Occurrence of PPCPs and evaluation of their consumption using wastewater-based epidemiology

Zhe Qian[1], Jiapei Yi[2], Huanfang Huang[3], Zhenhao Wu[2], Chi Zhang[2], Amily Wang Guenier[4], Junwu Xiong[2], Jianwei Bu[2,5], Yuan Zhang[1], Jiaquan Zhang[6], Shihua Qi[1,2], Kevin C. Jones[7], Wei Chen[1,2,5,6,7,8*]

[1.] State Key Laboratory of Geomicrobiology and Environmental Changes, China University of Geosciences, Wuhan 430078, China

[2.] School of Environmental Studies and MOE Key Laboratory of Groundwater Quality and Health, China University of Geosciences, Wuhan 430078, China

[3.] State Environmental Protection Key Laboratory of Water Environmental Simulation and Pollution Control, South China Institute of Environmental Sciences, MEE, Guangzhou 510535, China

[4.] Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PL, UK

[5.] Hubei Key Laboratory of Yangtze Catchment Environmental Aquatic Science, China University of Geosciences, Wuhan 430078, China

[6.] Hubei Key Laboratory of Mine Environmental Pollution Control and Remediation, Hubei Polytechnic University, Huangshi 435003, China

[7.] Lancaster Environment Centre, Lancaster University, Lancaster LA1 4YQ, UK

[8.] Institute of Natural Resource Survey, China University of Geosciences, Wuhan 430074, China

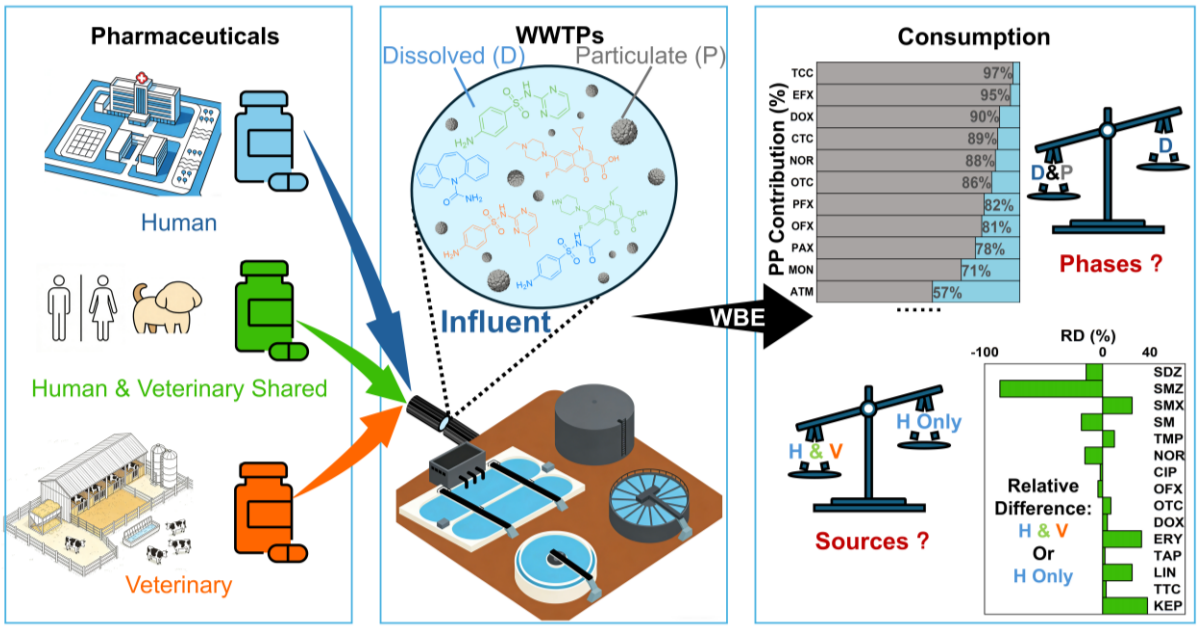
* Corresponding author, Email: wei.chen@cug.edu.cn.

ABSTRACT

Pharmaceuticals and personal care products (PPCPs) in wastewater are key indicators of chemical pollution and community health, yet most wastewater-based epidemiology (WBE) studies analyze only the dissolved phase and overlook veterinary contributions. Influent samples in 9 wastewater treatment plants (WWTPs) from Wuhan, China were collected to analyze 73 PPCPs in both dissolved phase (DP) and particulate phase (PP). The occurrence, and spatial-seasonal distribution of PPCPs, and their partitioning were investigated. PPCPs were ubiquitous in both phases, reaching up to 1.65×10^{4} ng/L (DP) and 2.00×10^{6} ng/g (PP). Inclusion of the PP substantially affected basic measurement of total wastewater concentrations. Partitioning was temperature-dependent, and showed correlation with physicochemical properties in winter and spring. The consumption of human, veterinary and shared pharmaceuticals were separately estimated using WBE. The population-normalized daily consumption of individual human pharmaceuticals ranged from 0 to 1.17×10^{5} mg/d/1000 inhabitants. Neglecting the PP of pharmaceuticals leads to consumption estimation errors, reaching up to 96.6%. Statistical analyses indicated that pharmaceutical consumption varied with disease prevalence, substitution and contraindication practices, and socioeconomic indicators. Linear mixed-effects models further suggested that aging, social-service maturity, population density, per-capita output were associated with consumption variability. The daily *Loads* of individual veterinary pharmaceuticals ranged from 0 to 1.53×10^{3} g/d. Strong correlations with shared-use pharmaceuticals indicated clear animal-derived inputs. Under the two specific source allocation scenarios, human- and veterinary-use *Loads* of pharmaceuticals across 9 WWTPs ranged from 3.52×10^{5} to 3.83×10^{5} g/d and 9.77×10^{2} to 4.26×10^{3} g/d, respectively. These findings demonstrate the need to include particulate-phase PPCPs and mixed human-animal sources to improve the accuracy of WBE-based research.

Keywords: Pharmaceuticals and Personal Care Products (PPCPs), Wastewater-Based Epidemiology (WBE), Partitioning Coefficients, Human-Veterinary Shared Pharmaceuticals.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Municipal wastewater contains a variety of contaminants, including pharmaceuticals and personal care products (PPCPs), which are a class of emerging contaminants (Tran et al., 2018; Yi et al., 2023). PPCPs are not efficiently removed from wastewater treatment plants (WWTPs) (Boxall et al., 2012; Gerrity et al., 2024), resulting in their continuously release to the environment through effluent discharge and sludge application (Lei et al., 2018; Chen et al., 2024). PPCPs can bioaccumulate and may have ecotoxicological effects (Yu et al., 2024; Du et al., 2025). Beyond their environmental impact, PPCPs also function as chemical indicators of human activity and health conditions (Choi et al., 2020). Wastewater surveillance has therefore been widely used to track viral outbreaks such as COVID-19 (Randazzo et al., 2020; Morvan et al., 2022) and assess illicit drug use (Mao et al., 2021; Shimko et al., 2023). Monitoring PPCPs in untreated municipal wastewater can thus support both pollution mitigation and public health assessment.

Wastewater-based epidemiology (WBE) is a powerful tool for monitoring population-level consumption or exposure to various substances (Thomas et al., 2017). Studies have demonstrated that WBE offers an objective and timely means to monitor illicit drugs (Kim and Oh, 2020; Ceolotto et al., 2024a), pharmaceuticals (Ceolotto et al., 2024b), alcohol (Chen et al., 2019), tobacco (Gao et al., 2020) and artificial sweeteners (Li et al., 2021a; Li et al., 2023). However, WBE estimations carry inherent uncertainty from variability in excretion rates and in-sewer transformation, which can bias absolute back-calculated consumption (Holton et al., 2022). Beyond these hard-to-control uncertainties, WBE estimations are also affected by two more tractable yet potentially influential factors: neglecting the particulate phase (PP) and failing to account for veterinary sources. Most WBE applications quantify only dissolved-phase PPCPs in influent wastewater (Bernier-Turpin et al., 2025). Increasing evidence indicates that the sorption of PPCPs onto suspended particulate matter (SPM) is significant (Lin et al.,

2018; Proctor et al., 2021). Current WBE research often neglects PPCPs in particulate phase (PP) and rely solely on concentrations of those in dissolved phase (DP) for back-calculation, which may lead to systematic underestimations of consumption.

More critically, the conventional WBE framework faces inherent limitations in identifying the sources of pharmaceuticals. Human-veterinary shared pharmaceuticals are often misattributed to human use because their origins are ambiguous (Beldean-Galea et al., 2025). Although a few studies have suggested that veterinary usage may interfere with consumption estimations (Xu et al., 2022), the influence has not been systematically characterized or quantified.

In this study, influent samples were collected seasonally from nine WWTPs in Wuhan, China, and the concentrations of PPCPs were analyzed in both DP and PP. This study aims to (1) characterize PPCP occurrence and spatial-seasonal patterns in both phases, and DP-PP partitioning, (2) estimate pharmaceutical consumption by using WBE methodology that incorporates both phases, and (3) evaluate the influence of veterinary inputs on human-veterinary shared pharmaceuticals.

2. MATERIALS AND METHODS

2.1 Chemicals and materials

A total of 73 PPCPs were analyzed, comprising seven categories of pharmaceuticals and four categories of personal care products (PCPs). The pharmaceuticals included 44 antibiotics, 3 β-blockers, 4 psychiatric medications, 1 antihypertensive drug, 5 estrogens, 5 non-steroidal anti-inflammatory drugs (NSAIDs) and 1 hypolipidemic drug. The PCPs included 5 preservatives, 1 antioxidant, 3 biocides and 1 bisphenol. Twenty-eight isotope-labeled internal standards (IL-ISs) were used for the quantification. Detailed information on all compounds,

their IL-ISs and other chemical reagents is provided in Supplementary data (SD, **Text S1**, **Tables S1 and S2**).

2.2 Study area and sampling campaign

Wuhan, a typical metropolis in central China, is renowned for its complex socioeconomic structure and demographic composition (Hu et al., 2023). The nine WWTPs were selected covering urban (BH, ELM, HJH, LBZ, LWZ, NT, SJT), suburban (BX) and industrial areas (ZL), and serving an area of 637.2 km^2. These WWTPs serve a population of about 7.24 million, accounting for 52.6% of Wuhan's permanent residents in 2023 (Wuhan Bureau of Statistics, 2024), and are representative of wastewater sources in typical Chinese metropolitan areas. (Detailed information of WWTPs are listed in **Table S3** and **Figure S1**).

Sampling was conducted quarterly from July 2023 to April 2024, to represent summer, autumn, winter and spring. To avoid dilution effects, sampling was scheduled at least one week after rainfall and only conducted on days without precipitation. Influent samples were grab-collected downstream of the coarse grid at each WWTP. Samples for PPCP analysis were stored in amber glass bottles, while those for hydrochemical parameters analysis were stored in PET plastic bottles. All samples were kept at <4℃ and transported immediately to the laboratory. Prior to sampling, all sampling equipment was pre-cleaned with acetonitrile, methanol and ultrapure water. and rinsed three times with the sample water before sampling.

2.3 Sample pretreatment and analysis

Sample pretreatment for PPCP analysis followed optimized procedures based on previous studies (Gago-Ferrero et al., 2015; Chen et al., 2016; Song et al., 2017). DP samples were subjected to solid-phase extraction (SPE) for enrichment and purification. PP samples were ultrasonically extracted and followed by SPE procedure. Detailed pretreatment procedures for both phases are provided in **Text S1**.

PPCPs were analyzed using an ultra-high performance chromatography tandem-mass spectrometer (UPLC-MS/MS, Vanquish Flex-TSQ Altis Plus, Thermo Fisher Scientific, USA) equipped with an electrospray ionization (ESI) source. PPCPs were separated using a XBridge BEH C18 column (2.5 μm, 2.1 mm × 100 mm, Waters). The analytical procedures were developed based on the previous reported methods (Zhou et al., 2012; Chen et al., 2016; Duan et al., 2022) with further optimization performed. The details of instrumental methods and parameters are given in **Text S2** and **Table S4**. Quality assurance and quality control (QA/QC) included solvent and procedure blanks, field duplicates, isotopically labelled-internal standards (IL-ISs) and a mixed QC standard (100 ng/L). Detailed information on the QA/QC procedures is given in **Text S3** and **Table S5**.

For hydrochemical parameters, ammonia nitrogen (NH_4-N) concentrations were measured on-site by using a portable spectrophotometer (DR1900, Hach, USA). Chemical oxygen demand (COD) was measured using a spectrophotometer (DR 2800, Hach, USA) according to the manufacturer's instructions, and total phosphorus (TP) was measured using a spectrophotometer following the Chinese National Standard GB 11893-89 (Ministry of Ecology and Environment of the People's Republic of China, 1989).

2.4 Data processing

2.4.1 Partitioning coefficient estimation

The partitioning coefficient (K_d, kg/L) was used to quantify PPCP partitioning between both phases and was calculated by Equation (1):

$$K_d = \frac{C_{PP}}{C_{DP}} \times 1000 \quad (1)$$

where C_{PP} (ng/g) and C_{DP} (ng/L) are the measured PPCP concentrations in PP and DP samples, respectively. The K_d values were calculated only when both concentrations (DP and PP)

exceeded the method detection limits (MDLs, see **Table S5**). Analytes were excluded when <20% of the sampling sites showed matching detections in both DP and PP samples.

Physicochemical properties of PPCPs were used to explore factors influencing partitioning. Specifically, the physicochemical properties include molecular weight (MW), octanol-water partition coefficient (K_{OW}), calculated octanol-water partition coefficient (Xlog P3), acid dissociation constant (pK_a), hydrogen bond donor count (HBDC), hydrogen bond acceptor count (HBAC), rotatable bond count (RBC), topological polar surface area (TPSA), heavy atom count (HAC), complexity (CPL) and biodegradation half-life days (BHD). Detailed information of each compound is provided in **Table S1**.

Fugacity fraction (*ff*) was used as an indicator of partitioning. The *ff* value > 0.5 and < 0.5 indicates that the PPCP is prone to migrate from PP to DP and the PPCP tends to diffuse from DP to PP, respectively (Mao et al., 2025). Detailed calculation process is provided in **Text S4**.

2.4.2 Consumption estimation

Population served by each WWTP was estimated using a hydrochemical-parameter model (Zheng et al., 2019). The served population (P_j, inh) of WWTP j was estimated by Equation (2):

$$P_j = W_U \times \frac{C_U \times Q_j}{m_U} \quad (2)$$

where W_U is the weight factor of each hydrochemical parameter U (NH_4-N, COD and TP). C_U (mg/L) is the concentration of U in wastewater. Q_j (m^3/day) is the flow rate of raw wastewater at WWTP j. And m_U (g/day/inh) is the daily excretion of U per capita. W_U of NH_4-N, COD and TP were set at 0.53, 0.33 and 0.14, respectively, and m_U of NH_4-N, COD and TP were set at 6, 43.9 and 0.8 g/day/inh, respectively (Zheng et al., 2019). The calculated results are listed in **Table S6**.

Pharmaceuticals were classified into human, veterinary and human-veterinary shared categories (**Table 1**) based on the National Medical Products Administration of China (NMPA) (NMPA, 2025) and the China Institute of Veterinary Drug Control (China Institute of Veterinary Drug Control, 2025), which list all pharmaceuticals approved for human and veterinary use in China. Estradiol (E2) and estriol (E3) although listed in NMPA, were excluded from consumption analysis because they can be endogenously produced and may not reliably reflect external usage (Stanczyk, 2024).

Table 1. Classification of pharmaceuticals based on intended use.

Category		Name of pharmaceuticals
Human pharmaceutical	Antibiotic	Sarafloxacin (SCM), Lomefloxacin (LFX), Fleroxacin (FLX), Pefloxacin (PFX), Clarithromycin (CLM), Azithromycin (ATM), Roxithromycin (RTM), Chloramphenicol (CAP)
	β-blocker	Atenolol (ATE), Propranolol (PRO), Metoprolol (MTP)
	Psychiatric medication	Fluoxetine (FLU), Paroxetine (PAX), Carbamazepine (CBZ), Venlafaxine (VEN)
	Estrogen	Ethinyl estradiol (EE2)
	NSAID	Fenoprofen (FEP), Ibuprofen (IBP)
	Hypolipidemic drug	Gemfibrozil (GFB)
Veterinary pharmaceutical	Antibiotic	Sulfamerazine (SMR), Sulfathiazole (STZ), Enrofloxacin (EFX), Marbofloxacin (MFX), Chlortetracycline (CTC), Tylosin (TLS), Florfenicol (FF), Ormetoprim (OMP), Monensin (MON)
Human-veterinary shared pharmaceutical	Antibiotic	Sulfadiazine (SDZ), Sulfamethazine (SMZ), Sulfamethoxazole (SMX), Sulfaguanidine (SGN), Sulfameter (SM), Trimethoprim (TMP), Norfloxacin (NOR), Ciprofloxacin (CIP), Ofloxacin (OFX), Tetracycline (TTC), Oxytetracycline (OTC), Doxycycline (DOX), Erythromycin (ERY), Thiamphenicol (TAP), Lincomycin (LIN)
	NSAID	Ketoprofen (KEP), Diclofenac (DCF), Naproxen (NAP)

Population-normalized daily consumption (*PNDC*, mg/day/1000 inh) of human and human-veterinary shared pharmaceuticals were estimated by Equation (3) using a back-calculation method (Luo et al., 2024):

$$PNDC_{i,j} = \frac{C_{i,j} \times Q_j}{CF_i \times P_j} \quad (3)$$

where $C_{i,j}$ (ng/L) is the observed concentration of PPCP *i* in the influent from WWTP *j*. CF_i is the excretion rate of human pharmaceutical *i,* and the *CF* data is provided in **Table S7**.

The daily loads of veterinary pharmaceuticals (*Load*, g/day) were estimated by using the following Equation (4) (Luo et al., 2024):

$$Load_{k,j} = \frac{C_{k,j} \times Q_j}{1000 \times CF_k} \quad (4)$$

where $C_{k,j}$ (ng/L) is the observed concentration of veterinary pharmaceutical *k* in WWTP *j*. CF_k is the excretion rate of veterinary pharmaceutical *k*, which is provided in **Table S7**. We used published excretion rates for back calculation. However, uncertainty of excretion rates and potential in-sewer transformation may introduce additional errors in *PNDC*.

Socioeconomic indicators, including indicators of economic structure, healthcare resource and population demographic (**Table S8**), were obtained from the Wuhan Statistical Yearbook 2024 (WStatistics, 2024). To evaluate source contributions for human-veterinary shared pharmaceuticals, two extreme attribution scenarios were constructed: (1) Human-dominant scenario, assuming 100% of the load originated from human use, and (2) Minimal-human contribution scenario, assuming the maximum contribution from veterinary sources. The specific results of source allocation for veterinary inputs under two scenarios are discussed and presented in ***Section 3.4***.

Unless otherwise specified, the concentrations of target compounds in PP samples are expressed on a dry weight (dw) basis (ng/g) when discussing their occurrence. For *PNDC* and *Load* calculations, PPCP concentrations are expressed as total concentrations per unit water volume (ng/L), obtained by combining the DP and PP concentrations.

2.5 Statistical analysis

Statistical analyses were conducted in IBM *SPSS* Statistics 29 with a significance threshold of 0.05. Data normality was assessed prior to hypothesis testing. The independent-

sample *t*–test, Wilcoxon rank sum test, Kruskal–Wallis (K–H) test and Mann–Whitney (M–W) test was used to evaluate group differences. Spearman correlation analysis was applied to assess associations among concentrations, K_d values, *PNDC*s, *Load*s, environmental parameters and socioeconomic indicators. Hierarchical cluster analysis was performed to group WWTPs based on PPCP concentration profiles. Linear mixed-effects models (LMMs) implemented by R using "lme4" package, were used to capture the complex associations between socioeconomic indicators and pharmaceutical consumption while accounting for seasonal effects. Figures were generated using Origin 2023. Concentrations below MDLs were treated as zero for statistical purposes.

3. RESULTS AND DISCUSSION

3.1 Occurrence of PPCPs in influent from WWTPs

3.1.1 Concentrations of PPCPs

The PPCPs were widely detected in the municipal influent. Seventy of 73 targeted PPCPs were detected at least once in the influent samples (**Table S9**), except for sarafloxacin (SFX), danofloxacin (DAX) and difloxacin (DIX). In DP samples, three were absent, while 32 exhibited a 100% detection rate (**Table S9**). In PP samples, five compounds were not detected, and 16 showed a 100% detection rate (**Table S9**). The high detection rates confirmed the widespread occurrence of PPCPs in influent from WWTPs in Wuhan.

Total PPCP concentrations in DP samples ranged from 656 to 1.65×10^4 ng/L (**Table S9**). Five categories of PPCPs exhibited average concentrations exceeding 50 ng/L (**Figures 1** and **S2**), including bisphenols (350 ng/L), NSAIDs (144 ng/L), preservatives (91.6 ng/L), antibiotics (79.3 ng/L) and *β*-blockers (68.0 ng/L). Among them, the average concentrations of RTM (1.32×10^3 ng/L) and CLM (1.21×10^3 ng/L) were significantly higher than those of other target compounds (*t*–test, $p < 0.01$) (**Table S9**), and both compounds are macrolide antibiotics.

The elevated concentrations of these compounds in municipal wastewater reflect their high usage in Wuhan, consistent with findings from other regions in China (Li et al., 2022; Xu et al., 2022). Total concentrations of PPCPs in PP samples ranged from 3.06×10^3 to 2.00×10^6 ng/g (**Table S9**). Five categories of PPCPs exhibited average concentrations exceeding 50.0 ng/g (**Figures 1** and **S2**), including antibiotics (7.69×10^3 ng/g), biocides (395 ng/g), bisphenols (91.3 ng/g), antihypertensive drugs (66.5 ng/g) and NSAIDs (51.7 ng/g).

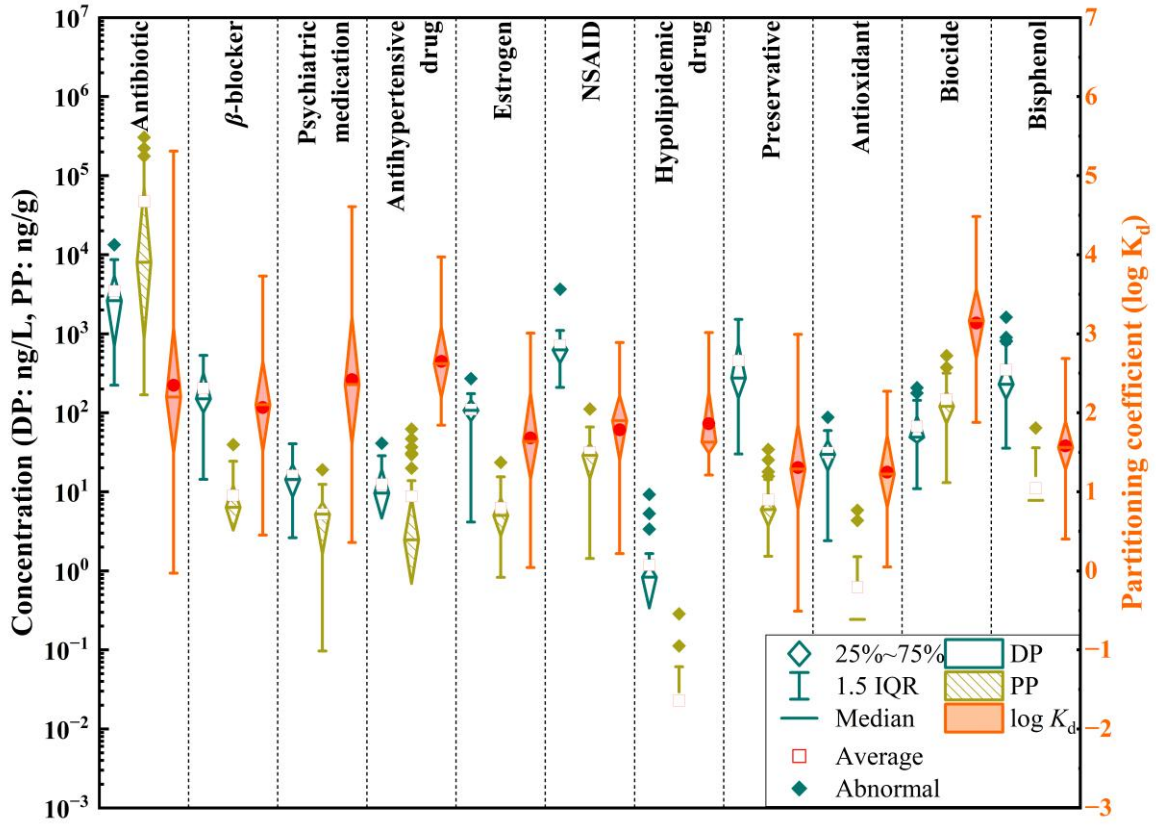


Figure 1. Concentrations of dissolved-phase (DP) and particulate-phase (PP) PPCPs from influent of WWTPs (left Y axis) and distribution coefficients (K_d) of different categories of PPCPs (right Y axis).

3.1.2 Spatial and seasonal variation of PPCPs

Seasonal average concentrations of total PPCPs in DP and PP samples ranged from 4.52 ng/L (ZL) to 6.91×10^3 ng/L (ELM) and from 5.70×10^4 ng/g (ZL) to 6.05×10^5 ng/g (SJT), respectively. Antibiotics were the dominant group of PPCPs, which accounted for 54.9% (BH) to 83.0% (ZL) of total PPCPs in DP samples and more than 98.9% in PP samples at all WWTPs.

Hierarchical cluster analysis of PPCP categories (**Figure S3**) showed that influent for WWTP ZL was distinct from those of the other eight WWTPs in both DP and PP samples. This difference is likely because pretreated industrial wastewater contributed ca. 40% supply of influent for WWTP ZL, which typically contains lower PPCP concentrations than those in domestic wastewater, leading to the dilution effect, lower overall concentrations and a distinct PPCP profile. Differences between DP- and PP-based clustering may also reflect phase-specific partitioning controls, including pH, dissolved organic matter and organic carbon content (Xu et al., 2014; Cheng et al., 2016; Aolin et al., 2024). These factors affect the partitioning of PPCPs between phases, leading to differences in composition observed across the two sample types.

In DP samples, all PPCP categories except bisphenols exhibited significantly higher concentrations (K–H test, $p < 0.05$) in cold seasons (winter and spring) than in warm seasons (summer and autumn) (**Figure S4**). This trend aligns with findings from other studies conducted in China (Sun et al., 2014; Wang et al., 2024), suggesting that seasonal variations in the consumption of pharmaceuticals. During colder seasons, increased incidences of infectious diseases such as influenza have been reported in cities including Beijing (Ma et al., 2017), Suzhou (Luo et al., 2024), and Nantong and Huzhou (Xu et al., 2022), which lead to higher usage of antibiotics and anti-inflammatory drugs. In addition to usage patterns, dilution, temperature and biodegradation may also influence the seasonal variability of PPCP concentrations. According to Sun et al. (2014) increased domestic water use and higher rainfall during summer and autumn may dilute influent, leading to reduced concentrations of PPCPs. Similarly, Li et al. (2022) observed higher levels of preservatives during cold seasons and attributed this to enhanced microbial activity during warmer periods, which promotes biodegradation of PPCPs before they reach WWTPs. Seasonal trends in PP samples differed markedly from those in DP samples (**Figure S4**). Antibiotics, NSAIDs, estrogens and antihypertensive agents showed significantly higher concentrations (K–H test, $p < 0.05$) in cold

seasons, whereas psychiatric medications and bisphenols were more abundant during warm seasons. Other PPCP categories did not exhibit significant seasonal variations (K–H test, $p > 0.05$). The behavior of PPCPs in PP samples is more strongly influenced by their phase partitioning. Elevated water temperatures during warm seasons may inhibit the transfer of PPCPs from DP samples to PP samples (Ohoro et al., 2022).

3.1.3 Partitioning of PPCPs in dissolved and particulate phase

Partitioning behavior strongly influenced compositional differences between DP and PP samples (Chen et al., 2022). Based on the average log K_d values of each compound group, biocides were identified as the PPCPs most prone (range -0.03 – 7.96, average 2.36) to adsorb onto particulate matter, whereas antioxidants were the most soluble (range 0.05 – 2.27, average 1.25) in the DP (**Figures 1** and **S2**, and **Table S9**). Specifically, among the 56 PPCPs with calculated log K_d values, NOR exhibited the highest median (4.00) and average (4.01) log K_d, while ethylparaben (ETP) showed the lowest (median: 0.06, average: 0.09), indicating their strong particle affinity and hydrophilicity, respectively (**Table S9**). Among antibiotics, tetracyclines (range 2.64 – 4.87, average 3.84), quinolones (range 2.17 – 5.67, average 3.60) and macrolides (range 0.71 – 7.96, average 2.44) showed strong affinities for particulates compared to others (sulfonamides: range -0.01 – 4.33, average 1.75; chloramphenicols: range -0.03 – 2.37, average 1.21) (**Table S9**). Previous studies suggested that the adsorption of macrolides to particulate is lower than that of quinolones and tetracyclines (Harrower et al., 2021), which is consistent with our findings (**Table S9**). Quinolones interact with particulates mainly through cation bridging and surface complexation (Zhao et al., 2023). For tetracyclines, the presence of multiple functional groups (e.g., hydroxyl, dimethylamino, carbonyl and amide) along with the zwitterionic properties enhances their adsorption onto particulate (Li and Zhang, 2010; Chen et al., 2022). Given the high prevalence and substantial particulate-phase

concentrations of PPCPs, neglecting particulate-bound fractions in WBE analyses will lead to substantial estimation errors.

The partitioning behavior of PPCPs between the dissolved and particulate phases may be influenced by both environmental factors and their own physicochemical properties (Martínez-Alcalá et al., 2017). Correlation analysis with environmental factors revealed that temperature was the most influential variable affecting the partitioning behavior of PPCPs (**Figure S5**). Among the 56 compounds investigated, 28 (50%) showed a significant correlation between log K_d and temperature (**Figure S5**). Since influent temperature is closely associated with sampling season (**Table S6**), they were grouped by season to explore the relationship between physicochemical properties and log K_d values.

During warm season, no physicochemical properties were significantly correlated with log K_d, and linear regressions were largely insignificant except for XLogP3 (R^2 = 0.116, p = 0.022). In contrast, cold season exhibited distinct patterns: three (HBAC, HAC and MW) and four parameters (HBAC, HAC, CPL and MW) were significantly correlated with log K_d in winter and spring ($p < 0.05$), respectively. And seven parameters (HBDC, HBAC, TPSA, HAC, CPL, MW and pK_a) exhibited significant linear relationships with log K_d values during the cold season (**Figure S6**).

The *ff* values (**Tables S10 and S11**) revealed that PPCPs were in a non-equilibrium state between PP and DP for most influent samples. In 93.1% of samples, *ff* values were <0.5, suggesting that PPCPs were generally diffusing from DP to the PP. A significant difference ($p < 0.05$, Wilcoxon rank sum test) was observed between cold and warm season, with the average of cold season closer to 0.5, indicating that PPCPs tended to be closer to PP-DP equilibrium in the cold season than in the warm season.

Two mechanisms may explain the seasonal differences in PPCP partitioning: (1) Higher temperatures in summer and autumn enhance degradation processes, reducing the proportion of compounds in dissolved phase (Ma et al., 2017; Duan et al., 2022). Consistent with this,

51.2% of compounds exhibited significantly higher (K–H test, $p < 0.05$) log K_d values in warm seasons, and another 22.0% showed higher, though nonsignificant (K–H test, $p > 0.05$) (**Table S9**). The lack of a significant correlation ($p > 0.05$) between log K_d and biodegradation half-lives suggested that hydrolysis and photolysis may also jointly influence partitioning (Bonnot et al., 2023). (2) In the cold season, lower temperatures stabilize the physicochemical conditions of water, making them closer to ideal laboratory states (equilibrium state, as confirmed by *ff* values in **Tables S10 and S11**), thereby allowing the physicochemical properties of PPCPs to play a more dominant role in controlling their partitioning behavior.

PPCPs were ubiquitous in wastewater influent in both dissolved and particulate phases, their partitioning was strongly influenced by temperature and compound physicochemical properties. Thus, PP substantially contributed to PPCP total concentrations and should not be neglected. This raises a key question: how much does ignoring the particulate phase underestimate actual pharmaceutical consumption? To address this, we integrated concentrations from both phases to quantify the particulate-phase contribution and evaluate the resulting bias, and to further examine how mixed human–veterinary sources of shared-use pharmaceuticals affect the estimations.

3.2 Human pharmaceutical consumption

3.2.1 Profiles of human pharmaceutical consumption

Average consumption of different pharmaceuticals ranged from 0.22 (FLX) to 2.15×10^4 (ATM) mg/d/1000 inh (**Figure S7** and **Table S12**). The PP contribution to the *PNDC* values of all pharmaceuticals ranged from 0.2% (EE2) to 82.5% (PFX) (**Table S12**), with an overall average contribution of 24.5%. Several pharmaceuticals, including ATM, RTM, FEP, IBP and CLM exhibited high consumption levels, each exceeding 1,000 mg/d/1000 inh on average.

Macrolide antibiotics (CLM, ATM and RTM) showed significantly (M–W test, $p < 0.05$) higher *PNDCs*, exceeding those of other pharmaceuticals by 3 to 5 orders of magnitude. Their

high consumption is consistent with national procurement statistics (Yang et al., 2022) and clinical prescription patterns in China (Zhu et al., 2021). MTP had a markedly higher *PNDC* compared to other *β*-blockers (PRO and ATE). MTP accounted for ~62.2% of *β*-blocker prescriptions in China (Yan et al., 2024), while both PRO and ATE represented less than 5%, corroborating with the consumption result we found. In the category of psychiatric medications, CBZ, an antiepileptic drug, exhibited a *PNDC* of 109 mg/d/1000 inh (74.2 mg/d/1000 inh in DP sample), which was higher than the average of 31.1 mg/d/1000 inh in DP sample reported by Shao et al. (2023) across 23 Chinese cities. VEN showed the highest *PNDC* among the antidepressant prescriptions (VEN, PAR and FLX). Zhao et al. (2024) reported that VEN accounted for 6.3% of antidepressant prescriptions in Chinese hospitals, higher than PAR (4.4%) and FLX (0.5%). Interestingly, FLU (average, 5.39 mg/d/1000 inh) consumption in Wuhan exceeded that of PAR (average, 1.85 mg/d/1000 inh) in our study, which differs from trends found in another province of China (Lu et al., 2023). This could be attributed to regional differences in prescribing habits. For instance, FLU is often preferred among female patients due to its better tolerability and lower risk of weight gain (Martényi et al., 2001; Dell'Osso et al., 2022), whereas PAR is associated with adverse effects on fertility (Milosavljević et al., 2022). The average *PNDC* of EE2 was 3.14 mg/d/1000 inh (3.13 mg/d/1000 inh in DP sample), substantially lower than the national average (14,275.44 mg/d/1000 inh in DP sample) reported in a previous study (He et al., 2024). However, this study also reported lower EE2 consumption in Central China (lower than other regions in China by about 1 to 3 orders of magnitude), where Wuhan is located. IBP, a common over-the-counter antipyretic, had an average *PNDC* of 1.13×10^{3} mg/d/1000 inh (1.12×10^{3} mg/d/1000 inh in DP sample), lower than the peak consumption during China's COVID-19 outbreak (above 1.00×10^{4} mg/d/1000 inh in DP samples in Changchun), but still higher than pre-pandemic levels (below 200 mg/d/1000 inh in most cities in China) (Yu et al., 2025). This may reflect increased usage following the surge in

respiratory infections after the relaxation of China's "zero-COVID" policy in late 2022 (Goldberg et al., 2023). FEP showed an average *PNDC* of 1.35×10^3 mg/d/1000 inh (1.16×10^3 mg/d/1000 inh in DP sample), and this study provides the first WBE-based estimation of its usage.

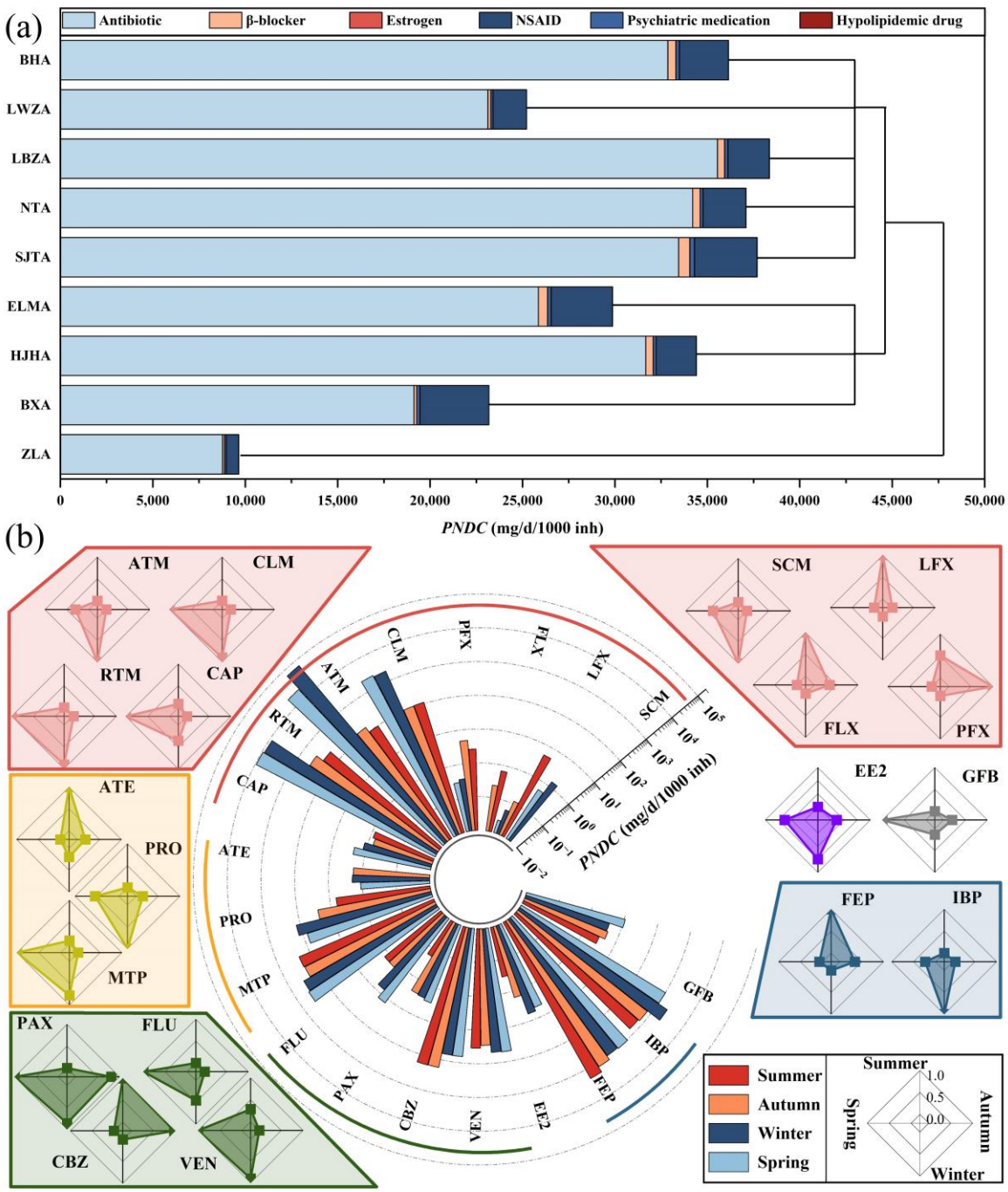
Overall, the *PNDC*s of the seven pharmaceutical categories in this study were generally consistent with those reported in previous studies. The pharmaceutical consumption patterns reflected by the back-calculation results using WBE were consistent with their clinical application patterns, demonstrating the effectiveness of WBE in assessing pharmaceutical consumption. Nevertheless, the particulate-phase contribution to the total consumption was substantial and should not be neglected.

3.2.2 Spatial and seasonal variation of human pharmaceutical consumption

Cluster analysis revealed that WWTP ZL exhibited a distinct pharmaceutical consumption pattern compared with other WWTPs (**Figure 2a**). This may be primarily attributed to two factors: (1) the influent from WWTP ZL contains industrial wastewater according to the on-site survey from the WWTP, and (2) the service population of WWTP ZL is different from other WWTPs, the ZL service area is mainly inhabited by an agricultural population. Although the clustering analysis grouped the suburban-WWTP BX with two urban WWTPs, its *PNDC* lower than those of other urban plants. This finding aligns with previous studies (Li et al., 2024), suggesting higher pharmaceutical consumption in urban areas compared to suburban regions in China, and indicating higher pharmaceutical loads and higher pharmaceutical discharges into the environment through the urban WWTPs.

The usage of PPCPs is closely intertwined with economic and social factors (He et al., 2024). In this study, we examined correlations between *PNDC*s and socioeconomic indicators across the nine WWTPs (**Figure S8a**). Gender and age structure may contribute to variability in pharmaceutical consumption. Eight pharmaceuticals (ATM, PRO, MTP, FLU, PAR, VEN,

EE2 and FEP) showed significant correlations ($p < 0.05$) with the proportion of females, and eight pharmaceuticals (ATM, PRO, MTP, PAR, CBZ, VEN, EE2 and FEP) were significantly correlated ($p < 0.05$) with the proportion of the elderly population (aged > 60). Economic structure may also co-vary with consumption patterns. The number of large industrial enterprises was significantly associated ($p < 0.05$) with the consumption of ATM, PRO, MTP, PAR, VEN and FEP, while the proportion of the tertiary sector was significantly related ($p < 0.05$) to CAP, MTP, VEN and FEP. Although many other pharmaceuticals showed no statistically significant ($p > 0.05$) relationships with the four socioeconomic indicators, most exhibited similar directional trends, with higher consumption associated with greater proportions of females, elderly residents, tertiary industry presence and hospital capacity within the service area (**Figure S8a**). These results revealed that socioeconomic characteristics influence pharmaceutical-consumption patterns. For example, regions with larger elderly populations tended to have more chronic-pharmaceutical (PRO and MTP) consumption, and districts with higher gross domestic product (GDP) exhibited greater usage of hypolipidemic drug (GFB) (**Figure S8a**). Many studies have reported similar correlations between socioeconomic indicators and pharmaceutical consumption (Rousis et al., 2022; Luo et al., 2024; Anh et al., 2025), but still, such associations may be arisen from similar distribution patterns just by chance (He et al., 2024). Notably, these Spearman correlations describe service-aera-level co-variation. Socioeconomic indicators co-vary with each other and with unavailable factors, so the observed associations may arise from shared spatial or seasonal gradients rather than direct effects of any single driver. Besides, interpretations of such results/findings should be approached with caution, as correlations cannot be directly attributed to the existence of influence or a causal relationship.



418

419 **Figure 2.** Spatial variation (a) among nine WWTPs and seasonal variation (b) among four seasons of
420 human pharmaceuticals, the radar charts illustrate the seasonal variation of individual pharmaceuticals
421 (min-max normalization was performed for each pharmaceutical across four seasons. Thus, 0 and 1
422 indicate the lowest and highest seasonal levels). Different categories of pharmaceuticals are presented
423 in different colors in the radar charts: antibiotic (red), *β*-blocker (yellow), psychiatric medications
424 (green), and NSAID (blue).

To strengthen inference beyond pairwise correlations, we fitted linear mixed-effects models (LMMs) that accounted for repeated seasonal observations within each WWTP and used principal components analysis (PCA) to reduce multicollinearity among socioeconomic indicators (**Text S5**). PCA yielded two principal components (PC). PC1 captures aging and social service maturity, whereas PC2 reflects a trade-off between agglomeration pressure and per-capita affluence (**Table S13**). The LMM results indicated that PC1 dominated the socioeconomic signal. PC1 showed significant positive associations ($p < 0.05$) with consumption for 7 pharmaceuticals (PRO, FLU, PAX, CAP, RTM, LFX, and ATE, **Table S14** and **Figure S8b**), consistent with higher consumption in service areas with older (and more female) populations and more developed healthcare and social services. By contrast, PC2 explained variation for only a few pharmaceuticals (CLM and ATE, **Table S14** and **Figure S8b**). Only FEP and ATE showed a significant PC1 × PC2 interaction (**Table S14** and **Figure S8b**, $p < 0.05$**)**, indicating that the interaction effects were limited and that the PC1 and PC2 acted largely additively for the remaining compounds. Overall, the LMMs confirmed the directions suggested by the correlation analysis and provided a more robust, confounder-aware assessment of socioeconomic drivers.

Seasonal *PNDC*s of 19 pharmaceuticals were estimated (**Figure 2b** and **Table S15**), and pairwise seasonal comparisons of each compound are presented in **Figure S9**. Except for MTP, FEP and GFB, the seasonal variation in the consumption of other pharmaceuticals was statistically significant (K–H test, $p < 0.05$). Most of them (e.g., SCM, CLM, ATM, RTM, CAP, PRO, MTP, FLU, VEN, EE2 and IBP) exhibited higher consumption during the cold seasons. In contrast, LFX, FLX, PFX, ATE, PAX and CBZ showed greater consumption during the warm seasons.

Seasonal variation in pharmaceutical consumption largely reflected the clinical indications of individual pharmaceuticals. Acute illness medications showed seasonal peaks aligned with disease prevalence. Fluoroquinolones, commonly used for gastrointestinal and

urinary tract infections (Xu et al., 2022), exhibited higher consumption in summer, whereas antibiotics used for respiratory tract infections, peaked in winter. EE2, used for emergency contraception and menstrual regulation, also showed higher winter consumption. This aligns with observations of birth peaks in October-November in China (Zhang et al., 2023), suggesting that winter contraceptive use may play a critical role in shaping the reproductive cycle. In contrast, pharmaceuticals used for chronic conditions, such as antidepressants, *β*-blockers (ATE, MTP) and hypolipidemic drug (GFB), are typically taken continuously. As a result, these compounds exhibited limited or no seasonal variation in consumption.

3.2.3 Correlation of consumption among 19 human pharmaceuticals

Correlation analysis of the *PNDC* of 19 human pharmaceuticals (**Figure 3**) highlighted three types of co-variation in pharmaceutical consumption patterns: co-consumption pattern (positive correlation), inverse consumption pattern (negative correlation) and independent consumption pattern (no significant correlation). Several factors may explain the positive correlations. (1) Therapeutic substitution within pharmaceutical classes: For example, LFX and FLX, both quinolones, showed significantly correlated ($p < 0.05$) usage patterns, likely due to synchronized demand during outbreaks (Adriaenssens et al., 2011). Similarly, FLU and VEN, or PAR and VEN, may be used sequentially when selective serotonin reuptake inhibitors (SSRIs) are ineffective and serotonin-norepinephrine reuptake inhibitors (SNRIs) are introduced (Baldomero et al., 2005). (2) Co-prescription for comorbid conditions: Pharmaceuticals like ATE and LFX or FLX may be co-administered in elderly patients experiencing both infections and cardiovascular conditions, such as angina triggered by infections (Corrales-Medina et al., 2010). (3) Combination therapies for side-effect management: For instance, EE2 may be co-prescribed with ATE to mitigate contraceptive-related migraines (Endrikat et al., 1997). These patterns did not demonstrate causal links or individual-level co-prescription.

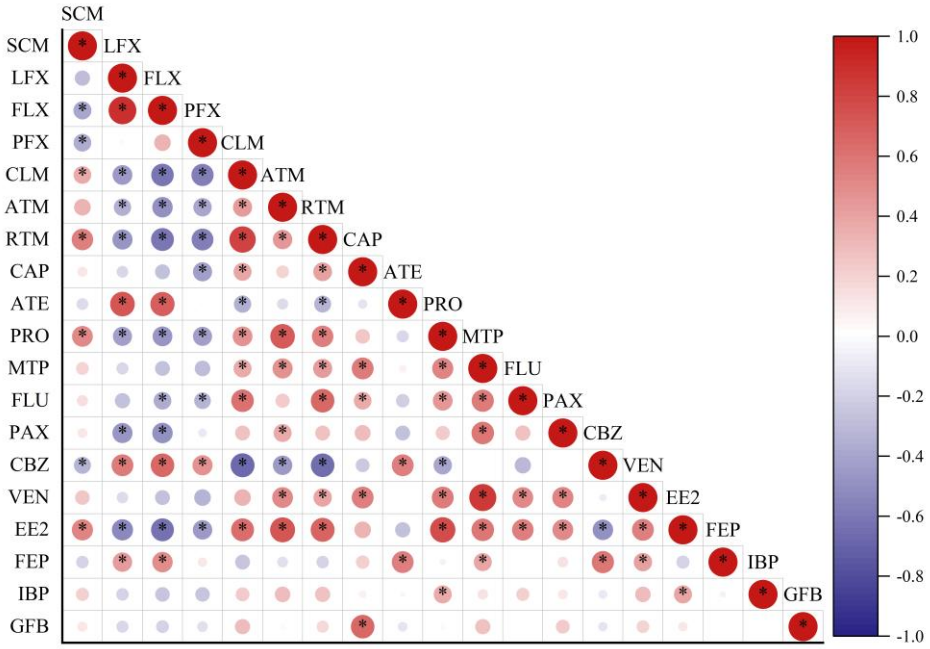


Figure 3. Spearman correlation between consumptions of different human pharmaceuticals (statistical significance was set at $p < 0.05$).

Negative correlations in pharmaceutical consumptions can arise from the following: (1) Contraindicated combinations: For example, co-use of quinolones and PRO can increase the risk of QT interval prolongation (Maideen et al., 2021); CBZ reduces the efficacy of EE2, increasing contraceptive failure risk (Davis et al., 2011); and co-administration of CBZ with CLM elevates CBZ plasma levels, potentially causing severe neurotoxicity (Connor and Fris, 1994). (2) Direct pharmacological substitution: Certain pharmaceuticals, such as ATM and FLX, are typically used as alternatives rather than in combination, where resistance profiles guide the selection of one over the other (Li et al., 2020).

3.3 Veterinary pharmaceutical consumption

3.3.1 Profiles of veterinary pharmaceutical consumption

Veterinary pharmaceuticals exhibited a clear stratified consumption pattern across the nine WWTPs (**Figure S10**): The primary tier (high consumption, >10.0 g/d) included EFX (average 47.6 g/d), MON (average 30.7 g/d), STZ (average 13.3 g/d) and FF (average 10.1 g/d); the

second tier (medium consumption, between 1.00 and 10.0 g/d) comprised MFX (average 3.33 g/d) and SMR (average 2.39 g/d), while the third tier (low consumption, <1.00 g/d) included TLS (average 0.25 g/d), OMP (average 0.18 g/d) and CTC (average 0.10 g/d). The PP contribution to the *Load* values of veterinary pharmaceuticals ranged from 0% (OMP) to 95.4% (EFX) (**Table S15**), with an overall average contribution of 29.8%.

High consumption of EFX and FF is consistent with their broad-spectrum activity and extensive use in livestock and aquaculture for infection control (Anadón et al., 2008; Lopez-Cadenas et al., 2013). In contrast, elevated STZ and SMR consumption reflects their high dosages requirements to achieve effective inhibitory concentration in animals (Fu, 1959).

In this study, MON was used as an indicator to estimate the number of livestock receiving veterinary pharmaceuticals. MON is primarily used as a growth promoter in ruminants and requires daily supplementation (Goodrich et al., 1984). Assuming that MON in Wuhan is exclusively used for promoting beef cattle growth, and based on a standard dosage of 150 mg/head/day (Lin et al., 2000), the estimated number of cattle treated with MON ranges from 0 to 2.46×10^3 (average: 204), which is substantially lower than the reported 25,332 head of beef cattle in Wuhan by the end of 2023 (WStatistics, 2024). Two main factors may account for this discrepancy: (1) Veterinary pharmaceuticals detected in municipal wastewater may not fully represent total veterinary pharmaceutical usage. These compounds are excreted via both urine and feces, but feces are often processed through composting or anaerobic digestion for use as fertilizer or biogas (Hong et al., 2023), while only a portion of the urine enters the municipal sewer system. (2) The nine WWTPs selected in this study primarily serve urban districts of Wuhan, where livestock farming is relatively limited.

Despite the aforementioned limitations, the consistent detection of all eight veterinary-exclusive pharmaceuticals indicates stable veterinary-related inputs to the influent within the study aera, likely originating from livestock feed additives, on-farm livestock medication and

517 veterinary pharmaceutical use in pet treatment (Zhou et al., 2012; Hong et al., 2023). Notably,
518 EFX, MFX, CTC, TLS and FF are classified as prescription-only veterinary pharmaceuticals.
519 Given the increasingly stringent regulations in China regarding the sale and use of such
520 pharmaceuticals (Zhu et al., 2024), their widespread occurrence suggests the potential
521 existence of intensive livestock operations in the region, with treated effluents from these
522 facilities being discharged into the municipal wastewater system.

523 ### 3.3.2 Spatial and seasonal variation of veterinary pharmaceutical
524 ### consumption

525 Spatial distribution of veterinary pharmaceutical usage (**Figure 4a**) across the service
526 areas of the nine WWTPs revealed significant regional differences in usage levels (*t*–test, $p <$
527 0.05). Notably, the WWTP LWZ exhibited the highest total veterinary pharmaceuticals
528 consumption, with an average consumption (559 g/d) approximately 1.3 times greater than the
529 combined usage of the other eight WWTPs (413 g/d). This result is consistent with the findings
530 of the cluster analysis (**Figure 4a**). WWTP LWZ is located in Wuhan's urban core (**Figure S1**),
531 where contributions from small-scale or backyard animal farming are limited (Li et al., 2021b).
532 This elevated usage likely results from either the presence of large-scale intensive livestock
533 operations within its service area or the inclusion of the region's largest agricultural and forestry
534 university. WWTPs NT (average, 131 g/d), SJT (average, 88.6 g/d) and BH (average, 85.6 g/d)
535 formed a second usage tier, while the remaining five WWTPs constituted the third tier (10.6
536 g/d (ZL) to 32.0 g/d (ELM). This result is consistent with the findings of the cluster analysis
537 (**Figure 4a**). These second-tier plants are generally located farther from the urban center,
538 consistent with the spatial development pattern in Wuhan, where primary industry (including
539 animal husbandry) is more prominent in suburban and rural areas (Li et al., 2021b).

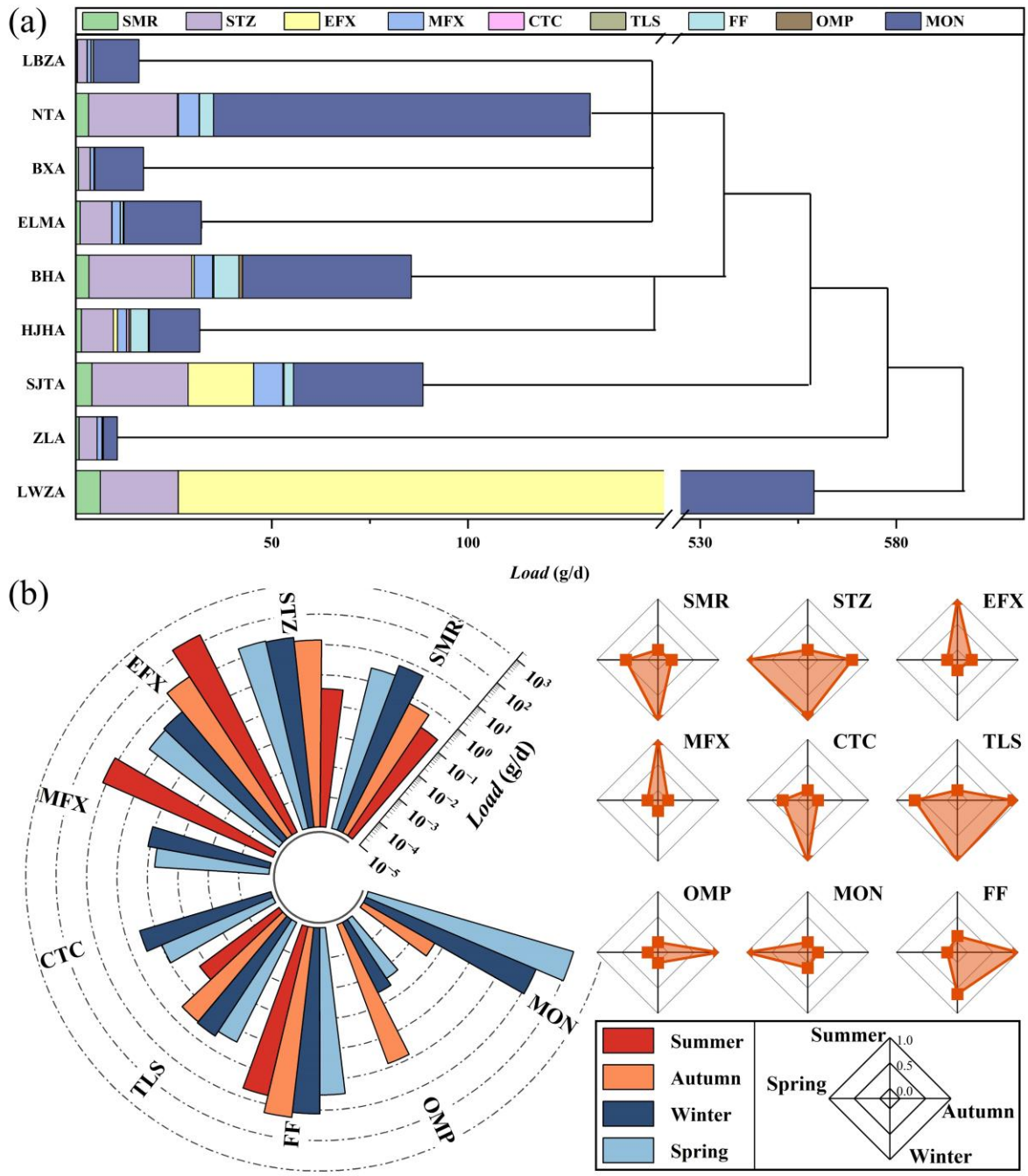


Figure 4. Spatial variation (a) among nine WWTPs and seasonal variation (b) among four seasons of veterinary pharmaceuticals' daily *Load*s, the radar charts illustrate the seasonal variation of individual pharmaceuticals (min-max normalization was performed for each pharmaceutical across four seasons. Thus, 0 and 1 indicate the lowest and highest seasonal levels). Antibiotics are shown in red in the radar charts.

Spatial variability was assessed using coefficients of variations (CV) for each veterinary pharmaceutical (**Table S15**). SMR and STZ showed relatively low CV values and were consistently detected across all WWTPs and seasons. Given that veterinary pharmaceutical inputs from intensive farms typically behave as point sources characterized by strong temporal and spatial variability, the widespread and stable presence of certain compounds suggests the existence of additional non-point source inputs. Such inputs may originate from smallholder farms, where diffuse discharges could enter municipal sewers via surface runoff or other indirect pathways.

Seasonal variation in the consumption of nine veterinary pharmaceuticals is shown in **Figure 4b** and **Table S15**. Five (SMR, STZ, MFX, TLS and MON) exhibited significant seasonal differences (K–H test, $p < 0.05$, **Figure S11**), while the remaining four showed no statistically significant variation (K–H test, $p > 0.05$). Of the five compounds with significant seasonal trends, four (STZ, SMR, TLS and MON) showed higher consumption during the cold season compared to the warm season. This pattern is consistent with that observed for human pharmaceuticals (***Section 3.2.2***) and is probably driven by the seasonal prevalence of diseases in livestock, which influences the demand for specific veterinary pharmaceuticals throughout the year (Du et al., 2022).

3.4 Human-veterinary shared pharmaceutical consumption

Correlation analysis between the 18 shared-use compounds and the 9 veterinary-exclusive pharmaceuticals (**Table 2**) showed that 83% of the shared-use compounds were significantly correlated ($p < 0.05$) with at least one veterinary pharmaceutical. Notably, SMX, SGN, SM, OTC, ERY and TAP exhibited significant correlations with more than 55% of the veterinary pharmaceuticals, suggesting a strong potential influence from animal-derived sources. Given the high likelihood of veterinary inputs being present in the influent, we assumed two extreme scenarios representing the minimum and maximum possible veterinary contributions (***Section***

571 ***2.4***). In Scenario 1, the contribution of veterinary source was set as zero. In Scenario 2, based
572 on the classification already established in ***Section 3.3.2***, where WWTPs were grouped into
573 high (LWZ), medium (BH, NT and SJT) and low (BX, ELM, HJH, LBZ and ZL) *Load*
574 categories, we assigned contribution of 100%, 50% and 20% to these groups, respectively. For
575 those WWTPs classified as "low" group, we assumed a non-zero contribution (20%, a
576 relatively high value to ensure maximum veterinary source), because veterinary
577 pharmaceuticals were detected in their influent. The 100%/50%/20% values used in Scenario
578 2 are logic-based parameters designed to define minimal-human cases. We informed these
579 values by the observed tiering of veterinary-exclusive pharmaceutical loads across WWTPs
580 rather than by livestock census data, which were not available. Accordingly, Scenario 2
581 provides bounding conditions to assess the potential bias from veterinary input rather than a
582 definitive quantitative apportionment.

583 The total *Load*s of human-veterinary shared pharmaceuticals were calculated separately
584 under the two scenarios (**Figure S12** and **Table S16**). The PP contribution to the *Load* values
585 of the shared pharmaceuticals ranged from 0.0% (TAP) to 96.6% (TTC) (**Table S16**), with an
586 overall average contribution of 35.9%. The *PNDC* values of pharmaceuticals under Scenario 2
587 were lower than those under Scenario 1. The highest average *PNDC*s were observed for two
588 NSAIDs (NAP and KEP, **Figure S12**). NAP exhibited the highest average *PNDC* in both
589 scenarios (Scenario 1, 5.47×10^3 mg/d/1000 inh; Scenario 2, 3.43×10^3 mg/d/1000 inh, **Table**
590 **S16**), significantly surpassing all other compounds (*t*–test, $p < 0.05$). Despite the more stringent
591 assumptions in Scenario 2, NAP consumption in this study (average 3.43×10^3 mg/d/1000 inh,
592 range 0 – 9.17×10^3 mg/day/1000 inh, **Table S16**) was still higher than the pre-COVID-19 levels
593 in Guangzhou, China (average 23.4 mg/d/1000 inh, range <MDL – 160.50 mg/day/1000 inh)
594 (Yan et al., 2021). The consumption of KEP (average 546 mg/day/1000 inh, range 0 – 1.53×10^3
595 mg/day/1000 inh, **Table S16**) in this study was relatively higher than a nationwide survey

(average 18.53 mg/day/1000 inh, range 0 – 4.39 mg/day/1000 inh) (He et al., 2024). This discrepancy may be attributed to the increased demand for NASIDs during the COVID-19 pandemic (Ferreira et al., 2023). Additionally, the inclusion of particulate-phase pharmaceuticals in the WBE calculation has contributed to the elevated consumption estimation. ERY, a macrolide antibiotic, had the highest *PNDC* (Scenario 1, 221 mg/d/1000 inh; Scenario 2, 144 mg/d/1000 inh, **Table S16**) among antibiotics. Previous studies in southern China reported comparable *PNDC*s for CLM and ERY (Xu et al., 2022). However, the average *PNDC* of CLM in this study was 5 to 8 times higher than that of ERY (**Figure S12)**. This discrepancy may be attributed to the higher hydrophobicity of CLM (log *Kow* = 3.18) relative to ERY (log *Kow* = 2.37, **Table S1**), which enhances its adsorption to particulate matter. Earlier WBE studies that quantified antibiotics only in the aqueous phase may therefore have underestimated CLM consumption due to the omission of particle-bound fractions.

Table 2. Correlation between consumption of 9 veterinary and 18 human-veterinary shared pharmaceuticals.

Veterinary pharmaceutical	Numbers of significantly correlated shared pharmaceuticals[a]
SMR	10
STZ	6
EFX	8
MFX	1
CTC	2
TLS	12
FF	7
OMP	0
MON	11

a: $p < 0.05$.

The ranking of shared pharmaceuticals by average *Loads* was consistent with the *PNDC*-based ranking under Scenario 1, whereas discrepancies emerged under Scenario 2. This is reasonable since the *PNDC* estimation does not account for the contribution of veterinary usage.

Further, the relative differences of individual pharmaceutical *Loads* between Scenario 1 and Scenario 2 were calculated (**Table S16**). They showed a significant positive correlation ($p < 0.05$) with the differences of excretion rates between human and animal. These findings demonstrated that excretion rate variations between human and animal can markedly influence *Load* estimation for shared-use pharmaceuticals. When veterinary contributions are neglected, the misestimation becomes more pronounced for pharmaceuticals with large interspecies differences in excretion.

Based on these results, we estimated the total average daily pharmaceutical consumption used for human- and animal-medication across nine WWTPs in Wuhan from July 2023 to April 2024 (**Tables S17** and **S18**). The consumption of 37 pharmaceuticals used for human medication ranged from 3.52×10^5 to 3.83×10^5 g/d, whereas that of 30 pharmaceuticals used for veterinary medication ranged from 9.77×10^2 to 4.26×10^3 g/d. Although the overall magnitude of veterinary pharmaceutical consumption was substantially lower than that of human pharmaceuticals, it still exerted a measurable influence on the estimation of human pharmaceutical *Loads*. When individual compounds were examined, this influence became more pronounced. Comparison of the average *PNDC* values between Scenario 2 and Scenario 1 showed relative differences of 54% to 109% for individual compounds. These results provide quantitative evidence veterinary inputs can materially affect WBE-based estimations of pharmaceutical consumption. They also highlight that the importance of accounting for human-veterinary shared pharmaceuticals to improve the accuracy of consumption assessments.

3.5 Limitations and practical implications for environmental management

We acknowledge that several limitations should be noted. First, excretion rates were unavailable for several pharmaceuticals, which prevented comprehensive calculation and interpretation of all target PPCPs. Moreover, excretion rates are not constant in the real world, their variability can propagate into fluctuations in back-calculated consumption estimations.

Holding other inputs constant, a ±20% change in excretion rates would translate into an approximately -16.7% to +25% change in the estimated consumption. Second, detailed livestock population statistics within each WWTP catchment were not available. As a result, *PNDCs* of animals and specific contribution of veterinary sources cannot be calculated in this study. Future work integrating GIS-based land-use data, land-cover information, field surveys and high-resolution imagery to quantify livestock production and the scale of animal hospital within each catchment, may enable more precise identification and quantitative apportionment of veterinary pharmaceutical sources.

Although the limitations existed, our results indicated that routine influent surveillance that targets dissolved-phase PPCPs alone may underestimate loads for particle-associated compounds, particularly for classes with high measured K_d (e.g., tetracyclines and quinolones), as current regulatory frameworks provide only limited criteria based on the PPCP concentrations and methodological guidance for PPCPs, particularly for PP-associated PPCPs. For example, China's Standard examination methods for drinking water (GB/T 5750-2023) (National Standardization Administration, 2023) does not include PPCPs as routine indicators, and organic-contaminant testing generally targets the dissolved fraction/phase of analytes. In the EU, the Urban Wastewater Treatment Directive (EU 2024/3019) (EU, 2024) introduces management/monitoring requirements for selected micropollutants, but it does not provide explicit analytical guidance or concentration-based criteria for micropollutants in the particulate phase. Based on our findings, we can now propose a more reliable monitoring guidance: WWTP monitoring programs should adopt both DP and PP sampling, particularly for compounds with high *K*ow or high site-specific K_d. These additions strengthen the translational value of our study and underscore the practical need to incorporate PP-associated PPCPs into routine monitoring.

4. CONCLUSIONS

This study demonstrated that PPCPs were widely present in both dissolved and particulate phases in the influent of WWTPs, with partitioning behavior closely related to environmental temperature and the physicochemical properties of individual compounds. Incorporating particulate-associated fractions is therefore essential for reducing substantial bias in WBE back-calculated consumption estimations, especially for compounds with high K_d or *K*ow. Human pharmaceutical consumption showed clear regional and seasonal variations driven by disease prevalence and socioeconomic factors, whereas veterinary pharmaceuticals was linked to intensive livestock farming in specific regions. Strong correlations between veterinary-exclusive and shared-use pharmaceuticals confirmed measurable animal-derived inputs. The daily *Load*s of human- and animal-medication were estimated under two extreme scenarios representing the minimum and maximum contribution from veterinary sources. The incorporation of veterinary sources exerted a non-negligible influence on *Load* estimations, with particularly pronounced effects for shared pharmaceuticals that exhibit differing excretion rates across human and animal. These findings highlight the need to explicitly account for particulate phase contributions and veterinary inputs to improve the accuracy and robustness of WBE applications in urban systems. The results further emphasize that for pharmaceuticals with large differences in excretion rates between humans and animals, unclear source apportionment could introduce substantial bias into WBE-based research.

CRediT authorship contribution statement

Zhe Qian: Investigation, Methodology, Data curation, Formal analysis, Visualization, Writing-original draft. **Jiapei Yi**: Investigation, Methodology, Data curation, Validation, Writing-review & editing. **Huanfang Huang**: Methodology, Resources, Writing-review & editing. **Zhenhao Wu**: Investigation, Methodology, Writing-review & editing. **Chi Zhang**: Methodology, Writing-review & editing. **Amily Wang Guenier**: Data curation, Writing-review

& editing. **Junwu Xiong**: Writing-review & editing. **Jianwei Bu**: Resources, Writing-review & editing. **Yuan Zhang**: Resources, Funding acquisition, Writing-review & editing. **Jiaquan Zhang**: Methodology, Writing-review & editing. **Shihua Qi**: Supervision, Resources, Writing-review & editing. **Kevin C. Jones**: Supervision, Writing-review & editing. **Wei Chen**: Conceptualization, Funding acquisition, Methodology, Data curation, Formal analysis, Resources, Supervision, Writing-review & editing.

Acknowledgements

The study was financially supported by National Natural Science Foundation of China (41907327), the Natural Science Foundation of Hubei (2019CFB372), Research Fund Program of Hubei Key Laboratory of Resources and Eco-Environment Geology (HBREGKFJJ-202301), Fundamental Research Funds (G1323523063 and G1323523150) for the Central Universities, China University of Geosciences (Wuhan). The authors thank Prof. Weijun Zhang, Yi Liu, Sihan Zeng, Yanni Wen, Junpeng Zhou and Dr. Hao Zhang for their assistance in sampling and sample pretreatment.

References

[1] Adriaenssens, N., Coenen, S., Versporten, A., Muller, A., Minalu, G., Faes, C., Vankerckhoven, V., Aerts, M., Hens, N., Molenberghs, G., and Goossens, H., 2011. European Surveillance of Antimicrobial Consumption (ESAC): Outpatient quinolone use in Europe (1997–2009). Journal of Antimicrobial Chemotherapy, 66(6):47-56.

[2] Anadón, A., Martínez, M.A., Martínez, M., Ríos, A., Caballero, V., Ares, I., and Martínez-Larrañaga, M.R., 2008. Plasma and tissue depletion of florfenicol and florfenicol-amine in chickens. Journal of Agricultural and Food Chemistry, 56(22):11049-11056.

[3] Anh, P.N., Ngo, H.K.T., Wang, Z., Nguyen, D.M., Binh, V.N., Kieu Anh, N.T., Yang, C., Trung, N.Q., and Thai, P.K., 2025. Six years of alcohol consumption in Hanoi, Vietnam, by wastewater analysis: Assessing changes impacted by socio-economical factors. Public Health, 245:105771.

[4] Aolin, H., Qin, L., Zhu, S., Hu, X., and Yin, D., 2024. Combined effects of pH and dissolved organic matter on the availability of pharmaceuticals and personal care products in aqueous environment. Science of The Total Environment, 929:172637.

[5] Baldomero, B.E., Ubago, G., Cercós, L.C., Ruiloba, V.J., Calvo, G.C., and López, P.R., 2005. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. Depression and Anxiety, 22(2):68-76.

[6] Beldean-Galea, M.S., Herghelegiu, M.-C., Combès, A., Vial, J., Tötös, R., Bruzzoniti, M.C., and Coman, M.-V., 2025. A surveillance of paracetamol and nonsteroidal anti-inflammatory drug consumption in Cluj-Napoca, Romania, using wastewater-based epidemiology. Metabolites, 15(9):576.

[7] Bernier-Turpin, G., Moilleron, R., Cenik, C., Alliot, F., Guérin-Rechdaoui, S., and Thiebault, T., 2025. Do suspended particles matter for wastewater-based epidemiology? Water Research, 280:123543.

[8] Bonnot, K., Benoit, P., Mamy, L., and Patureau, D., 2023. Transformation of PPCPs in the environment: Review of knowledge and classification of pathways according to parent molecule structures. Critical Reviews in Environmental Science and Technology, 53(1):47-69.

[9] Boxall, A.B., Rudd, M.A., Brooks, B.W., Caldwell, D.J., Choi, K., Hickmann, S., Innes, E., Ostapyk, K., Staveley, J.P., Verslycke, T., Ankley, G.T., Beazley, K.F., Belanger, S.E., Berninger, J.P., Carriquiriborde, P., Coors, A., Deleo, P.C., Dyer, S.D., Ericson, J.F., Gagne, F., Giesy, J.P., Gouin, T., Hallstrom, L., Karlsson, M.V., Larsson, D.G.J., Lazorchak, J.M., Mastrocco, F., McLaughlin, A., McMaster, M.E., Meyerhoff, R.D., Moore, R., Parrott, J.L., Snape, J.R., Murray-Smith, R., Servos, M.R., Sibley, P.K., Straub, J.O., Szabo, N.D., Topp, E., Tetreault, G.R., Trudeau, V.L., and Van Der Kraak, G., 2012. Pharmaceuticals and personal care products in the environment: What are the big questions? Environmental Health Perspectives, 120(9):1221-1229.

[10] Ceolotto, N., Jagadeesan, K., Xu, L., Standerwick, R., Robertson, M., Barden, R., Barnett, J., and Kasprzyk-Hordern, B., 2024a. Assessment of restriction measures implemented during COVID pandemics on community lifestyle choices via wastewater-based epidemiology. Journal of Hazardous Materials, 471:134264.

[11] Ceolotto, N., Jagadeesan, K., Xu, L., Standerwick, R., Robertson, M., Barden, R., Barnett, J., and Kasprzyk-Hordern, B., 2024b. Understanding treatment of pain during SARS-CoV-2 pandemic in a two-year intercity longitudinal study using wastewater-based epidemiology. Journal of Hazardous Materials, 471:134121.

[12] Chen, J., Venkatesan, A.K., and Halden, R.U., 2019. Alcohol and nicotine consumption trends in three US communities determined by wastewater-based epidemiology. Science of The Total Environment, 656:174-183.

[13] Chen, W., Huang, H., Chen, C.-E., Qi, S., Price, O.R., Zhang, H., Jones, K.C., and Sweetman, A.J., 2016. Simultaneous determination of 20 trace organic chemicals in waters by solid-phase extraction (SPE) with triple-quadrupole mass spectrometer (QqQ-MS) and hybrid quadrupole Orbitrap high resolution MS (Q-Orbitrap-HRMS). Chemosphere, 163:99-107.

[14] Chen, X., Lu, X., Zhao, R., Su, G., Meng, J., Li, Q., Hua, Y., and Shi, B., 2024. Occurrence and risks of PPCPs of a typical mountainous region: Implications for sustainable urban water systems. Science of The Total Environment, 951:175714.

[15] Chen, X., Yang, Y., Ke, Y., Chen, C., and Xie, S., 2022. A comprehensive review on biodegradation of tetracyclines: Current research progress and prospect. Science of The Total Environment, 814:152852.

[16] Cheng, D., Xie, Y., Yu, Y., Liu, X., Zhao, S., Cui, B., and Bai, J., 2016. Occurrence and partitioning of antibiotics in the water column and bottom sediments from the intertidal zone in the Bohai Bay, China. Wetlands, 36(1):167-179.

[17] Choi, P.M., O'Brien, J.W., Tscharke, B.J., Mueller, J.F., Thomas, K.V., and Samanipour, S., 2020. Population socioeconomics predicted using wastewater. Environmental Science & Technology Letters, 7(8):567-572.

[18] Connor, N.K., and Fris, J., 1994. Clarithromycin-carbamazepine interaction in a clinical setting. The Journal of the American Board of Family Practice, 7(6):489.

[19] China Institute of Veterinary Drug Control, 2025. National database of veterinary drugs. http://vdts.ivdc.org.cn:8099/cx/.

[20] Corrales-Medina, V.F., Madjid, M., and Musher, D.M., 2010. Role of acute infection in triggering acute coronary syndromes. The Lancet Infectious Diseases, 10(2):83-92.

[21] Davis, A.R., Westhoff, C.L., and Stanczyk, F.Z., 2011. Carbamazepine coadministration with an oral contraceptive: Effects on steroid pharmacokinetics, ovulation, and bleeding. Epilepsia, 52(2):243-247.

[22] Dell'Osso, B., Di Nicola, M., Cipelli, R., Peduto, I., Pugliese, A.C., Signorelli, M.S., Ventriglio, A., and Martinotti, G., 2022. Antidepressant prescription for major depressive disorder: Results from a population-based study in Italy. Current Neuropharmacology, 20(12):2381-2392.

[23] Du, D., Zhou, J., Zhang, K., and Zhi, S., 2022. Seasonal pollution characteristics of antibiotics on pig farms of different scales. International journal of environmental research and public health, 19(14):8264.

[24] Du, J., Xu, J., Luo, Y., Li, X., Zhao, L., Liu, S., Jia, X., Wang, Z., Ge, L., Cui, K., Ga, Y., Zhu, M., Ji, T., Huang, Z., and Xia, X., 2025. High-Throughput monitoring of 323 pharmaceuticals and personal care products (PPCPs) and pesticides in surface water for environmental risk assessment. Environmental Science & Technology, 59(22):11275-11285.

[25] Duan, L., Zhang, Y., Wang, B., Yu, G., Gao, J., Cagnetta, G., Huang, C., and Zhai, N., 2022. Wastewater surveillance for 168 pharmaceuticals and metabolites in a WWTP: Occurrence, temporal variations and feasibility of metabolic biomarkers for intake estimation. Water Research, 216:118321.

[26] Endrikat, J., Müller, U., and Düsterberg, B., 1997. A twelve-month comparative clinical investigation of two low-dose oral contraceptives containing 20 µg ethinylestradiol/75 µg gestodene and 30 µg ethinylestradiol/75 µg gestodene, with respect to efficacy, cycle control, and tolerance. Contraception, 55(3):131-137.

[27] EU. 2024. Directive (Eu) 2024/3019 of The European parliament and of The council of 27 November 2024 concerning urban wastewater treatment. https://eur-lex.europa.eu/eli/dir/2024/3019/oj/eng.

[28] Ferreira, B.L., Ferreira, D.P., Borges, S.F., Ferreira, A.M., Holanda, F.H., Ucella-Filho, J.G.M., Cruz, R.S., Birolli, W.G., Luque, R., and Ferreira, I.M., 2023. Diclofenac, ibuprofen, and paracetamol biodegradation: Overconsumed non-steroidal anti-inflammatories drugs at COVID-19 pandemic. Frontiers in Microbiology, 14:1207664.

[29] Fu, Z., 1959. The application of sulfonamides (in Chinese). People's Medical Publishing House.

[30] Gago-Ferrero, P., Borova, V., Dasenaki, M.E., and Thomaidis, N.S., 2015. Simultaneous determination of 148 pharmaceuticals and illicit drugs in sewage sludge based on ultrasound-assisted extraction and liquid chromatography–tandem mass spectrometry. Analytical and Bioanalytical Chemistry, 407(15):4287-4297.

[31] Gao, J., Zheng, Q., Lai, F.Y., Gartner, C., Du, P., Ren, Y., Li, X., Wang, D., Mueller, J.F., and Thai, P.K., 2020. Using wastewater-based epidemiology to estimate consumption of alcohol and nicotine in major cities of China in 2014 and 2016. Environment International, 136:105492.

[32] Gerrity, D., Crank, K., Oh, E.C., Quinones, O., Trenholm, R.A., and Vanderford, B.J., 2024. Wastewater surveillance of high risk substances in Southern Nevada: Sucralose normalization to translate data for potential public health action. Science of The Total Environment, 908:168369.

[33] Goldberg, E.E., Lin, Q., Romero-Severson, E.O., and Ke, R., 2023. Swift and extensive Omicron outbreak in China after sudden exit from ‘zero-COVID’ policy. Nature Communications, 14(1):3888.

[34] Goodrich, R.D., Garrett, J.E., Gast, D.R., Kirick, M.A., Larson, D.A., and Meiske, J.C., 1984. Influence of monensin on the performance of cattle. Journal of Animal Science, 58(6):1484-1498.

[35] Harrower, J., McNaughtan, M., Hunter, C., Hough, R., Zhang, Z., and Helwig, K., 2021. Chemical fate and partitioning behavior of antibiotics in the aquatic environment—A review. Environmental Toxicology and Chemistry, 40(12):3275-3298.

[36] He, R., Chen, L., Mu, H., Ren, H., and Wu, B., 2024. Correlations between China's socioeconomic status, disease burdens, and pharmaceuticals and personal care product levels in wastewater. Journal of Hazardous Materials, 463:132867.

[37] Holton, E., Sims, N., Jagadeesan, K., Standerwick, R., and Kasprzyk-Hordern, B., 2022. Quantifying community-wide antimicrobials usage via wastewater-based epidemiology. Journal of Hazardous Materials, 436:129001.

[38] Hong, B., Li, Q., Li, J., Zhou, M., Wang, X., He, B., and Yu, S., 2023. Spectrum of pharmaceutical residues in commercial manure-based organic fertilizers from multi-provinces of China mainland in relation to animal farming and possible environmental risks of fertilization. Science of The Total Environment, 894:165029.

[39] Hu, Y., Li, L., Li, B., Peng, L., Xu, Y., Zhou, X., Li, R., and Song, K., 2023. Spatial variations and ecological risks assessment of pharmaceuticals and personal care products (PPCPs) in typical lakes of Wuhan, China. Process Safety and Environmental Protection, 174:828-837.

[40] Kim, K.Y., and Oh, J.-E., 2020. Evaluation of pharmaceutical abuse and illicit drug use in South Korea by wastewater-based epidemiology. Journal of Hazardous Materials, 396:122622.

[41] Lei, K., Zhu, Y., Chen, W., Pan, H.-Y., Guo, B.-B., Zhang, X., Cao, Y.-X., Sweetman, A.J., and Lin, C.-Y., 2018. The occurrence of home and personal care products in the Haihe River catchment and estimation of human exposure. Science of The Total Environment, 643:63-72.

[42] Li, B., and Zhang, T., 2010. Biodegradation and adsorption of antibiotics in the activated sludge process. Environmental Science & Technology, 44(9):3468-3473.

[43] Li, D., O'Brien, J.W., Tscharke, B.J., Choi, P.M., Ahmed, F., Thompson, J., Mueller, J.F., Sun, H., and Thomas, K.V., 2021a. Trends in artificial sweetener consumption: A 7-year wastewater-based epidemiology study in Queensland, Australia. Science of The Total Environment, 754:142438.

852 [44] Li, D., Wang, X.L., and Sun, Y.H., 2020. Cost-effectiveness analysis of three schemes
853 in treatment of Patients with nongonococcal urethritis (in Chinese). Chinese Journal of Clinical
854 Pharmacology and Therapeutics, 8(6):692-695.

855 [45] Li, D., Zheng, Q., Thomas, K.V., Dang, A.K., Binh, V.N., Anh, N.T.K., and Thai, P.K.,
856 2023. Use of artificial sweeteners and caffeine in a population of Hanoi: An assessment by
857 wastewater-based epidemiology. Science of The Total Environment, 868:161515.

858 [46] Li, J., Li, W., Liu, K., Guo, Y., Ding, C., Han, J., and Li, P., 2022. Global review of
859 macrolide antibiotics in the aquatic environment: Sources, occurrence, fate, ecotoxicity, and
860 risk assessment. Journal of Hazardous Materials, 439:129628.

861 [47] Li, Z., Jiao, L., Zhang, B., Xu, G., and Liu, J., 2021b. Understanding the pattern and
862 mechanism of spatial concentration of urban land use, population and economic activities: A
863 case study in Wuhan, China. Geo-spatial Information Science, 24(4):678-694.

864 [48] Li, Z., Li, J., Hu, Y., Yan, Y., Tang, S., Ma, R., and Li, L., 2024. Evaluation of
865 pharmaceutical consumption between urban and suburban catchments in China by wastewater-
866 based epidemiology. Environmental Research, 250:118544.

867 [49] Lin, H., Li, H., Chen, L., Li, L., Yin, L., Lee, H., and Yang, Z., 2018. Mass loading
868 and emission of thirty-seven pharmaceuticals in a typical municipal wastewater treatment plant
869 in Hunan Province, Southern China. Ecotoxicology and Environmental Safety, 147:530-536.

870 [50] Lin, X., Xie, Y., Wang, Z., Li, F., and Gao, X., 2000. Application of monensin in
871 livestock production (in Chinese). Journal of Yello Cattle Science, 26(3):1001-9111.

872 [51] Lopez-Cadenas, C., Sierra-Vega, M., Garcia-Vieitez, J.J., Diez-Liebana, M.J.,
873 Sahagun-Prieto, A., and Fernandez- Martinez, N., 2013. Enrofloxacin: Pharmacokinetics and
874 metabolism in domestic animal species. Current Drug Metabolism, 14(10):1042-1058.

875 [52] Lu, H., Fan, J., Guo, C., Yang, J., Zhang, H., Chen, M., Liu, Y., Liu, W., and Xu, J.,
876 2023. Estimating the prevalence of depression using wastewater-based epidemiology: A case
877 study in Qinghai Province, West China. Science of The Total Environment, 882:163303.

878 [53] Luo, X., Han, S., Wang, Y., Du, P., Li, X., and Thai, P.K., 2024. Significant differences
879 in usage of antibiotics in three Chinese cities measured by wastewater-based epidemiology.
880 Water Research, 254:121335.

881 [54] Ma, R., Wang, B., Yin, L., Zhang, Y., Deng, S., Huang, J., Wang, Y., and Yu, G., 2017.
882 Characterization of pharmaceutically active compounds in Beijing, China: Occurrence pattern,
883 spatiotemporal distribution and its environmental implication. Journal of Hazardous Materials,
884 323:147-155.

885 [55] Maideen, N.M.P., Rajkapoor, B., Muthusamy, S., Ramanathan, S., Thangadurai, S.A.,
886 and Sughir, A.A., 2021. A Review on pharmacokinetic and pharmacodynamic drug interactions

of adrenergic β-blockers with clinically relevant drugs-An overview. Current Drug Metabolism, 22(9):672-682.

[56] Mao, K., Yang, Z., Zhang, H., Li, X., and Cooper, J.M., 2021. Paper-based nanosensors to evaluate community-wide illicit drug use for wastewater-based epidemiology. Water Research, 189:116559.

[57] Mao, X., Huang, Y., Huo, Z.T., Guo, J., Li, C., and Huang, F.C., 2025. Occurrence, migration, and ecological risk assessment of neonicotinoid insecticides in water and sediments of Dongting Lake, China. China Geology, 8(3):550-559.

[58] Martényi, F., Dossenbach, M., Mraz, K., and Metcalfe, S., 2001. Gender differences in the efficacy of fluoxetine and maprotiline in depressed patients: A double-blind trial of antidepressants with serotonergic or norepinephrinergic reuptake inhibition profile. European Neuropsychopharmacology, 11(3):227-232.

[59] Martínez-Alcalá, I., Guillén-Navarro, J.M., and Fernández-López, C., 2017. Pharmaceutical biological degradation, sorption and mass balance determination in a conventional activated-sludge wastewater treatment plant from Murcia, Spain. Chemical Engineering Journal, 316:332-340.

[60] Ministry of Ecology and Environment of the People's Republic of China, 1989. Water Quality-Determination of Total Phosphorus-Ammonium Molybdate Spectrophotometric Method. https://www.mee.gov.cn/ywgz/fgbz/bz/bzwb/jcffbz/199007/t19900701_67131.shtml.

[61] Milosavljević, J.Z., Milosavljević, M.N., Arsenijević, P.S., Milentijević, M.N., and Stefanović, S.M., 2022. The effects of selective serotonin reuptake inhibitors on male and female fertility: A brief literature review. International Journal of Psychiatry in Clinical Practice, 26(1):43-49.

[62] Morvan, M., Jacomo, A.L., Souque, C., Wade, M.J., Hoffmann, T., Pouwels, K., Lilley, C., Singer, A.C., Porter, J., Evens, N.P., Walker, D.I., Bunce, J.T., Engeli, A., Grimsley, J., O'Reilly, K.M., and Danon, L., 2022. An analysis of 45 large-scale wastewater sites in England to estimate SARS-CoV-2 community prevalence. Nature Communications, 13(1):4313.

[63] National Standardization Administration, 2023. Standard examination methods for drinking water (GB/T 5750-2023). https://openstd.samr.gov.cn/bzgk/gb/newGbInfo?hcno=7F76F47FDE2925B21571DCB6C6C8B5DC.

[64] NMPA. 2025. Datrasearch of drugs. https://www.nmpa.gov.cn/datasearch/home-index.html#category=yp

[65] Ohoro, C.R., Adeniji, A.O., Elsheikh, E.A.E., Al-Marzouqi, A., Otim, M., Okoh, O.O., and Okoh, A.I., 2022. Influence of physicochemical parameters on PPCP occurrences in the wetlands. Environmental Monitoring and Assessment, 194(5):339.

[66] Proctor, K., Petrie, B., Lopardo, L., Muñoz, D.C., Rice, J., Barden, R., Arnot, T., and Kasprzyk-Hordern, B., 2021. Micropollutant fluxes in urban environment – A catchment perspective. Journal of Hazardous Materials, 401:123745.

[67] Randazzo, W., Truchado, P., Cuevas-Ferrando, E., Simón, P., Allende, A., and Sánchez, G., 2020. SARS-CoV-2 RNA in wastewater anticipated COVID-19 occurrence in a low prevalence area. Water Research, 181:115942.

[68] Rousis, N.I., Li, Z., Bade, R., McLachlan, M.S., Mueller, J.F., O'Brien, J.W., Samanipour, S., Tscharke, B.J., Thomaidis, N.S., and Thomas, K.V., 2022. Socioeconomic status and public health in Australia: A wastewater-based study. Environment International, 167:107436.

[69] Shao, X.T., Liu, S.Y., Zhao, Y.T., Jiang, B., Lin, J.G., and Wang, D.G., 2023. Evaluation of eight psychoactive drugs used in Chinese cities by wastewater-based epidemiology. Science of The Total Environment, 855:158982.

[70] Shimko, K.M., O'Brien, J.W., Tscharke, B.J., Brooker, L., Goebel, C., Shiels, R., Speers, N., Mueller, J.F., and Thomas, K.V., 2023. Emergence and occurrence of performance-enhancing substance use in Australia determined by wastewater analysis. Nature Water, 1(10):879-886.

[71] Song, S., Zhang, X., Zhou, J., and Li, R., 2017. Simultaneous determination of 12 antibiotics in sewage sludge by ultra performance liquid chromatography-electrospray ionization tandem mass spectrometry (in Chinese). Environmental Chemistry, 36(09):1923-1931.

[72] Stanczyk, F.Z., 2024. Metabolism of endogenous and exogenous estrogens in women. The Journal of Steroid Biochemistry and Molecular Biology, 242:106539.

[73] Sun, Q., Lv, M., Hu, A., Yang, X., and Yu, C.P., 2014. Seasonal variation in the occurrence and removal of pharmaceuticals and personal care products in a wastewater treatment plant in Xiamen, China. Journal of Hazardous Materials, 277:69-75.

[74] Thomas, K.V., Amador, A., Baz-Lomba, J.A., and Reid, M., 2017. Use of mobile device data to better estimate dynamic population size for wastewater-based epidemiology. Environmental Science & Technology, 51(19):11363-11370.

[75] Tran, N.H., Reinhard, M., and Gin, K.Y.-H., 2018. Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions-A review. Water Research, 133:182-207.

[76] Wang, B., Xu, Z., and Dong, B., 2024. Occurrence, fate, and ecological risk of antibiotics in wastewater treatment plants in China: A review. Journal of Hazardous Materials, 469:133925.

[77] Wuhan Bureau of Statistics, 2024. Wuhan Statistical Yearbook 2024 (in Chinese). https://tjj.wuhan.gov.cn/tjfw/tjnj/202511/t20251111_2675660.shtml.

[78] Xu, J., Zhang, Y., Zhou, C., Guo, C., Wang, D., Du, P., Luo, Y., Wan, J., and Meng, W., 2014. Distribution, sources and composition of antibiotics in sediment, overlying water and pore water from Taihu Lake, China. Science of The Total Environment, 497-498:267-273.

[79] Xu, L., Zang, J., Cong, W., Holton, E., Jiang, L., Sheppard, S.K., Wang, Y., Wang, N., Weeks, J., Fu, C., Jiang, Q., Lambert, H., and Kasprzyk-Hordern, B., 2022. Assessment of community-wide antimicrobials usage in Eastern China using wastewater-based epidemiology. Water Research, 222:118942.

[80] Yan, J., Lin, W., Gao, Z., and Ren, Y., 2021. Use of selected NSAIDs in Guangzhou and other cities in the world as identified by wastewater analysis. Chemosphere, 279:130529.

[81] Yan, Y., An, W., Mei, S., Zhu, Q., Li, C., Yang, L., Zhao, Z., and Huo, J., 2024. Real-world research on beta-blocker usage trends in China and safety exploration based on the FDA Adverse Event Reporting System (FAERS). BMC Pharmacology and Toxicology, 25(1):86.

[82] Yang, Y., Geng, X., Liu, X., Wen, X., Wu, R., Cui, D., and Mao, Z., 2022. Antibiotic use in China's public healthcare institutions during the COVID-19 pandemic: An analysis of nationwide procurement data, 2018–2020. Frontiers in Pharmacology, 13:813213.

[83] Yi, J., Huang, X., Hou, J., Xiong, J., Qian, Z., Liu, S., Zhang, J., Yin, D., Li, J., Su, Q., Qi, S., and Chen, W., 2023. Occurrence and distribution of PPCPs in water from two largest urban lakes of China: First perspective from DGT in-situ measurement. Science of The Total Environment, 904:166656.

[84] Yu, C., Zhang, J., Fu, X., Zhou, B., Huang, J., Qin, J., and Li, X., 2025. Wastewater-based monitoring of antipyretics use during COVID-19 outbreak in China and its associated ecological risks. Environmental Research, 267:120680.

[85] Yu, Y., Wang, Z., Yao, B., and Zhou, Y., 2024. Occurrence, bioaccumulation, fate, and risk assessment of emerging pollutants in aquatic environments: A review. Science of The Total Environment, 923:171388.

[86] Zhang, C., Wang, D., and Zhang, X., 2023. Which month to give a birth? The analysis on birth seasonality of China. China Population and Development Studies, 7(3):220-238.

[87] Zhao, H., Lyu, Y., Hu, J., Li, M., Chen, H., Jiang, Y., Tang, M., Wu, Y., and Sun, W., 2023. Reveal the major factors controlling quinolone adsorption on mesoporous carbon: Batch

experiment, DFT calculation, MD simulation, and machine learning modeling. Chemical Engineering Journal, 463:142486.

[88] Zhao, M., Chang, L., Yu, J., Wang, J., Song, Y., Su, S., Chen, C., Lun, Y., Cheng, F., Zhao, Y., and Zhou, C., 2024. A multicenter retrospective study of antidepressant use in outpatient clinics in China pre- and post-COVID. International Journal of Clinical Pharmacy, 46(5):1215-1224.

[89] Zheng, Q.D., Wang, Z., Liu, C.Y., Yan, J.H., Pei, W., Wang, Z., and Wang, D.G., 2019. Applying a population model based on hydrochemical parameters in wastewater-based epidemiology. Science of The Total Environment, 657:466-475.

[90] Zhou, L.J., Ying, G.G., Liu, S., Zhao, J.L., Chen, F., Zhang, R.Q., Peng, F.Q., and Zhang, Q.Q., 2012. Simultaneous determination of human and veterinary antibiotics in various environmental matrices by rapid resolution liquid chromatography–electrospray ionization tandem mass spectrometry. Journal of Chromatography A, 1244:123-138.

[91] Zhu, W., Chen, J., Liang, X., Li, D., and Chen, K., 2024. Government regulations, benefit perceptions, and safe production behaviors of family farms – A survey based on Jiangxi Province, China. Journal of Cleaner Production, 450:141824.

[92] Zhu, Y., Qiao, Y., Dai, R., Hu, X., and Li, X., 2021. Trends and patterns of antibiotics use in China's urban tertiary hospitals, 2016–19. Frontiers in Pharmacology, 12:757309.