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Environmental Impact

Residual pharmaceuticals in the environment pose a serious threat to human health and aquatic ecosystems. Municipal wastewater treatment plants (WWTPs) are major barriers to the release of pharmaceuticals and their metabolites from wastewater to aquatic environment. In the present study, the fate and potential removal pathways of 30 pharmaceuticals of multiple classes in two WWTPs (conventional vs. upgraded) located in East China were clarified based on mass balance analysis, and their ecological risks to aquatic environment were assessed using calculated risk quotients. This study helps understand the behavior and fate of pharmaceuticals in WWTPs as well as the ecological risks induced by effluent discharge and sludge disposal, thus providing useful information for better control of micro-pollutants in WWTPs.

Distribution, mass load and environmental impact of multiple-class pharmaceuticals in conventional and upgraded municipal wastewater treatment plants in East China

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ABSTRACT

The occurrence, fate and environmental impact of 30 pharmaceuticals including sulfonamides, fluoroquinolones, tetracyclines, macrolides, dihydrofolate reductase inhibitors, β-blockers, antiepileptics, lipid regulators, and stimulants were studied in two municipal wastewater treatment plants (WWTPs) located in Wuxi City, East China. A total of 23 pharmaceuticals were detected in wastewater samples, with a maximum concentration of 16.1 μg L^{-1} (caffeine) in influent and 615.5 ng L^{-1} (azithromycin) in effluent; 19 pharmaceuticals were detected in sludge samples at concentrations up to 12.13 mg kg^{-1}, with ofloxacin, azithromycin and norfloxacin being the predominant species. Mass balance analysis showed that biodegradation primarily accounted for the removal of sulfonamides, most of the macrolides, and other miscellaneous pharmaceuticals, while adsorption onto sludge was the primary removal pathway for fluoroquinolones, tetracylines, and azithromycin during biological treatment. The total mass loads of target pharmaceuticals per capita in the two WWTPs were in the ranges of 2681.8–4333.3, 248.0–416.6 and 214.6–374.5 μg d^{-1} $inhabitant^{-1}$ in the influent, effluent and dewatered sludge, respectively. The upgraded Plant A adopting the combined anaerobic/anoxic/oxic and moving bed biofilm process exhibited a much higher removal of target pharmaceuticals than the conventional Plant B adopting the C-Orbal oxidation ditch process. The concentration levels of sulfamethoxazole, ofloxacin, ciprofloxacin and clarithromycin in the effluent, ofloxacin in the sludge, and the mixture of all target pharmaceuticals in both effluent and sludge posed a high risk to algae in aquatic environment.

***Keywords**:* Pharmaceuticals, wastewater treatment plant, mass balance, fate, ecological risk

1. Introduction

Pharmaceuticals which contain diverse groups of organic compounds, such as antibiotics, anti-inflammatories/analgesics, antiepileptics, steroid compounds, β-blockers, lipid-regulating agents, and H2-receptor antagonists, have attracted considerable attention in recent years because of their potential undesirable effects on human health and aquatic ecosystems.[1] These pharmaceuticals cannot be metabolized completely in human and animal bodies, but are excreted as parent compounds, metabolites or conjugates via urine and feces into the sewer systems.[2]

Municipal wastewater treatment plants (WWTPs) are major barriers to the release of pharmaceuticals and their metabolites from wastewater to aquatic environment. However, WWTPs are not specifically designed to eliminate pharmaceuticals, but are built to remove biodegradable carbon, nitrogen, phosphorus, and pathogens. WWTPs have limited capability in removing pharmaceuticals from wastewater.[3,4] Most pharmaceuticals are consistently present in effluent because of their hydrophilic and recalcitrant properties, some of which such as carbamazepine (CBZ), diclofenac and metoprolol (MET) are even more abundant in effluent than in influent.[5,6] Some pharmaceuticals, especially the hydrophobic ones, are prone to release into the environment through sludge disposal because of their limited mobility and low biodegradability in sludge.[7] Therefore, determining the concentrations of residual pharmaceuticals in both effluent and sludge can provide an important indication of their pollution levels in the environment.

The occurrence and behavior of various pharmaceuticals in WWTPs have been well investigated in America, Europe, Australia, and Asia.[8] Their concentrations and distributions vary from country to country because of the differences in usage patterns. Meanwhile, their removal efficiencies also vary significantly in different WWTPs, as affected by the compound-specific properties and the treatment processes adopted. China, as the world's largest producer and user of pharmaceutical products, consumes more than 25000 tons of antibiotics each year.[9] This usage pattern may result in significant occurrence and wide distribution of pharmaceuticals in the environment. In

recent years, many WWTPs have upgraded their biological treatment process to improve the removal efficiency of chemical oxygen demand, nitrogen and phosphorus.[10,11] To date, most studies only focus on determination of pharmaceuticals present in wastewater in conventional WWTPs;[12-15] whereas the fate and mass load of pharmaceuticals in both wastewater and sludge in upgraded WWTPs are rarely reported. As a result, this work aimed to investigate the occurrence and behavior of 30 target pharmaceuticals, including sulfonamides (SAs), fluoroquinolones (FQs), tetracyclines (TCs), macrolides (MLs), dihydrofolate reductase inhibitors, β-blockers, antiepileptics, lipid regulators, and stimulants, in two WWTPs with different treatment processes in Wuxi City, East China. Mass balance analysis was performed to clarify the fate of pharmaceuticals and to explore their potential removal pathways in the conventional and upgraded WWTPs. The ecological risks induced by residual pharmaceuticals to aquatic environment were also assessed based on calculated risk quotients (RQs). This study provides useful information to WWTPs for better control of micro-pollutants.

2. Materials and methods

2.1. Chemicals

The standards for sulfadiazine (SDZ), sulfathiazole (STZ), sulfamerazine (SMR), sulfamethizole (SML), sulfamethoxazole (SMX), sulfisoxazole (SFX), sulfamethazine (SMN), sulfadimethoxine (SDM), trimethoprim (TMP), ofloxacin (OLF), norfloxacin (NOR), ciprofloxacin (CIP), enrofloxacin (ENR), MET, propranolol (PROP), CBZ, erythromycin (ERY), clarithromycin (CLA), roxithromycin (ROX), bezafibrate (BF), and atenolol (ATE) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Lomefloxacin (LOM), oxytetracycline (OTC), chlortetracycline (CTC), tetracycline (TCN), doxycycline (DOX), tiamulin (TIA), tylosin (TYL), azithromycin (AZN), and caffeine (CAF) were provided by Dr. Ehrenstorfer GmbH (Augsburg, Germany). Sulfamethazine-$^{13}C_6$ hemihydrate (SMN-$^{13}C_6$) and ofloxacin-D_3 (OLF-D_3) from Witega (Berlin, Germany), caffeine-$^{13}C_3$ (CAF-$^{13}C_3$) from Cerilliant (Round Rock, TX, USA), and demeclocycline (DMC) from Dr. Ehrenstorfer GmbH (Augsburg,

Germany), were used as internal standards. All of the standards were of the highest purity available (≥ 98%), and their major physicochemical properties are summarized in Table S1.

HPLC-grade methanol and formic acid (> 99%) were obtained from Fisher Scientific (Geel, Belgium) and Dikma Technologies, Inc. (Lake Forest, CA, USA), respectively. Ultrapure water was produced by Milli-Q water purification system (Advantage A10, Millipore, Billerica, MA, USA). Anhydro-erythromycin (ERY-H_2O), a major degradation byproduct of ERY, was prepared using the method introduced by McArdell *et al.*[16] Stock solutions of individual compounds and internal standards were prepared in methanol and stored in amber glass bottles at –20 ºC. The working solutions with different concentrations were prepared immediately before use by diluting the stock solutions.

2.2. Sample collection

Samples were collected from two full-scale municipal WWTPs (referred as Plants A and B) in Wuxi City, Jiangsu Province. Plant A serves about 820,000 inhabitants and treats about 200,000 m^3 d^{-1} of mainly domestic wastewater. This plant was upgraded in 2008 and was one of the first upgraded WWTPs in China. For the upgrade, moving bed biofilm reactor (MBBR) was added to the original biological treatment to enhance pollutant removal. As a result, the effluent discharge quality was raised from Level 1-B to Level 1-A according to the Discharge Standard of Pollutants for Municipal Wastewater Treatment Plant in China (GB 18918–2002). The wastewater treatment processes in Plant A consist of screen, horizontal-flow grit chamber, an upgraded anoxic/anaerobic/oxic (A/A/O) and MBBR process, and secondary clarifier. The secondary effluent is treated further with rotary fiber disc filters (RFDFs) before discharge to a receiving river. Plant B serves about 660,000 inhabitants and treats about 150,000 m^3 d^{-1} of mixed domestic and industrial wastewater. The treatment processes in Plant B comprise screen, rotational-flow grit chamber, C-Orbal oxidation ditch (OD), and secondary clarifier. The secondary effluent is treated further with UV disinfection and RFDFs before discharge to constructed wetlands. The schematic diagram of the two WWTPs is shown in Fig. 1,

and the operational parameters and the characteristics of wastewater and sludge are presented in Tables S2 and S3, respectively.

Fig. 1

Wastewater and sludge samples were collected from the two WWTPs during November 10–30, 2013, and the sampling points along the treatment processes are illustrated in Fig. 1. During this sampling period, the wastewater temperature in different treatment units was in the range of 12–15 ºC, and there was no rainfall event recorded. Flow-proportional (24 h) composite samples were collected using automatic samplers (SD900, HACH, Loveland, CO, USA), except the return and excess sludge samples, which were collected twice per day and mixed together. All the samples were analyzed in triplicate.

2.3. Analytical methods

The extraction of pharmaceuticals from wastewater and sludge samples followed the methods developed in our previous study.[17] Briefly, the target pharmaceuticals were extracted from sludge by ultrasonic solvent extraction. The sludge extract or wastewater was enriched and purified by solid phase extraction (SPE) with an Oasis HLB cartridge (6 mL, 500 mg, Waters, Milford, MA, USA). Subsequently, the target pharmaceuticals were separated using Agilent 1290 UPLC system equipped with Agilent Zorbax SB-C18 column (100 mm × 2.1 mm, 1.8 μm), and detected by Agilent 6420 Triple Quad LC/MS equipped with a positive electrospray ionization source (Agilent, Wilmington, DE, USA) in multiple reaction monitoring mode (Table S4). Quantification of the pharmaceuticals was performed with the internal standard method to minimize the matrix effect. The recoveries of target pharmaceuticals were in the range of 69−131% for wastewater and 58−130% for sludge at different spiked concentration levels, and the limits of quantification (LOQs) ranged from 0.02 to 0.73 ng L^{-1} in wastewater and from 0.02 to 1.00 μg kg^{-1} in sludge (Table S5). Detailed information on the pretreatment, extraction, and analysis of wastewater and sludge samples is provided in Text S1 (Supplementary Information).

2.4. Mass balance analysis

Mass balance was performed to analyze the mass flow of a target pharmaceutical

entering and leaving a WWTP through both wastewater and sludge. To evaluate the contribution of each treatment unit, the aqueous removal efficiency (RE_{aq}) is calculated with:

$$RE_{aq}(\%) = \frac{C_{inf} - C_{eff}}{C_{inf}} \times 100 \quad (1)$$

where C_{inf} and C_{eff} (ng L^{-1}) are the concentrations of a target pharmaceutical in the influent and effluent of a treatment unit, respectively.

To assess the specific contributions of adsorption and biodegradation of a target pharmaceutical during the whole treatment processes, the influent is considered as the total mass input (100%), and the system output consists of the final effluent and dewatered sludge. The difference between the mass input and output is defined as the removed mass, which is calculated using:

$$W_{rem} = W_{inf} - W_{eff} - W_{slu} \quad (2)$$

$$W_{rem}(\%) = \frac{W_{inf} - W_{eff} - W_{slu}}{W_{inf}} \times 100 \quad (3)$$

where W_{inf}, W_{eff} and W_{slu} (g d^{-1}) are the mass load of a target pharmaceutical in the influent, effluent and dewatered sludge, respectively; and W_{rem} (g d^{-1}) is the removed mass.

In each treatment unit, the daily mass load of a target pharmaceutical can be calculated as follows:

$$W = \frac{C_{aq} \times Q}{10^6} + \frac{C_{slu} \times Q \times C_{SS}}{10^9} \quad (4)$$

where W (g d^{-1}) is the daily mass load of a target pharmaceutical passing through each treatment unit; C_{aq} (ng L^{-1}) and C_{slu} (μg kg^{-1}) are the pharmaceutical concentrations in wastewater and sludge, respectively; Q (m^3 d^{-1}) is the daily wastewater flow; and C_{SS} (mg L^{-1}) is the concentration of suspended solids in the sludge.

2.5. Potential risk assessment

The ecological risk induced by the studied pharmaceuticals on aquatic organisms is assessed according to the European Commission's Technical Guidance Document.[18]

The RQ values for aquatic environment are calculated using:

$$RQ = \frac{MEC}{PNEC} \quad (5)$$

where MEC is the maximum measured environmental concentration, and PNEC is the predicted no-effect concentration. The PNEC for wastewater ($PNEC_{aq}$) is calculated as follows:

$$PNEC_{aq} = \frac{LC50 \text{ or } EC50}{AF} \quad (6)$$

where LC50 or EC50 is the lowest effective median concentration to aquatic organisms at different trophic levels (*i.e.*, algae, invertebrates, and fish); and AF is the safety factor set at 1000 as recommended by the Water Framework Directive (Directive 2000/60/EC) for acute/short-term toxicity assessment. The L(E)C50 values are mostly obtained from the literature (provided in the Supplementary Information); if the literature data are unavailable, the Ecological Structure Activity Relationships (ECOSAR, U.S. EPA) model is adopted to estimate the EC50 values.[19] Assuming the worst-case scenario, the maximum concentration detected, in combination with the lowest L(E)C50 values, was applied in the risk assessment.

The PNEC for sludge ($PNEC_{slu}$) can be estimated from the above $PNEC_{aq}$:[20]

$$PNEC_{slu} = K_d \times PNEC_{aq} \quad (7)$$

where K_d is the solid-water distribution coefficient of a target pharmaceutical (*i.e.*, C_{slu}/C_{aq}).

The total risk (RQ_{tot}) is calculated by summing up the RQs of all individual pharmaceuticals at each trophic level:[21]

$$RQ_{tot} = \sum_{i=1}^{n} RQ_i \quad (8)$$

Note that ERY-H_2O is structurally similar to its parent form (ERY) and may have similar effects on non-target organisms. Hence, this compound is assessed based on the toxicity of ERY as relevant information is unavailable.[22] The common ranking criteria are adopted: RQ ≥ 1, high risk; 0.1 ≤ RQ < 1, medium risk; and RQ < 0.1, low

risk.

3. Results and discussion

3.1. Occurrence of pharmaceuticals in two WWTPs

3.1.1 Influent and final effluent

A total of 23 pharmaceuticals including 4 SAs (SDZ, STZ, SMN, SMX), 4 FQs (NOR, OLF, CIP, LOM), 4 TCs (TCN, CTC, OTC, DOX), 4 MLs (CLA, ERY-H_2O, ROX, AZN), and 7 other miscellaneous pharmaceuticals (ATE, MET, PROP, CBZ, BF, CAF, TMP), were detected in the wastewater samples (Fig. 2). By contrast, SMR, SML, SFX, DOX, ENR, TYL, and TIA, which are widely used in veterinary medicine to control infection and promote the growth of livestock, were not detected in the majority of wastewater samples from both WWTPs studied. Thus, these substances are excluded from subsequent discussions.[23,24]

Fig. 2

The most abundant compounds detected in the influent were CAF (5763.3−16099.1 ng L^{-1}), OLF (338.8−1101.5 ng L^{-1}), and AZN (232.5−876.9 ng L^{-1}) in the two studied WWTPs, probably because of the large consumption of soft drinks containing CAF (*e.g.*, coffee, tea, and coke) and the extensive use of FQs and MLs in China. Meanwhile, ROX, NOR, SMX, CIP, MET, and CLA also showed relatively high concentrations (> 0.1 μg L^{-1}) in the influent. As illustrated in Fig. 2, the average levels of target pharmaceuticals in the final effluent were all below 0.5 μg L^{-1}. OLF, ROX, AZN, and MET were identified as the predominant pharmaceuticals in the final effluent, with average concentrations of 230.5, 186.6, 163.1, and 136.5 ng L^{-1} in Plant A, and 327.3, 286.6, 495.6, and 106.2 ng L^{-1} in Plant B, respectively. The distributions of target pharmaceuticals in the influent of both WWTPs exhibited similar trends, demonstrating similar consumption patterns in the same city.

SMX was the most frequently detected SA, whose concentration in the influent was in the range of 72.27−182.3 ng L^{-1} in Plant A and 86.43−283.85 ng L^{-1} in Plant B. OTC appeared to be the dominant TC and its maximum concentration was 114.5 ng L^{-1} in the influent and 37.17 ng L^{-1} in the effluent of Plant B. Given the decreasing

efficacy in humans, TCs have been gradually replaced by other antibiotics such as β-lactam and MLs in the last 20 years.[25] This change explains why TCs exhibited low concentrations in the influent. Four FQs were frequently found in the influent and effluent, whose concentrations showed a descending order: OLF > NOR > CIP > LOM. This result agrees with those reported in other regions of China[7,26] and in some developed countries[14,15,27]. In the present study, AZN appeared to be the most abundant ML in all the influent and effluent samples, followed by ROX, CLA and ERY-H_2O. To date, very limited information is available on the occurrence and fate of AZN in WWTPs. The AZN level in Plant B was in the range of 529.6–876.9 ng L^{-1} in the influent and 414.7–615.5 ng L^{-1} in the effluent, much higher than the results obtained in Southwest China.[26,28] The ERY-H_2O concentration (4.11–42.01 ng L^{-1}) detected in the influent was much lower than those detected in South China.[22,29] Of the other miscellaneous pharmaceuticals, CAF and MET were dominant. The concentrations of ATE, CBZ, TMP, PROP, and BF in the present study are much lower than those measured in Korea[12], UK[30], and Finland[15]. It is seen that the occurrence and distribution patterns of target pharmaceuticals can vary from region to region in the same country and from country to country as well.

3.1.2 Sludge

Analyses of the sludge samples showed the presence of 19 out of the 30 target pharmaceuticals (Fig. 3). SDZ, ATE, CBZ, and BF appeared either in only a few samples or at a concentration below their LOQs in the sludge, thus they are excluded from subsequent discussions.

Fig. 3

FQs, MLs, and TCs were dominant in the sludge, contributing more than 90% of the total pharmaceutical load. For individual compounds, OLF (5528.0−12127.2 μg kg^{-1}) was the most abundant in the sludge, followed by AZN (5315.5–8466.4 μg kg^{-1}) and NOR (1833.5–3661.4 μg kg^{-1}), as shown in Fig. 3. FQs and AZN, which contain positively-charged nitrogen and dimethylamino moieties, have high adsorption potential because of electrostatic interactions with negatively-charged sludge particles.[26] High concentrations of OLF and NOR were also observed in other regions

of China[7,31] as well as in Switzerland[27]. At present, few reports are available on the occurrence of AZN in WWTPs. Our study is the first to report the presence of AZN in sludge in East China. SAs and β-blockers were detected at low levels, which could be attributed to their weak adsorption capacity and persistency to remain in aqueous phase. TCs can adsorb strongly onto solid particles through hydrogen bonding with organic matter or complexing with metal cations.[32] Therefore, the relatively low concentrations of TCs in sludge show that they have been gradually replaced by other antibiotics for treatment of human diseases in this region.

To summarize, the physicochemical properties and usage pattern of each target pharmaceutical as well as the removal efficiency of the treatment process adopted can all affect the presence of these substances in the sludge. In the present study, the concentrations of each pharmaceutical in the sludge of the two studied WWTPs were similar and kept stable during our investigation, implying that the presence of these pharmaceuticals in sludge depends mostly on their physicochemical properties.

3.2. Removal of pharmaceuticals in two WWTPs

The concentrations of target pharmaceuticals in the wastewater and sludge samples collected from various treatment units in both WWTPs are summarized in Tables S6–S8. Based on these values, the removal efficiencies of these pharmaceuticals during the primary, secondary and tertiary treatments were calculated and presented in Table 1.

Table 1

The removal efficiency by the primary treatment was generally low except TCN, PROP, and TMP (> 40%) in Plant A, indicating insignificant adsorption of most pharmaceuticals to the suspended particles removed at this stage. The horizontal-flow grit chamber combined with the primary clarifier in Plant A showed a better removal of MLs and other miscellaneous pharmaceuticals than the rotational-flow grit chamber in Plant B. In addition, the overall removal efficiency of target pharmaceuticals was compound specific, which ranged from "negative" (*i.e.*, SMN and CBZ) to 99.9% (CAF). Gao *et al.*[6] reported a large variation in the removal of SMX, LOM, and ROX in different WWTPs, which ranged from −5% to 62%, from

−60% to 100%, and from −190% to 37%, respectively. The removal efficiencies of SMX and OLF were 0−84% and 0−62% in six Italian WWTPs, respectively.[13] Negative removals were observed for SMN, LOM, and CBZ in Plant A and ERY-H_2O, ROX, CBZ, and BF in Plant B, which have also been reported in previous studies.[6,12] This result probably arose from the hydraulic lag in sampling and the transformation of unidentified human metabolites (*e.g.*, glucuronide conjugates, hydroxylated metabolites, methylates, and glycinates) into parent compounds in WWTPs.[33,34] CAF was almost completely removed and did not accumulate in the sludge regardless of the type of treatment process adopted, so its removal was mainly attributed to biodegradation.[35]

The overall removal of target pharmaceuticals during the one-week monitoring period was statistically assessed using the Paired Samples Test at a significance level of 0.05 (SPSS 18, IBM, USA). SAs, FQs and MLs showed significantly different removals between Plants A and B ($p < 0.01$), while the removals of TCs and Others showed insignificant difference between the two plants. This result indicates that the treatment efficiency of Plant A (upgraded) for pharmaceuticals was notably improved compared with that of Plant B (conventional). The removal of pharmaceuticals in different WWTPs depends on many factors, such as the treatment process adopted, sludge retention time (SRT), hydraulic retention time, the physicochemical properties of target compounds, and the sampling method used.[36,37] However, the type of biological treatment process is likely to be the dominant factor in this study, as revealed by the statistical significance. For example, the removal efficiency of each group of target pharmaceuticals ranged from 63.3% to 97.7% in Plant A (A/A/O-MBBR) and from 31.1% to 97.1% in Plant B (C-Orbal OD). Meanwhile, the removal efficiency of the tertiary treatment was negligible in both WWTPs (Table 1). The RFDFs and UV disinfection were used to reduce suspended solids and inactivate pathogens, respectively,[38] which could not effectively remove most of the pharmaceuticals at trace levels (< 1 μg L^{-1}). Thus, advanced treatment technologies (*e.g.*, nanofiltration/reverse osmosis, O_3, UV/H_2O_2) are required to enhance the removal of residual pharmaceuticals in the effluent.

3.3. Mass load and mass balance of target pharmaceuticals

The mass flow and mass balance of target pharmaceuticals were determined to clarify their fate and potential removal pathways in the two studied WWTPs. The total mass loads of all target pharmaceuticals in the influent and effluent were 3553 and 203 g d^{-1} in Plant A, and 1770 and 275 g d^{-1} in Plant B, respectively (Fig. 4 and Fig. S1). Among the different groups, other miscellaneous pharmaceuticals (75.3−86.2%, mainly CAF) were dominant in the influent, whereas MLs (43.4−56.6%) were dominant in the effluent. The total mass load in the dewatered sludge was 307 and 142 g d^{-1} in Plants A and B, respectively. FQs and MLs (mainly AZN) were dominant in the sludge, which accounted for more than 90% of the total mass load.

Fig. 4

The removal of the total mass load of target pharmaceuticals in Plant A reached 94.3%, much higher than the 84.5% removal in Plant B. Although Plant A was upgraded to improve the removal of biodegradable carbon, nitrogen and phosphorus, the combined A/A/O-MBBR process could also enhance the removal of pharmaceuticals because most pharmaceuticals are removed in the biological treatment (primarily under aerobic conditions). On the one hand, the possible removal mechanism of pharmaceuticals during the biological treatment is co-metabolism. In the present study, part of nitrogen was removed through nitrification/denitrification in the MBBR in Plant A, which could enhance the removal of some pharmaceuticals through co-metabolism. On the other hand, the longer SRT in Plant A could also improve the removal of target pharmaceuticals during biological treatment.[36] Batt *et al.*[39] reported that nitrifying bacteria were important for biodegradation of iopromide and TMP in the activated sludge process with an extended SRT. Dorival-García *et al.*[40] also found that the removal of FQs was enhanced by nitrification in a membrane bioreactor with a high SRT. In addition, the absence of primary clarifier in Plant B could lead to a higher load to the biological treatment process, and subsequently a lower removal of target pharmaceuticals.

The mass proportions of target pharmaceuticals, relative to the calculated initial mass load, in the effluent, dewatered sludge, and removed in both WWTPs are

illustrated in Fig. 5. The removed proportion was primarily attributed to biodegradation, and other removal pathways such as volatilization, hydrolysis, photolysis, and epimerization may also have certain contributions depending on the specific physicochemical properties of each target pharmaceutical.

Fig. 5

The removed proportions of studied SAs (except SMN) were all above 50% in the two WWTPs and only a low proportion (< 9%) of SAs was found in the sludge, indicating that adsorption onto sludge was insignificant and biodegradation was the primary removal pathway for most SAs. For FQs and TCs, high proportions (up to 731%) were detected in the dewatered sludge, indicating that sludge adsorption was the primary removal pathway. Previous researches have reported that FQs and TCs could be adsorbed strongly to sludge particles with little or even no biodegradation.[41] FQs, as a group of hydrophobic and zwitterionic compounds, have a high adsorption affinity for sludge as a result of electrostatic interactions with suspended solids.[29] Meanwhile, TCs can interact strongly with clay, natural organic matter and metal oxides through cation exchange, surface complexation, hydrophobic partitioning, and electron donor-acceptor interactions.[42] The removed proportions of MLs varied from −15.7% to 84.5%, while the proportions in the sludge ranged from 0.6% to 3.1% for CLA, ERY-H_2O and ROX, and from 36.7% to 86.7% for AZN. Therefore, biodegradation was mainly responsible for the removal of CLA, ERY-H_2O and ROX, while sludge adsorption was important for the removal of AZN. AZN, with the dimethylamino group positively charged under nearly neutral pH conditions, could be easily adsorbed onto the negatively charged sludge particles through electrostatic interactions.[26] For other miscellaneous pharmaceuticals, their low proportions (< 1%) detected in the dewatered sludge implied that sludge adsorption was of minor importance for their removal. CAF and ATE were biodegraded effectively with the removed proportions reaching 90−100% in both WWTPs, which is consistent with their aqueous removal efficiencies (Table 1). By contrast, large proportions of BF, PROP, and TMP were observed in the effluent, indicating their low biodegradability. From the aqueous removal efficiencies (< 5%) in the two plants, MET and CBZ

appeared resistant to both biodegradation and adsorption regardless of the type of the treatment process adopted. The negative removal of CBZ was likely due to the deconjugation of conjugated CBZ metabolites during the biological treatment.[33]

The influent mass load of a target pharmaceutical per capita reflects its usage pattern in the service area, whereas the mass load per capita in the effluent and sludge denotes its potential pollution to the environment. The total influent mass load of target pharmaceuticals amounted to 4333.3 μg d^{-1} $inhabitant^{-1}$ in Plant A and 2681.8 μg d^{-1} $inhabitant^{-1}$ in Plant B (Table 2), much lower than those reported in Spain[43] (7485 μg d^{-1} $inhabitant^{-1}$) and the United States[44] (15440 μg d^{-1} $inhabitant^{-1}$). The OLF level (about 160 μg d^{-1} $inhabitant^{-1}$) in the influent of both WWTPs was comparable to the reported maximum values in Spain[43] (130.4 μg d^{-1} $inhabitant^{-1}$) and Sweden[45] (155.8 μg d^{-1} $inhabitant^{-1}$), but much lower than that detected in Italy[13] (614 μg d^{-1} $inhabitant^{-1}$). The total mass loads of target pharmaceuticals per capita in the two WWTPs were in the ranges of 248.0–416.6 and 214.6–374.5 μg d^{-1} $inhabitant^{-1}$ in the effluent and dewatered sludge, respectively. Our results showed that SAs, most of the MLs, and other miscellaneous pharmaceuticals reached the environment mainly through effluent discharge, whereas FQs and AZN were mainly released through sludge disposal.

Table 2

3.4. Environmental impact

Residual pharmaceuticals are released into the environment through effluent discharge and sludge disposal, which may cause adverse impacts to ecosystems and human health. Meanwhile, land application and landfill, as two common ways for sludge disposal in China, are potential pollution sources of pharmaceuticals to soil, surface water, and groundwater.[46] The continual input of pharmaceuticals to aquatic environments have been shown to impose selective pressure on bacterial populations, resulting in the prevalence of antimicrobial resistance.[26] Recently, bacteria that are resistant or multi-resistant to antibiotics have been identified in aquatic environments and soils, and significant correlations between the concentrations of SAs and MLs and the presence of antibiotic resistance genes have been reported.[47–49] Exposure to

antibiotics may exert adverse effects on the reproductivity of different organisms in their early life stages.[49,50] Therefore, it is necessary to assess the ecological risks of pharmaceuticals in both effluent and sludge to the aquatic environment.

Each kind of test aquatic organism (*i.e.*, algae, invertebrates, and fish) exhibited different susceptibilities to different pharmaceuticals (Table S9).[51] The susceptibility of the test organisms to pharmaceuticals generally followed a descending order: algae > invertebrate > fish, suggesting that algae be the most susceptible to pharmaceuticals in the aquatic environment.[52] For the final effluent, high RQs of SMX (2.19), OLF (17.96), CIP (9.05) and CLA (1.27) were found for algae in Plant A, and SMX (5.33), OLF (25.10), and CIP (10.40) in Plant B, indicating a high risk of the effluent to algae. Meanwhile, LOM, CTC, OTC, ERY-H_2O, ROX, and AZN could pose a medium risk to algae, and OTC and AZN could further pose a medium risk to invertebrates in the aquatic environment. A previous study conducted in France found that DOX, OLF, CIP, CLA, ROX, AZN, SMX, and TMP required prioritized attention because of their high ecological risk to aquatic environment.[53] In addition, the risk assessment on 6 most commonly used antibiotics in Italy revealed that ERY, lincomycin, and CLA posed a high risk to the aquatic environment.[54]

For the sludge, only OLF in Plant B posed a high risk to algae, while a medium risk to algae could be induced by SMX, CIP, and CLA. All the RQs for other miscellaneous pharmaceuticals were less than 0.1, no matter in the effluent or sludge. In addition, the total risk of all target pharmaceuticals in the effluent or sludge was estimated by RQ_{tot} for the worst case scenario. The RQ_{tot} values for algae ranged from 31.29 to 42.30 in the effluent and from 1.96 to 4.40 in the sludge, indicating a high risk to algae. Meanwhile, the effluent could further pose a medium risk to invertebrates (RQ_{tot} = 0.317–0.584). A most recent study conducted in the Three Gorges Reservoir Area of China has also reported that SDZ, SMX, OLF, AZN, ERY-H_2O, and the mixture of all detected pharmaceuticals in both WWTP effluent and sludge could pose a high risk to algae.[26]

To summarize, the results demonstrated that the occurrence of some pharmaceuticals in the effluent and excess sludge could pose a medium-to-high risk to

aquatic organisms. Many pharmaceuticals, even if their ecological risks are estimated to be low, are discharged continuously to the environment, which can induce adverse impacts on aquatic ecosystems in the long term because of their chronic and combined toxicities. Therefore, it is urgent to improve the removal of pharmaceuticals during wastewater and sludge treatment, so as to reduce the ecological risks induced by residual pharmaceuticals.

4. Conclusions

The occurrence and fate of 30 pharmaceuticals of multiple classes were investigated in both conventional and upgraded WWTPs. A total of 23 and 19 pharmaceuticals were detected in wastewater and sludge, respectively. The removal efficiencies of target pharmaceuticals in both WWTPs varied largely from "negative" (*i.e.,* SMN and CBZ) to 99.9% (CAF), depending on their physicochemical properties and the wastewater treatment process adopted. Based on the mass balance analysis, the behavior and fate of target pharmaceuticals were clarified. The removal of SAs, most of the MLs, and other miscellaneous pharmaceuticals was mainly attributed to biodegradation, whereas the removal of FQs, TCs, and AZN was mainly attributed to sludge adsorption. The total mass load of target pharmaceuticals was removed by 94.3% in the upgraded Plant A adopting A/A/O-MBBR, which is considerably higher than that in the conventional Plant B adopting C-Orbal OD (*i.e.*, 84.5%). The ecological risk assessment indicated that four pharmaceuticals (SMX, OLF, CIP, and CLA) in the effluent, one pharmaceutical (OLF) in the sludge, and the mixture of all target pharmaceuticals in both effluent and sludge could pose a high risk to algae in the aquatic environment. This study helps understand the behavior and fate of pharmaceuticals in both conventional and upgraded WWTPs as well as the ecological risks induced by effluent discharge and sludge disposal, thus providing useful information for better control of micro-pollutants in WWTPs.

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Electronic supplementary information (ESI) Available

Additional information is available on the analytical method (Text S1), physicochemical properties of pharmaceuticals, operational parameters of two studied WWTPs, wastewater and sludge characteristics, optimized operational parameters of MS/MS, pharmaceutical concentrations in wastewater and sludge, calculated RQs (Tables S1–S9) and total mass flows of pharmaceuticals (Fig. S1). See DOI:

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606 ## Figure captions

607 Fig. 1 Schematic diagram of two studied WWTPs and sampling points.

608 Fig. 2 One-week monitored concentrations of target pharmaceuticals in the influent
609 and effluent of two studied WWTPs.

610 Fig. 3 One-week monitored concentrations of target pharmaceuticals in the excess
611 sludge of two studied WWTPs.

612 Fig. 4 Mass flow composition and daily mass load of target pharmaceuticals in the
613 influent, effluent, and dewatered sludge of two studied WWTPs.

614 Fig. 5 Mass proportion of target pharmaceuticals in the effluent, dewatered sludge,
615 and removed in two studied WWTPs.

616

Table 1 Aqueous removal efficiencies (%) of target pharmaceuticals in different treatment units of two studied WWTPs

Compound	Plant A			Plant B		
	Primary treatment	Secondary treatment	Tertiary treatment	Primary treatment	Secondary treatment	Tertiary treatment
SDZ	14.6	60.8	70.0	2.4	77.2	71.5
STZ	38.4	91.2	94.3	ND [a]	ND	ND
SMN	–20.8	–9.8	–9.4	4.9	47.2	58.8
SMX	6.7	67.1	75.8	5.2	64.6	51.1
NOR	18.2	79.0	79.4	24.3	71.5	70.3
OLF	23.0	84.9	83.7	12.9	54.8	52.7
CIP	19.1	80.3	78.0	14.0	79.0	78.5
LOM	–25.9	78.5	57.5	37.7	94.6	88.4
TCN	58.1	79.1	69.5	30.0	46.2	59.2
CTC	30.9	50.6	54.1	19.6	65.0	46.9
OTC	18.9	93.8	93.1	9.9	81.3	74.0
DOX	26.5	57.1	82.0	34.0	84.4	82.0
CLA	3.6	59.9	66.2	1.1	86.9	85.2
ERY-H_2O	13.0	60.8	75.8	–3.2	52.5	53.9
ROX	13.6	53.7	60.3	–2.1	20.8	27.9
AZN	17.5	76.2	71.0	7.1	29.7	32.8
ATE	30.3	83.1	89.9	9.5	83.8	94.3
MET	6.8	1.7	4.2	2.4	3.6	5.4
PROP	45.5	24.2	17.6	4.9	0.8	14.6
CBZ	–4.1	–49.4	–43.8	–8.8	–80.3	–69.7
BF	22.2	32.8	35.1	–38.1	80.4	69.3
CAF	25.2	99.9	99.9	3.5	99.9	99.9
TMP	44.8	28.8	24.0	2.3	14.9	18.5
∑SAs	6.8	66.0	74.5	5.1	64.0	51.9
∑FQs	21.7	83.5	82.4	15.9	60.8	58.8
∑TCs	23.7	89.0	88.8	14.0	79.7	73.4
∑MLs	13.3	63.3	65.5	3.3	31.1	35.2
∑Others	24.9	97.6	97.7	3.5	97.1	97.2

[a] ND: not detected.

Table 2 Average mass loads of target pharmaceuticals per capita (μg d^{-1} $inhabitant^{-1}$) in two studied WWTPs

Compound	Plant A			Plant B		
	Influent	Effluent	Dewater sludge	Influent	Effluent	Dewatered sludge
SDZ	0.80	0.24	ND [a]	1.27	0.36	ND
STZ	0.79	0.04	0.07	ND	ND	ND
SMN	0.96	1.05	0.02	2.75	1.13	0.01
SMX	54.24	13.13	0.35	56.12	27.42	0.22
NOR	33.82	6.95	52.82	38.47	11.42	26.05
OLF	166.9	27.16	190.4	164.1	77.60	93.86
CIP	22.11	4.86	14.72	15.84	3.41	6.77
LOM	0.81	0.35	5.94	8.27	0.96	4.29
TCN	0.72	0.22	0.74	0.37	0.15	0.53
CTC	0.24	0.11	0.22	0.38	0.20	1.12
OTC	5.73	0.40	5.71	7.83	2.04	5.54
DOX	0.37	0.07	0.20	1.21	0.22	0.22
CLA	55.79	18.85	0.72	28.42	4.22	0.18
ERY-H_2O	1.53	0.37	0.04	1.25	0.58	0.04
ROX	137.8	54.64	0.73	130.1	93.74	0.61
AZN	116.7	33.83	101.1	204.1	137.1	74.91
ATE	7.24	0.73	ND	10.76	0.61	ND
MET	66.15	63.34	0.14	42.54	40.25	0.07
PROP	0.55	0.46	0.02	0.75	0.64	0.01
CBZ	5.13	7.38	ND	2.74	4.65	ND
BF	2.32	1.51	ND	0.49	0.15	ND
CAF	3641.3	3.73	0.35	1954.7	2.17	0.12
TMP	11.36	8.64	0.13	9.34	7.61	0.07
∑SAs	56.79	14.46	0.43	60.15	28.92	0.23
∑FQs	223.7	39.32	263.9	226.7	93.38	131.0
∑TCs	7.06	0.79	6.88	9.79	2.61	7.41
∑MLs	311.8	107.7	102.6	363.9	235.6	75.74
∑Others	3734.0	85.78	0.64	2021.3	56.08	0.27
∑All	4333.3	248.0	374.5	2681.8	416.6	214.6

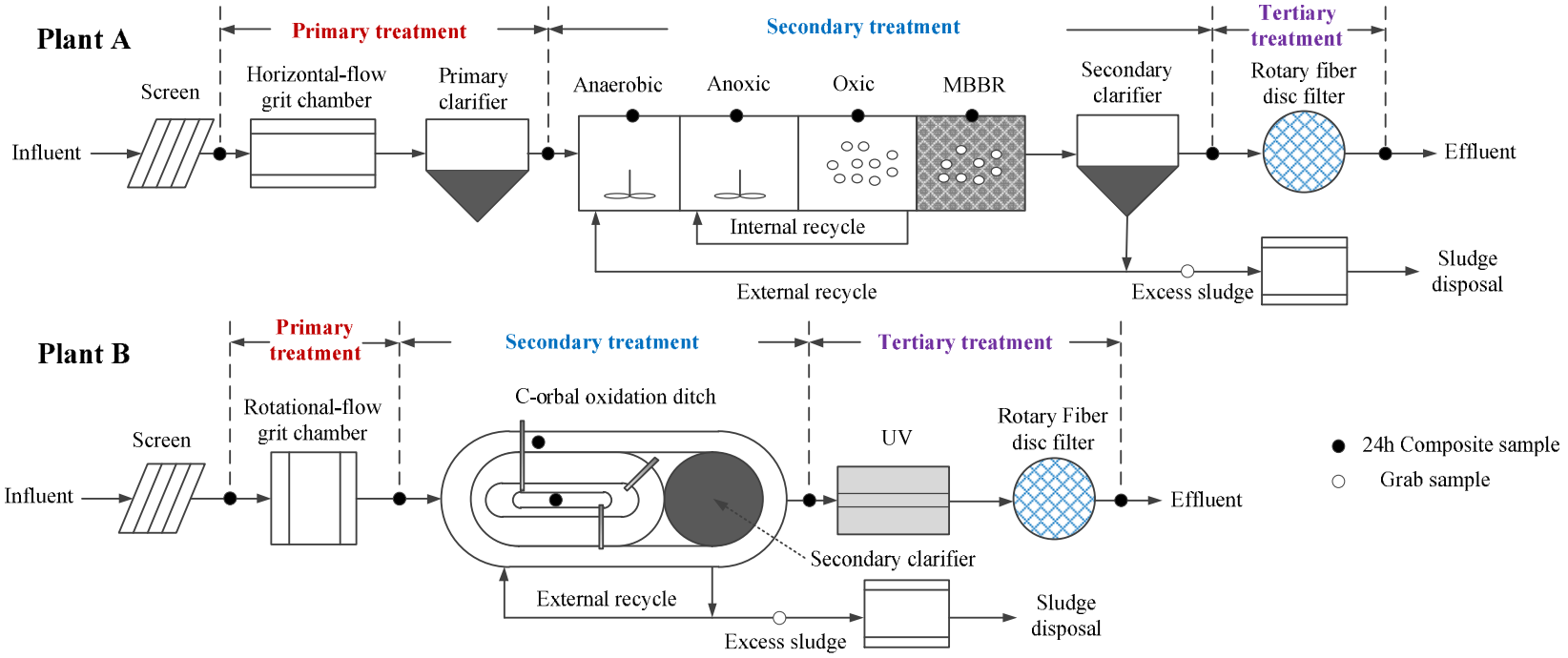

Fig. 1 Schematic diagram of two studied WWTPs and sampling points.

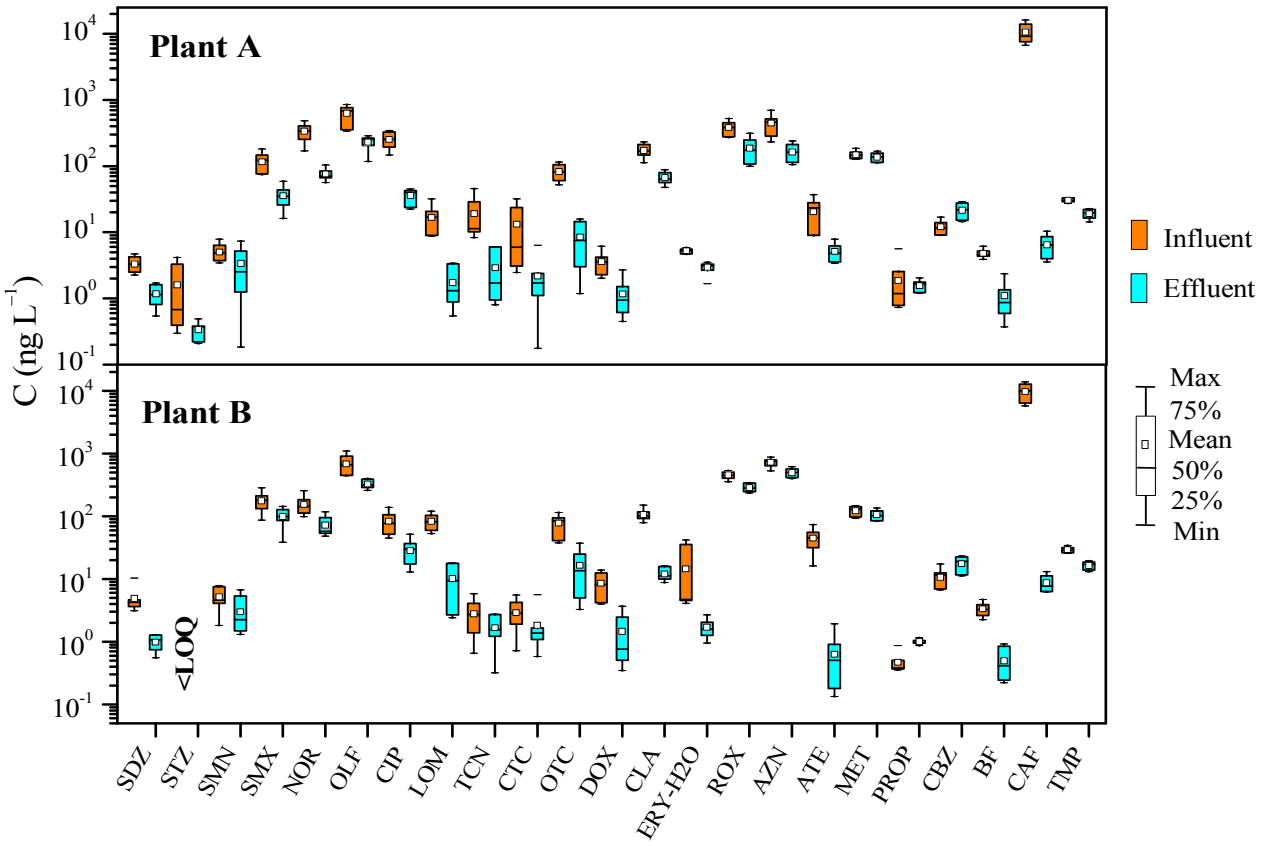

Fig. 2 One-week monitored concentrations of target pharmaceuticals in the influent and effluent of two studied WWTPs.

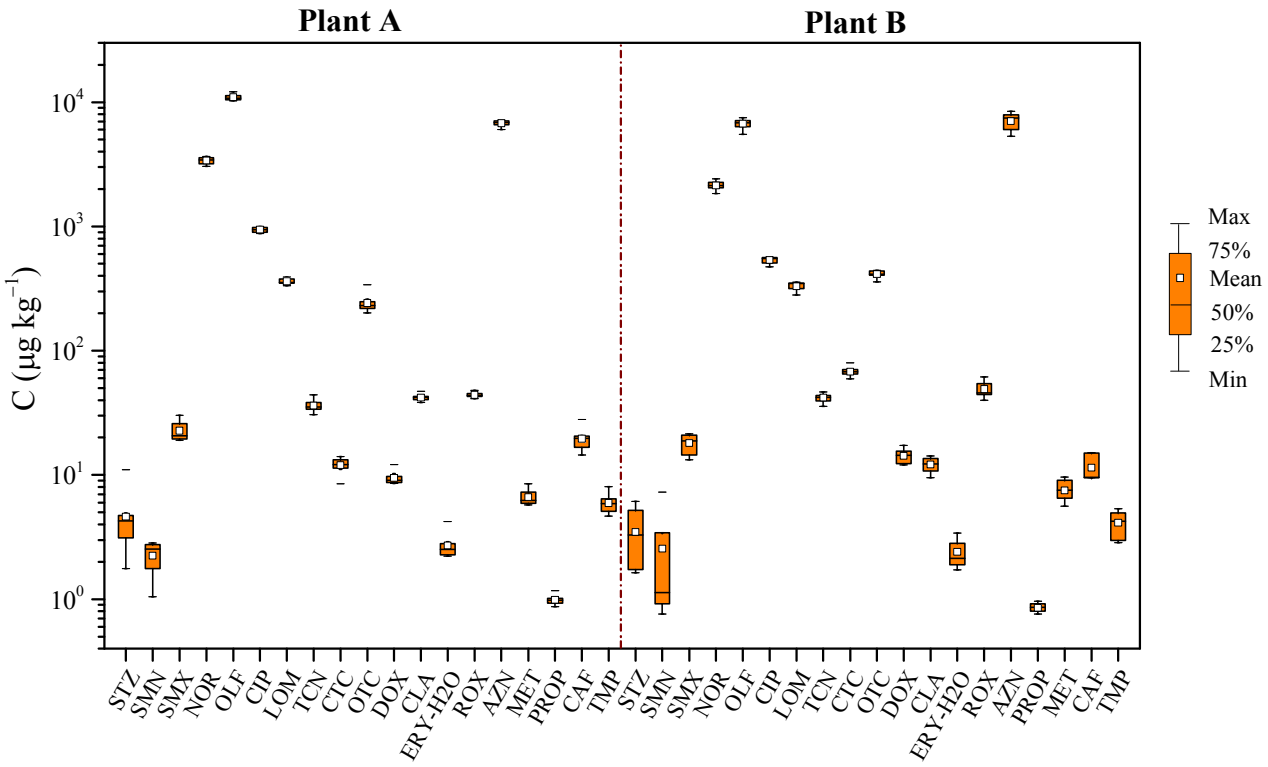

Fig. 3 One-week monitored concentrations of target pharmaceuticals in the excess sludge of two studied WWTPs.

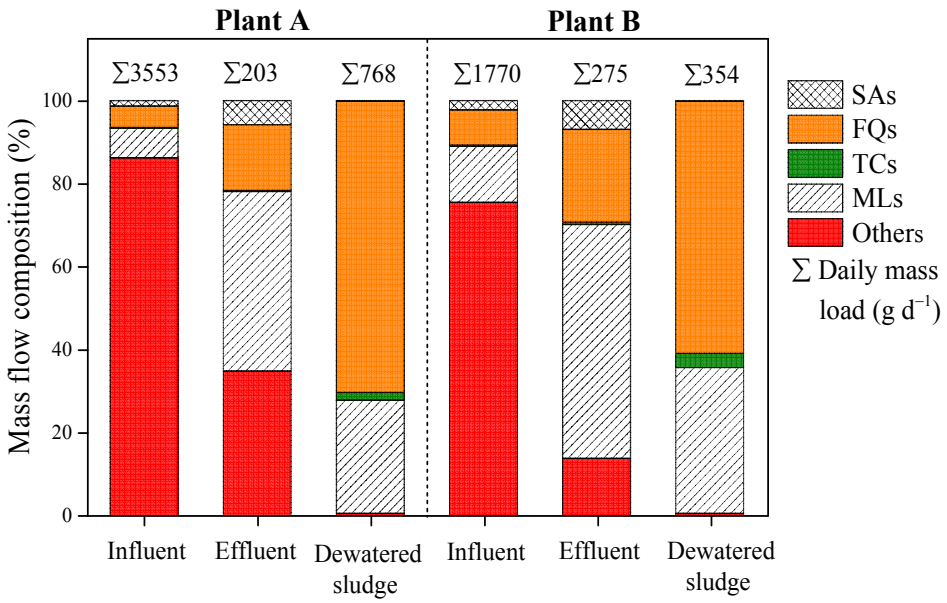

Fig. 4 Mass flow composition and daily mass load of target pharmaceuticals in the influent, effluent, and dewatered sludge of two studied WWTPs.

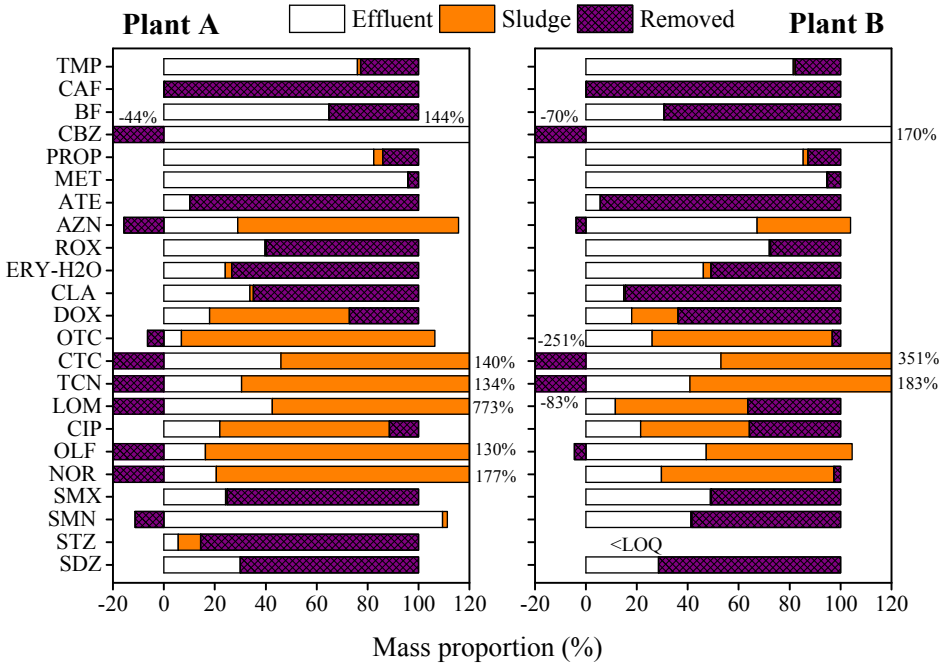

Fig. 5 Mass proportion of target pharmaceuticals in the effluent, dewatered sludge, and removed in two studied WWTPs.