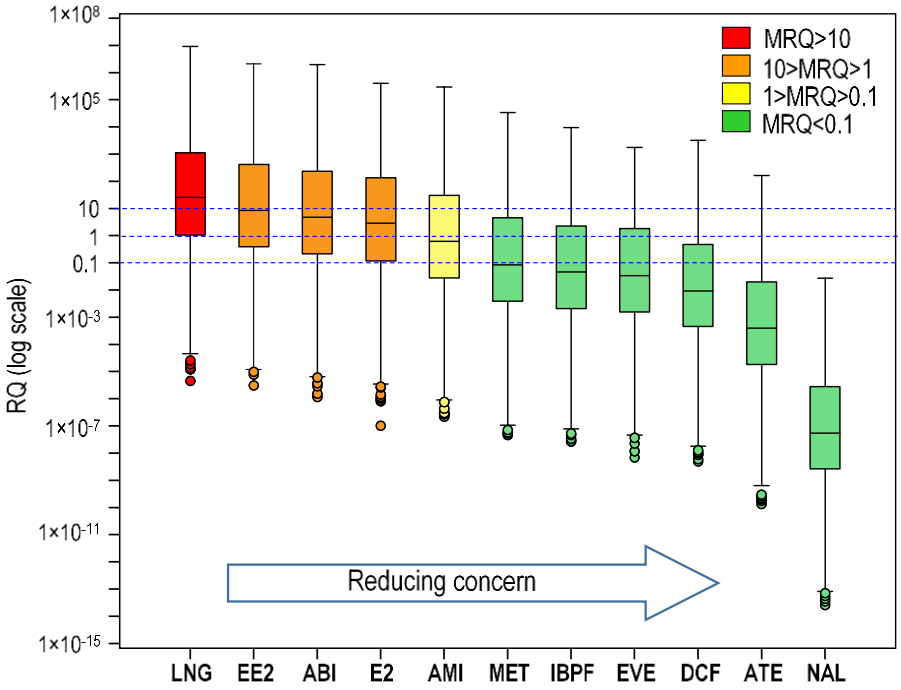


Fig. 5 Boxplot of predicted RQ for APIs from the probabilistic study for China; the horizontal solid line in the box is the median RQ (MRQ as shown in the figure); the top and bottom of the box are the 75$^{th}$ (Q3) and 25$^{th}$ (Q1) percentiles respectively; the top and bottom of the whisker are the highest and lowest values within 1.5 times of the interquartile range (IQ, i.e. [Q1-1.5IQ, Q3+1.5IQ]). The circles are outliers with RQs out of the range of the whiskers.

**Environmental risks of APIs from probabilistic study** The probabilistic study has estimated the RQ probability range and frequency for each API as shown in Fig. 5. The median RQ is compared with threshold values, which can provide a rank order of chemicals with the environmental risk from high to low. Fig. 5 shows the sequence of RQ, which is almost the same as that obtained from the deterministic study. For each of the APIs 50% of the distribution of ranges over three orders of magnitude (i.e. 25$^{th}$ to 75$^{th}$ percentile). The outliers represent RQ values that would have a low probability of occurrence in the Chinese environment. As no high-end outliers were identified (Fig. 5), the top of the whisker shows the maximum RQ. Some are extremely high but will only likely occur with low probability when the excreted APIs are discharged with untreated wastewater to remarkably dry regions without surface water (DF = 1). The distribution is slightly positively skewed. LNG probably represents the highest risk to the environment. EE2, ABI and E2 have a higher probability to cause moderate environmental risk and limited potential to cause high environmental risk for China. AMI likely represents a low environmental risk for China. MET, IBPF, EVE, DCF and ATE would not likely cause a significant environmental risk. NAL is the least likely to lead to any significant environmental risk in China.

**Comparison with other studies and regulated chemicals** There are limited studies on surface water concentrations and relevant environmental risks of LNG and ABI, which have been identified in this study as representing potentially high environmental risks in China. Chen et al. found that the RQ of IBPF ranged between 0.31-3.64 and DCF had a RQ < 0.1 in China.[21] However, they used different methods to produce PECs and different PNEC values, and the studied scale and resolution was different to this study. If adopting PECs by Chen et al. and using PNECs by this study, estimated RQ is less than 0.1 for both IBPF and DCF. IBPF and DCF were not found to have significant environmental risk in the urban rivers in Shanghai in a previous study.[20] Our study focussing on the same region suggests that DCF does not represent a significant environmental risk under all four scenarios and IBPF is only identified to have low environmental risk in Sc1, the worst-case scenario, but not in other scenarios. Zhao et al.[19] has found that DCF has low to moderate environmental risk and IBPF has low environmental risk in the Pearl River with the measured values sampled during 2007-2008. Our study suggested that IBPF represents a low environmental risk under Sc1 with insignificant environmental risk attributed to DCF in the same region. Donnachie et al. have ranked the environmental risk of a number of pharmaceuticals in the UK using both measured and predicted river concentrations.[53] They used a precautionary approach and found the same relative risk ranking of EE2, IBPF, ATE and DCF as in this study for China. Helwig et al. found a completely different sequence of chemical risk to the environment in Scotland, which was MET > EE2 > IBPF > ATE > DCF.[54] AMI, DCF and IBPF were ranked top among a number of APIs (over 42 compounds) in Switzerland in two previous studies.[46, 55]

As already mentioned, environmental risks of the selected APIs were compared with those of some regulated chemicals. More mature regulation has been performed on these chemicals in China and worldwide. Fig. 6 shows the ranking of the environmental risk of the APIs alongside the regulated chemicals. It was found that LNG, EE2, ABI and E2 are still the top four chemicals with higher environmental risk than the other chemicals in China. They are followed by TCS and AMI with the median RQ > 0.1. All other chemicals have a median RQ < 0.1, which probably indicates that these substances are of less concern in most regions in China. NAL is still the chemical with the lowest environmental risk from those examined. In accordance with this study, Donnachie et al. (2016) also found a high rank for TCS following EE2 in the UK.[53] TCS has been restricted in several countries due to the concern on its potentially adverse effect to environment or human health.[48, 56] There have not been any regulations in China to restrict triclosan (TCS) use in the Chinese market; however TCS might be phased out in the future. In contrast to this study, Donnachie et al. found that Cu and Zn are of greater concern than EE2, IBPF, DCF and some other pharmaceuticals in surface water in the UK.[53] The regularly monitored water quality indexes such as COD and $BOD_5$ and several

heavy metals with high production, generally have relatively lower ranking among these chemicals, except Cu. Thus, although the concentrations of these regulated indices suggest they are at a safe level, some other emerging chemicals such as the APIs ranked top in this study might represent a potential environmental risk.

Adverse effects of EE2 and E2 in the environment are relatively well studied compared to LNG and ABI. EE2 and E2 mainly affect the reproductive physiology of exposed wild fish populations. As a synthetic progestin, LNG is commonly used in conjunction with EE2 in contraceptive medications, which suggests it has similar negative effects on wildlife, such as acting as a potent fish androgen.[57] Current research on such effects of LNG are mostly undertaken on fish, but rarely on other aquatic wildlife or mammals. Studies on environmental exposure levels are also scarce especially in China. Studies on ecotoxicological effects and environmental monitoring for ABI and AMI (RQ > 0.1) are currently lacking.

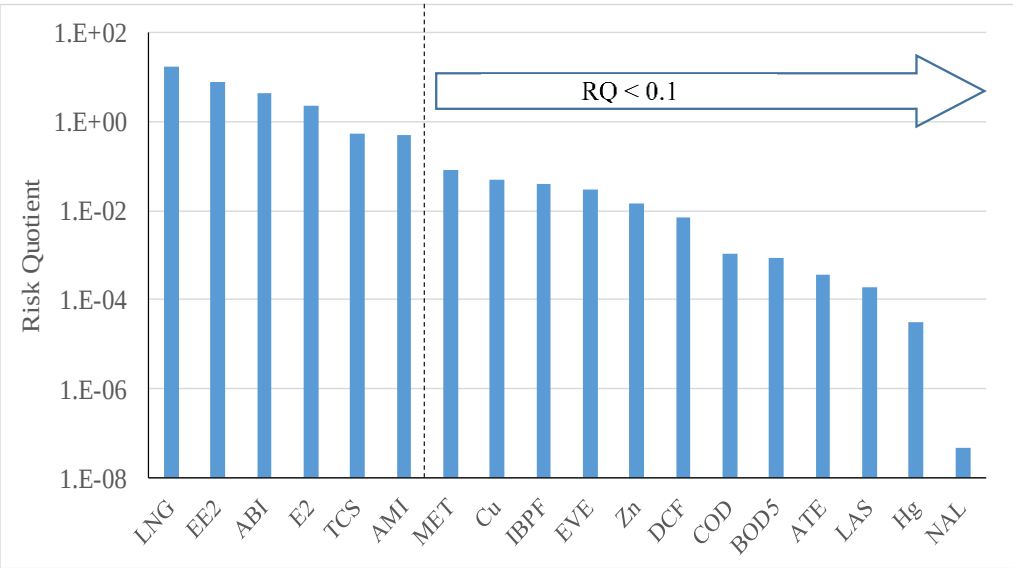


Fig. 6 ranking of median RQ for APIs selected in this study (Sc3) and Cu, Zn, Hg, LAS and TCS

**Uncertainties and limitations** The inherent uncertainty in this study derives in part from the possible error of projected parameters used as input to the model and the intrinsic uncertainty of the modelling method itself. For example, the approach did not consider photo- and biodegradation of APIs in the environment, which may result in and overestimation of concentrations. The choice of the selected PNEC value or guideline value also influences the estimation of the risk or the relative risk. However, this is considered to be an effective and efficient method to provide a preliminary environmental assessment and prioritization.

The adoption of European per capita usage across China may have led to overestimation of environmental risk. The average usage level adopted is probably higher than that currently in China as explained above. Additionally, spatial variation of usage is likely to exist due to

uneven economic development across China, but constant usage was applied across China for the deterministic study. However, as the per capita usage data was collected for a range of different European countries, the range of values may overlap those currently being consumed in China. There are no currently available usage data for China as mentioned above, so the uncertainty is difficult to quantify. However, a comparison of predictions with measured concentrations from field studies reveals that although uncertainty might be varied between APIs but is within an acceptable range for a preliminary assessment.

It is important to note that this study has only considered domestic release as mentioned above. The lack of information on the release within manufacturing effluents may produce uncertainties regionally. Hotspots may occur due to such effluents, especially for those released untreated, but are not easily captured and can be mitigated by site specific interventions. However, as domestic release to surface water is the most important release nationally, as stated above, the uncertainty should be low at the national scale.

**Implications and perspectives**

This study provides an effective and efficient methodology for initial risk screening of APIs in Chinese surface waters. The findings suggest that there is a high potential environmental risk for LNG, EE2, ABI and E2 in surface waters compared to other APIs. These substances can all act as endocrine disruptors. The study also suggested that the potential risk is higher than those of currently regulated chemicals in China and as such warrant further attention from scientists and policy makers, especially for LNG. Given the broad range of chemical risks identified in this study, prioritisation of risks of chemicals in China should cover a broader scope and requires further investment. An important caveat to these calculations is that European usage data was used for the calculations in the absence of Chinese data. Whilst there is potential for usage to increase to European levels, it is important that regional data are obtained.

More attention is needed covering a wide range of hormonal APIs, including those not being covered in this study. Most importantly a spatially resolved usage and emission map for China will significantly contribute to a refined prediction and ERA and reduce uncertainty. These estimates could be based on marketing data and supported by the epidemiology of particular diseases. Beyond this it would be useful to survey manufacturing effluents, to provide data on mass loadings and location, to complete the release map for China, although this may require substantial effort. The overlap of the range of PECs provided by this study and the range of PECs/MECs from previous studies suggests that consumption levels in some regions of China have already reached the European levels for some APIs. It is also important that extensive targeted monitoring work is undertaken to evaluate the environmental exposure level of these APIs, especially in northern China in areas of higher water stress. Additionally, more research

is required on ecotoxicity of hormonal APIs, especially those rarely studied such as ABI. Mixture toxicity should also be considered in future studies, which may result in higher risks than predicted for a single API as some substance may act on similar receptors/organs.

Assessment and prioritization can be also conducted using this methodology for a wider range of APIs within or beyond the selected categories. For example, it is likely that ATE has an insignificant environmental risk across China, however, other β-blockers, such as metoprolol, oxprenolol and propranolol, have been identified with varied toxicological profiles in mammalian studies and may have a different risk profile.[15] AMI also has a relatively high median RQ > 0.1 but the research on its ecotoxicity and environmental exposure is limited. It is also important to consider the presence of potential metabolites in environment as many of them are also biologically active. This is suggested as the future scientific research strategy to support policy makings on environmental regulations relevant to APIs. Meanwhile, when considering policy implications of this study it appears that some APIs identified may represent a potential higher environmental risk than some regulated chemicals. As a result, it might be worth investing more effort to identify important marker APIs or those with high environmental risks or potential human health risks. Based on this, it would be essential to formulate standard guidelines to regulate drug release and disposal and to provide environmental thresholds for identified specific APIs.

## Supporting Information

Supporting Information can be found online.

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