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Accurate prediction of pharmaceutical concentrations using numerical correction factors to prescribing information will reduce the reliance on water sampling and analysis. This sustainable monitoring approach will be used to identify high risk pharmaceuticals in the environment and inform the development of mitigation strategies.

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Improved prediction of pharmaceutical concentrations in wastewater using numerical correction factors applied to prescribing information

Bruce Petrie[a]*, Elise Cartmell[b]

[a]School of Pharmacy, Applied Sciences and Public Health, Robert Gordon University, Aberdeen, AB10 7GJ, UK

[b]Scottish Water, 55 Buckstone Terrace, Edinburgh EH10 6XH, UK

*Corresponding author email: b.r.petrie@rgu.ac.uk

Abstract

Pharmaceuticals and metabolites excreted by humans are a threat to aquatic ecosystems globally. Gaps exist in environmental data sets which can be filled by predicting concentrations using prescribing data available at suitable spatial (e.g., wastewater treatment plant [WWTP] catchment area) and temporal scale (e.g., monthly). The aim was to improve the accuracy of predicted pharmaceutical concentrations in untreated influent wastewater. A conventional prediction approach of applying human excretion information to prescribing data found three of 12 analytes (metformin, desmethylvenlafaxine and clarithromycin) had acceptable predictions (within ± 50 % of their measured concentration) at three WWTPs of varying size. Several analytes had systematic underestimated predictions across WWTPs related to low analyte excretion rates. Laboratory-scale gravity sewer experiments revealed an important contributor was glucuronide metabolite deconjugation back to their parent pharmaceutical which could not be accounted for using excretion information. Therefore, numerical correction factors were derived (0.027 – 0.86) from prescribing and wastewater data to establish the fraction of prescribed pharmaceuticals found in wastewater. These account for changes between prescription of a pharmaceutical and its presence in wastewater (e.g., human metabolism and in-sewer transformation) without the need to quantify and correct for them individually. This enabled acceptable predictions for another six analytes (carbamazepine, propranolol, venlafaxine, fluoxetine, norfluoxetine and desmethylclarithromycin). Therefore, incorporating this approach in prediction models for treated effluents and river water can improve their accuracy for improved risk assessment. This is key to

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identify where subsequent technological or 'upstream' intervention is needed to target pharmaceutical environmental impacts.

Keywords: emerging contaminant; drug; micropollutant; model; sustainable

1. Introduction

Prescribing pharmaceuticals is the most common medical intervention with > 1,500 substances approved for human use in the UK.[1] A portion of a pharmaceutical's dose is excreted unchanged and as metabolites in urine and faeces and enters a network of sewers as wastewater. This is transported to a wastewater treatment plant (WWTP) for treatment prior to discharge into the environment. However, conventional WWTPs are not designed to eliminate pharmaceuticals. In the aquatic environment they pose a threat to the ecology of receiving environments, even at sub-µg/L concentrations.[2,3] Therefore, it is essential to reduce the discharge of pharmaceuticals from WWTPs where they pose the greatest risk. A key challenge is identifying where an intervention is needed and for what pharmaceuticals. This can be achieved by measuring pharmaceutical concentrations in WWTPs and the receiving environment, particularly at locations with low effluent-river dilution ratios. Measured concentrations can then be compared to predicted no effect concentrations which indicate a threshold below which no adverse effects are expected. The high cost of sample collection and analysis can make this approach prohibitive at suitable scale, particularly for countries such as Scotland which have populations spread across a large geographical area. Nevertheless, the availability of prescription data at fine spatial (e.g., individual WWTP catchment) and temporal scale (e.g., monthly) offers the opportunity to predict pharmaceutical concentrations in wastewaters and the environment.

Previous research has found low accuracy of predicted pharmaceutical concentrations for influent (untreated) wastewater (i.e., out with ± 50 % of measured concentrations) for several analytes studied.[4-6] It is not uncommon for predicted and measured concentrations to differ by more than an order of magnitude. A common approach to predict pharmaceutical concentrations in wastewater is by applying available literature excretion information to prescribing information.[7-9] When national or regional prescription data is used then the theoretical population size served by the WWTP as well as the flow of wastewater is accounted for to determine the average concentration in wastewater. Improved

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predictions are possible using WWTP catchment prescribing information for the specific time of year. Accounting for people movement in or out of a WWTP catchment where prescription data relates can help refine predictions. Ideally this would be done using bulk wastewater parameters that are measurable by online monitors (e.g., ammonium[10]).

Some studies reporting the accuracy of predicted concentrations in wastewater rely on measured concentrations from 24-hour time-weighted composite samples with sub-sample collection frequencies ranging from 10 minutes to 1 hour.[5,6] Due to the heterogenous composition and flow of wastewater this sampling approach is subject to error. This error increases as catchment population size (and number of toilet 'flushes' containing a given pharmaceutical) decreases.[11] Representative wastewater samples can be collected using flow-weighted composite sampling. Although this brings increased logistical and operational challenges (e.g., calibration of sampler collection volumes), commercially available samplers capable of collecting true flow-weighted composites do not exist. Alternatively, samplers with 24 individual collection bottles can be used to collect hourly time-weighted composites for 24 hours. These individual samples can then be used with flow data to manually prepare a flow-weighted composite in the laboratory.[4]

Once the accuracy of predicted pharmaceutical concentrations in influent wastewater is established then the cause for poor correlations can be better understood and prediction methods refined, or alternatives explored. Failing to measure the 'total' pharmaceutical concentration present in wastewater (i.e., the combined dissolved and particle bound concentrations), not quantifying the degradation of pharmaceuticals during sample collection, overlooking the contribution of hospital prescription data and not accounting for the transformation of pharmaceuticals and metabolites in sewers can all contribute to inaccurate predictions of concentrations in wastewater. In particular, the in-sewer transformation of unstable conjugated metabolites (e.g., glucuronides) back to the parent pharmaceutical is possible[12,13] For example, Gao *et al*[12] found 15 – 40 % of morphine and codeine glucuronide conjugates transform back to the parent compound. This can result in an underestimation of the parent pharmaceutical concentration. It is proposed that an alternative means of predicting pharmaceutical concentrations in wastewater is possible whereby a numerical correction factor can be

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applied to prescription data. This would account for all losses for a given pharmaceutical between prescription and its presence in wastewater. However, such an approach requires validation using representative wastewater concentration from WWTPs of varying population size. A similar approach is taken for illicit drugs (and some prescription pharmaceuticals) albeit in the opposite direction whereby concentrations in wastewater are converted to population use information by a pre-derived correction factor.[14,15] Establishing accurate prediction of pharmaceuticals in wastewater then allows this approach to be explored for river waters.

To address the shortcomings of previous research aimed at predicting pharmaceuticals concentrations and to improve the use of prescribing information for this purpose, the objectives of the research are to (*i*) establish how accurately pharmaceutical concentrations in wastewater can be predicted using prescribing information and pharmacokinetic data, (*ii*) investigate the cause of poor predictions, and (*iii*) determine whether numerical correction factors can be applied to prescribing information to predict pharmaceutical concentrations in wastewater (and river water). This was achieved by studying eight prescription pharmaceuticals and six of their metabolites in three WWTPs of varying population sizes served. Pharmaceuticals were selected to include a range of therapeutic uses and those identified as a possible risk in the Scottish environment (*Table 1*).[16,17]

2. Experimental

2.1. Materials

The analytical reference standards used were metformin hydrochloride, carbamazepine, carbamazepine 10,11 epoxide, propranolol hydrochloride, propranolol β-D-glucuronide, venlafaxine, desmethylvenlafaxine, fluoxetine hydrochloride, norfluoxetine oxalate, citalopram hydrobromide, desmethylcitalopram, ranitidine, ranitidine-N-oxide, clarithromycin and desmethylclarithromycin. The isotopically labelled surrogates were metformin-d_6, carbamazepine-d_{10}, propranolol-d_7, venlafaxine-d_6, fluoxetine-d_6, norfluoxetine-d_6, citalopram-d_6 and clarithromycin-^{13}C-d_3. All standards were purchased at 1,000 or 100 µg/mL (as free base) or in powder form from either Sigma Aldrich (Gillingham, UK) or LGC Standards (Middlesex, UK). Those in powder form were prepared at 1,000 µg/mL in methanol. Methanol, ammonium formate and formic acid were of high-performance liquid chromatography grade

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and purchased from Sigma Aldrich. Polyvinylidene fluoride (PVDF) syringe filters (3 mm, 0.45 µm) were obtained from Fisher Scientific (Loughborough, UK).

2.2. Wastewater monitoring

Sampling was performed at three WWTPs in North-east Scotland (locations A, B and C) with population equivalent numbers served being 254,716 (high), 45,780 (mid) and 23,700 (low), respectively (*Table 2*). Influent wastewater was collected upstream of any sludge return as hourly composites (15-minute sampling frequency and sub-sample collection volume of 100 mL) for 24 hours using Aquacell P2 automated samplers (Aquamatic, Manchester, UK). The hourly composites together with hourly flow data was used to prepare 24-hour flow-weighted composites in the laboratory within 4 hours of collection. The final volume of each composite sample was 2 L. Each location was sampled during five random days in the final two weeks of August 2023 (*Table S1*).

As the automated samplers were not temperature-controlled, stability assessments of the analytes were conducted at the average wastewater temperature within the composite samplers during the 24 hours collection period. These were 16.5 °C, 17.0 °C and 20.0 °C for WWTPs A, B and C, respectively. This was done in high density polyethylene bottles containing 1 L of wastewater from each WWTP using an all-round toxkit incubator TE21 (MicroBioTests, Gent, Belgium) in dark conditions. Samples were collected initially and then after 12 hours. The background concentration of pharmaceuticals and metabolites present in wastewater (i.e., unspiked samples) were monitored.

2.3. Laboratory-scale gravity sewers

Laboratory-scale gravity sewers of 1.2 L volume were prepared in triplicate using both vitrified clay and plastic (polyvinylchloride – PVC) pipe. In the upright position, the bottom of each pipe was sealed using an endcap. A lid was placed on top enabling the wastewater to be continually mixed by an overhead stirrer as well as facilitating aerobic conditions. Mixing was achieved using a Stuart SW6 flocculator set at a mixing speed of 50 rpm (Cole-Palmer, Cambridgeshire, UK) (*Figure S1*). Influent wastewater from location A was used to replenish the wastewater twice a week. A peristaltic pump was used to empty each pipe from a draw height that left the final 50 mL volume to establish a layer of

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sludge prior to the addition of 950 mL fresh wastewater. The internal surface area of both clay and PVC pipes exposed to wastewater was 400 cm^2. The sewers were operated for six months prior to any experiments to establish a biofilm on the pipe surfaces. The first experiment monitored the concentration of analytes already present in wastewater. Sampling begun 30 minutes after a wastewater change. A single sample (1 mL) was collected from each pipe at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours. Equivalent 'control' sewer pipes were prepared which were not previously exposed to wastewater and therefore had no biofilm or sludge present. These were sampled in the same way. A second experiment was conducted whereby each pipe was spiked with 5 µg/L propranolol β-D-glucuronide following a wastewater change and sampled at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours.

2.4. Direct injection UHPLC-MS/MS analysis

Pharmaceuticals and metabolites were analysed by direct injection using an Acquity UPLC system coupled to a Xevo TQ-XS triple quadrupole mass spectrometer (Waters Corporation, Manchester). Full method details including chromatography and mass spectrometry conditions are available in the Supplementary Information (*Table S2, Table S3, Table S4*). To prepare samples for analysis a 1 mL aliquot of wastewater was spiked with 0.5 µg/L of all isotopically labelled surrogates (50 µg/L for metformin-d_6) and mixed using a vortex mixer for one minute and left to stand for 60 minutes. Samples were then centrifuged at 8,609 × *g* before the supernatant was filtered through a PVDF syringe filter ready for analysis. Samples were frozen at - 20 °C and analysed within one week. All extractions were performed in triplicate. The accuracy of the method was determined by spiking wastewater with 0.5 µg/L of each pharmaceutical and metabolite (50 µg/L for metformin due to its higher concentration in wastewater). This was conducted with wastewater from each location to ensure any differing wastewater composition did not affect the method's performance.

2.5. Pharmaceutical concentration predictions

The quantity of each pharmaceutical dispensed in the community was obtained for the three WWTP catchment areas for August 2023 (A, B and C). This was taken from Scotland's national data visualisation tool which holds NHS primary care data for selected pharmaceuticals.[16] Pharmaceutical use in hospitals within the catchment areas was obtained via a request made to Public Health Scotland.

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Wastewater from the hospitals enter the municipal sewer network within that WWTP catchment and therefore contribute to the pharmaceuticals in influent wastewater. The combined community and hospital data was used to predict the concentration of pharmaceuticals and metabolites in influent wastewater ($Influent_{PC}$) using the following equation:

$$Influent_{PC}\ (\mu g/L) = \frac{Prescription \times CF_{pop} \times CF_{exc} \times 10^6}{Flow_{WW}} \quad [1]$$

Prescription is the average amount prescribed within the WWTP catchment area during August 2023 (g/d as free base) (*Table 3*). CF_{pop} is the correction factor for the difference in population size which the prescription data relates to, and the actual population size contributing wastewater on a given day (*Table 2*). CF_{exc} is the correction factor for the human excretion of the given pharmaceutical or metabolite (*Table 3, Table S5*). $Flow_{WW}$ is the total flow of wastewater for a given day (L/d) (*Table 2*).

An alternative prediction approach was also assessed where numerical correction factors (NF_{Inf}) which account for all processes that influence the analyte concentration observed in influent wastewater were calculated:

$$NF_{Inf} = \frac{Influent_{MC} \times Flow_{WW}}{Prescription \times 10^6} \quad [2]$$

Here $Influent_{MC}$ is the measured concentration of the analyte (µg/L) in influent wastewater. The NF_{Inf} was determined for each individual data point (n = 15, five for each WWTP) and the median value taken to minimise the influence of any outliers. The NF_{Inf} was then incorporated into a modified equation to predict analyte concentrations in influent wastewater:

$$Influent_{PC}\ (\mu g/L) = \frac{Prescription \times NF_{Inf} \times 10^6}{Flow_{WW}} \quad [3]$$

This approach was expanded for the predictions of river water concentrations downstream of WWTP discharge. Numerical correction factors were determined for activated sludge treated wastewater (NF_{AS}) using the following equations:

$$NF_{AS} = NF_{Inf} \times \frac{(100 - Rem_{AS})}{100} \quad [4]$$

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Rem_{AS} is the removal of the given analyte by activated sludge treatment (median removal value from the UK National Chemicals Investigation Programme 2).[18] NF_{AS} was then incorporated into a modified equation to predict analyte concentrations in river water ($River_{PC}$):

$$River_{PC}\ (\mu g/L) = \frac{Prescription \times NF_{AS} \times 10^6}{Flow_{River}} \quad [5]$$

Here $River_{PC}$ is the concentration increase observed in the river as the existing analyte concentration in the river water from upstream WWTPs is unknown. $Flow_{River}$ is the total flow of river water for a given day (L/d). Analyte concentrations in river water were predicted downstream of two WWTPs (D and E) in Central Scotland. These WWTPs utilise activated sludge treatment and serve populations of 270,439 and 12,940, respectively. They were selected as they have a suitably placed river flow meter for concentration predictions and existing river concentration data for comparison. The river flow data was obtained from the National River Flow Archive,[19] and the prescription and measured analyte concentrations from the data visualisation tool as it also contains data from national monitoring programmes (e.g., the Chemical Investigation Programme)[20]. Predictions were made on 12 days (one per month) from 2017 that had measured analyte concentrations available. Measured concentrations used for comparison were reported as the concentration input from the WWTP (i.e., the concentration measured in the river upstream of the WWTP subtracted from the concentration determined at five river widths below the effluent discharge point).

3. Results and discussion

3.1. Analytical method performance and sampling method

This analytical approach achieved trueness values in the range 80 – 110 % with relative standard deviations ≤ 8 % for most analytes spiked into influent wastewater from WWTP A, B and C (*Table S6*). Exceptions to this were observed for analytes without their own isotopically labelled surrogate such as carbamazepine 10,11 epoxide and ranitidine. Their mean trueness values were in the ranges 119 – 130 % and 93 – 132 %, respectively. By utilising an alternative labelled surrogate for their quantitation, their analysis can only be considered semi-quantitative with care needed for their interpretation. The protocol achieved method quantitation limits of 0.1 µg/L for metformin and 0.01 µg/L for all the

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DOI: 10.1039/D6EW00193A

remaining analytes (*Table S4*). These are sufficient to determine the analytes present in influent wastewater based on previously reported concentrations.[16]

Isotopically labelled surrogates were spiked into wastewater prior to filtration. The purpose of this was to allow them to adsorb to particulates such that any adsorbed labelled surrogate is removed during the filtration step. Assuming similar adsorption of the labelled surrogate and the corresponding (non-labelled) pharmaceutical occurs to particulates in wastewater, then the 'total' pharmaceutical concentration is measured instead of the dissolved concentration when the labelled surrogate is spiked after filtration. The ability to measure the 'total' pharmaceutical concentration avoids the assumption that urinary excreted pharmaceuticals remain in the dissolved phase of wastewater, or the uncertainty of applying an additional correction factor to the dissolved concentration to determine the total concentration in wastewater.[21] Measuring concentrations in this way is important for pharmaceuticals such as fluoxetine which have notable particulate bound concentrations (> 35 % of the total concentration) in untreated wastewaters.[22,23] This helps to better assess the accuracy of pharmaceutical concentrations predicted using prescription information.

A limitation of our sampling approach was that the samplers were not temperature controlled, and the collected sub-samples remained at ambient temperature during the collection process. To address this the concentration of pharmaceuticals in wastewater were measured before and after being incubated at the average wastewater temperature within samplers for 12 hours (the average time a sub-sample remains in the sampler). Stability of those detected analytes were all in the range 83 – 114 % for wastewaters from WWTPs A, B and C (*Figure S2*). There was also little variation in the stability observed between wastewater from different locations. Their stability in wastewater agrees with other similar studies conducted using influent wastewaters and the same analytes.[24-26] Only ranitidine-N-oxide was not found at detectable concentrations in the wastewaters studied. Therefore, the stability experiment was repeated with ranitidine-N-oxide spiked at 0.5 µg/L. It showed a significant reduction in wastewater over 12 hours with stability values of 12, 25 and 3 % for wastewaters from WWTP A, B and C, respectively.

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DOI: 10.1039/D6EW00193A

3.2. Prediction of pharmaceutical concentrations in influent wastewater using pharmacokinetic data

The conventional method of predicting pharmaceuticals concentrations using prescription data and pharmacokinetic information (e.g., using *Equation 1*) found 17 of 36 predicted pharmaceutical or metabolite concentrations in wastewater were within an acceptable threshold of ± 50 % of the measured concentration (*Table 3*). This threshold is stricter than a previous study which reported predicted concentrations in the range - 50 % to + 100 % as acceptable,[6] albeit they also apply this criterion to river water predictions where additional error is expected. The predicted concentrations of metformin, desmethylvenlafaxine and clarithromycin were within ± 50 % of the measured concentrations at all three WWTPs. Therefore, using this approach is considered acceptable to predict their concentrations in influent wastewater. Acceptable metformin predictions are expected based on its high use, high excretion from the body unchanged and its known stability within sewers.[26] Nine of the remaining predicted concentrations were in the range ± 51 – 75 % of the measured concentration and the remaining 10 had > 75 % difference (*Table 3*). The range of accuracies observed generally agree with previous studies comparing analyte concentrations in influent wastewater and prescription information.[4-9]

The number of toilet flushes containing the pharmaceutical can influence the level of error associated with the measured concentration. Influent wastewater comprises intermittent discharges from households containing a given pharmaceutical (i.e., toilet flushes). Lower number of toilet flushes can result in greater sampling errors. However, there was no clear trend in the number of toilet flushes containing the pharmaceutical or metabolite of interest and the accuracy of the predicted concentration (*Table 3*). Clarithromycin had the lowest number of toilet flushes with ~ 100 expected at WWTP B and WWTP C. This is expected to give errors of < 20 %.[27] The predicted metabolite concentrations were more accurate than predicted concentrations for the parent pharmaceutical (except for desmethylclarithromycin). Overall, predicted concentrations were underestimated indicating inappropriate disposal of medicines may not be a key factor in the inaccuracy of predictions. Interestingly, ranitidine was found at low concentrations in wastewater at all three locations, despite it no longer being prescribed (*Table 3*). Assuming a daily dose of 0.3 g, the number of doses in wastewater

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were 49, 5 and 1 for WWTP A, B and C, respectively. Ranitidine was used acutely as a histamine-2 blocker to stop the release of stomach acid. Its presence in wastewater despite not being prescribed for over a year demonstrates the number of factors that can influence predicted concentrations and the challenge of accounting for them individually.

Importantly, lower percentage human excretion of pharmaceuticals resulted in greater prediction inaccuracy (*Figure S3*). Carbamazepine, propranolol, venlafaxine, and fluoxetine are excreted by < 5 % and all demonstrated inaccuracies > 75 % (*Table 3*). Similarity in their inaccuracy between locations (e.g., - 97 %, - 98 % and - 96 % for propranolol at WWTP A, B and C, respectively) demonstrate a common error in their predictions. An error of such nature could be introduced by the correction factor applied to account for the excretion from the human body. For such pharmaceuticals a small difference between the literature excretion percentage used in predictions and the actual excretion by the population can lead to large prediction inaccuracies. Also, available literature data often does not account for total excretion (e.g., faecal excretion is not measured). For example, carbamazepine had a median excretion of 1.2 % (n = 7 studies) (*Table S5*). Only one study investigated its faecal excretion which was more than six times greater than the urinary excretion.[28] Therefore, the lack of faecal excretion data will result in underestimation of predicted pharmaceutical concentrations for those also excreted in faeces. Indeed, most predicted concentrations were underestimated (30 of 36 determinations). Another factor which can lead to the systematic underestimation of pharmaceutical concentrations in wastewater is not accounting for the transformation of metabolites (e.g., deconjugation of glucuronide metabolites) back to the parent pharmaceuticals within sewers and prior to sample collection. This could have greater influence on those pharmaceuticals with low percentage human excretion and an expected higher excretion of associated metabolites.

3.3. Deconjugation of propranolol glucuronide in gravity sewers

The sewer systems within the catchment of WWTP A, B and C were primarily gravity systems (≥ 89 % by length) with a small contribution from rising mains (1 – 11 %) (*Table 2*). Of the gravity sewers the common pipe materials were vitrified clay (61 – 71 %), PVC (8 – 26 %) and concrete (11 – 21 %). Therefore, vitrified clay and PVC laboratory-scale gravity sewers were constructed as two contrasting

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materials for biofilm development and transformation studies. Initially, the stability of all target analytes in wastewater were investigated over 24 hours. In clay and PVC control sewers with no established biofilm or sludge all analytes were considered stable (i.e., concentration changes were ± 20 % of their initial concentration) except for clarithromycin (*Figure 1*). Clarithromycin was reduced by 22 ± 2 % and 23 ± 10 % in clay and PVC sewers over 24 hours, respectively. In the test sewers with biofilm and sludge present those that reduced in concentration by > 20 % were metformin (PVC only, 28 %), citalopram (clay and PVC, 45 % and 40 %), desmethylcitalopram (clay only, 23 %) and clarithromycin (clay and PVC, 44 % and 39 %) (*Figure 1*). These analytes all showed a significant difference in reduction of concentrations between test and control sewers (ANOVA, $p < 0.05$). However, there was no statistical difference between clay and PVC sewers (ANOVA, $p > 0.05$) indicating little impact of the pipe material on analyte stability. Both clarithromycin and citalopram have been reported to reduce in concentration by > 20 % in laboratory scale sewers.[26,29] It should be noted that fluoxetine, norfluoxetine, ranitidine and ranitidine-N-oxide were below the analytical method quantification limit in the wastewater used in the study so no stability data for these analytes is available.

The wastewater used in these experiments had already been through a sewer system thus allowing deconjugation of glucuronide metabolites to take place. To assess the possible impact of glucuronide deconjugation on pharmaceutical concentrations in wastewater a further experiment was conducted whereby propranolol β-D-glucuronide was spiked into the wastewater. Propranolol β-D-glucuronide was selected due to the parent pharmaceutical's stability in sewers (*Figure 1*), a considerable portion of propranolol's dose being metabolised through glucuronidation (10 – 25 %),[30] a large and systematic underestimation of propranolol's predicted concentrations in wastewater (*Table 3*) and the commercial availability of an analytical reference standard. The initial concentration of propranolol β-D-glucuronide spiked in the control sewers (4.7 ± 0.2 µg/L and 5.1 ± 0.6 µg/L) was reduced to 3.1 ± 0.2 µg/L and 2.8 ± 0.3 µg/L for vitrified clay and PVC after 24 hours, respectively (*Figure 2*). This resulted in > 100 % increase in the propranolol concentration during the study with no significant difference between the vitrified clay and PVC sewer pipes (ANOVA, $p > 0.05$).

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In the test pipes the reduction of propranolol β-D-glucuronide was significantly greater (ANOVA, $p \leq 0.05$) and was ≥ 90 % (*Figure 2*). The concentration of propranolol increased by 230 ± 22 % in the vitrified clay sewer pipe and by 259 ± 30 % in the PVC pipe. This was not significantly different from one another but significantly greater than the control sewer pipes (ANOVA, $p < 0.05$), demonstrating the biofilm and sludge augment the deconjugation of the glucuronide. Considering molar concentrations (and the stability of propranolol previously established in sewers) revealed the deconjugation of propranolol β-D-glucuronide to propranolol is its main transformation pathway. The summed molar concentrations of propranolol β-D-glucuronide and propranolol after 24 hours were ≥ 82 % of the initial summed molar concentration (*Figure S4*). An important consideration is the residence time of wastewater within sewers. During peak flows where greater pharmaceutical loading is expected the dry weather flow sewer residence times were in the range 1.5 to 3.5 hours for WWTPs A, B and C (*Table 2*). The laboratory sewer studies were conducted over 24 hours as environmental attenuation rates in field conditions can be 10 times greater than laboratory batch tests.[31] The findings suggest that the systematic underestimation of pharmaceutical concentrations in wastewater, particularly those with low human excretion rates in the unchanged parent form (e.g., propranolol) and known to undergo glucuronidation in the human body, is likely caused by the deconjugation of metabolites excreted with the parent pharmaceutical. Unfortunately, glucuronide metabolites cannot be incorporated into prediction calculations using pharmacokinetic data (as in Section 3.3) due to a lack of data on their human excretion percentage or their back transformation to the parent pharmaceutical.

3.4. Numerical factors to predict pharmaceutical concentrations in wastewater and river water

There is insufficient human excretion data on glucuronide metabolites to incorporate them into prediction calculations. Therefore, the numerical correction factor (NF_{Inf}) approach was taken to predict analyte concentrations in influent wastewater. The determined median NF_{Inf} values ranged from 0.027 to 0.86 for all analytes (*Table 3*). The range of individual values for each WWTP is provided (*Table S7*). The carbamazepine NF_{Inf} value was 0.090. Using data obtained for 31 WWTPs in Australia an NF_{Inf} value of 0.115 for carbamazepine can be derived.[14] Data from three WWTPs in Sweden over 17 years

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resulted in an NF_{Inf} value of 0.06.[32] Although both studies had access to regional specific data it was not available down to the WWTP catchment area scale which may contribute to the difference observed.

Applying the modified equation (*Equation 3*) to the obtained data (used to derive the NF_{Inf}) found that nine analytes were predicted within ± 50 % of their measured concentration for WWTPs A, B and C. These were metformin, carbamazepine, propranolol, venlafaxine, desmethylvenlafaxine, fluoxetine, norfluoxetine, clarithromycin and desmethylclarithromycin (*Table 3*). This demonstrates that taking the NF_{Inf} approach can help account for the processes that influence the concentration that is observed in influent wastewater (e.g., excretion from the body, faecal excretion and in-sewer deconjugation of glucuronides) and these processes have similarities between the three studied WWTPs. The NF_{Inf} also reflects influences from the proportion of prescribed medicines that go unused or the rate of improper disposal via household sinks or toilets. However, the NF_{Inf} derived for carbamazepine 10,11 epoxide, citalopram and desmethylcitalopram resulted in data from one WWTP being out with the acceptable ± 50 % threshold indicating location specific influences. For example, citalopram is the only chiral pharmaceutical studied that is prescribed as an equal dose of both its enantiomers (racemate) and as a single enantiomer formulation (escitalopram). The other chiral pharmaceuticals studied (propranolol, venlafaxine and fluoxetine) are prescribed in Scotland as the racemate only. Importantly, citalopram enantiomers have differences in their clearance.[33] The total amount of citalopram prescribed as escitalopram in the catchment of WWTP A, B and C was 11, 15 and 58 % respectively. Indeed, predicted concentrations were out with the acceptable threshold for citalopram (+ 67 %) and its metabolite desmethylcitalopram (+ 79 %) at WWTP C suggesting this is caused by differences in its prescription. This demonstrates that prescribing behaviour even at a local scale can impact predictions. The predicted concentration of carbamazepine 10,11 epoxide at WWTP A were + 92 % of the measured concentration with no clear indication of the reasoning, especially considering that the parent pharmaceutical carbamazepine had acceptable predicted concentrations at all three WWTPs. However, it had the lowest NF_{Inf} value of all the studied analytes (0.027) (*Table 3*), and likely subject to greater error.

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Pharmaceuticals that had acceptable concentration predictions in influent wastewater and available measured river concentration data (metformin, carbamazepine, propranolol, fluoxetine and clarithromycin) had their concentration increase in river water directly downstream of WWTP D and E effluent discharge points predicted. Greatest agreement between predicted and measured river concentrations were observed for carbamazepine and clarithromycin at WWTP D. They had 9 / 12 and 10 / 12 predicted concentrations within ± 50 % of their corresponding measured concentration, respectively (*Figure 3*). Predictions were generally better in river water downstream of WWTP D compared to WWTP E. WWTP D treats wastewater for > 20 times more people than WWTP E and the average flow of the receiving river is considerably greater (> 30 times) than WWTP E. The reliance on grab sampling for the river water measured concentrations is a likely contributor to the poorer predictions for WWTP E as greater concentration variation can be expected throughout the day here. Grab sampling can only provide a concentration for a specific point in time and may not be representative of the average daily concentration. Poorest predictions were observed for metformin whereby predicted concentrations were underestimated. For example, predicted concentrations at WWTP D were in the range 0.016 to 0.070 µg/L and measured concentrations in the range 0.10 to 3.9 µg/L (*Figure 3*). Its high removal during wastewater treatment used in prediction calculations (99 %, *Table 3*) will see a small reduction in its removal efficiency during wastewater treatment increasing its concentration in river water significantly. Removal efficiencies < 80 % have been previously reported for activated sludge WWTPs.[34] Therefore, differences in removal achieved by the two WWTPs despite adopting the same treatment technology (activated sludge) could contribute to the disparity in predicted concentrations in river water.

3.5. Considerations and future perspectives

Taking the NF_{Inf} approach to predict pharmaceutical and metabolite concentrations in influent wastewater was proven to provide more accurate concentration predictions than a conventional approach of making predictions using human excretion information (*Table 3*). An important consideration is that representative wastewater concentration data from a range of WWTPs is needed to derive (and validate) the NF_{Inf} values if this approach is to be extended for further analytes. However,

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it was demonstrated that differences in prescribing behaviour (and excretion) of chiral pharmaceuticals is an important consideration and cannot be accounted for with a single NF_{Inf} value for that pharmaceutical. To expand this approach to other geographical locations it is important to establish variations in NF_{Inf} values that may result from differences in the pharmacokinetics of different populations due to genetic variations, population demographic (e.g., age) and environmental factors (e.g., diet and lifestyle).[35,36]

Applying this approach to treated wastewater and river waters receiving treated effluent requires further work. It is expected that predicting concentrations of pharmaceuticals in treated effluents can have *NF* values derived which account for WWTP removal. This approach is expected to be successful for those analytes with limited removal during treatment (e.g., carbamazepine). The prediction of these analytes in river water will require a whole river catchment modelling approach for accurate predictions. This will enable analyte concentrations already present in the river from upstream WWTPs to be incorporated into predictions. Nevertheless, utilising *NF* values which account for WWTP removal will be essential for this modelling approach. Findings demonstrated positive results for both carbamazepine and clarithromycin at WWTP D but further validation is necessary using measured analyte concentrations from representative river water samples (i.e., collected as flow weighted 24-hour composites).

4. Conclusion

Predicting pharmaceutical concentrations in influent wastewater by the conventional approach of applying excretion data to prescription data is limited. Most predicted analyte concentrations were out with an acceptable range (± 50 % of the measured concentration). This was mainly attributed to in-sewer deconjugation of glucuronide metabolites back to the parent pharmaceutical resulting in the systematic underestimation of predicted concentrations. The use of numerical correction factors which account for changes between the prescription of an analyte and its presence in wastewater can reduce the error in prediction of pharmaceutical concentrations. This approach is most suited to prescription only pharmaceuticals and their metabolites. Expanding this approach to treated wastewaters and river water by accounting for their removal during wastewater treatment is a sustainable way of providing

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comprehensive data for environmental risk assessment. This is essential to inform where technological or 'upstream' intervention (e.g., environmentally informed prescribing) may be needed to target pharmaceutical environmental impacts.

Author contributions

Bruce Petrie: writing – original draft, methodology, investigation, formal analysis, data curation, conceptualisation, project administration, funding acquisition. Elise Cartmell: writing – review & editing, resources, conceptualisation.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information.

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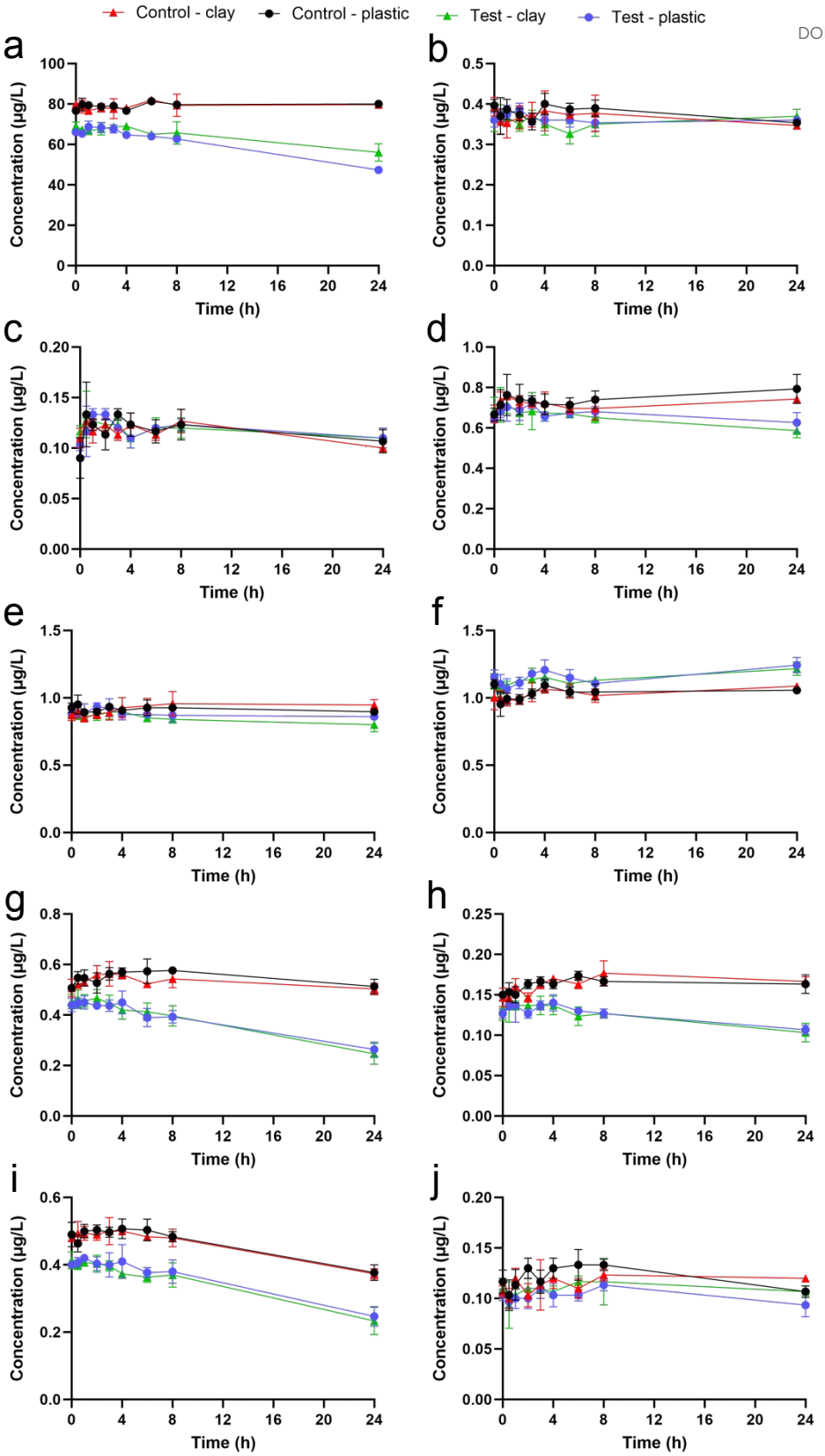

Figure 1. Pharmaceutical and metabolite concentrations in wastewater of laboratory-scale control and test gravity sewers during 24 hours (n = 3). Control sewers have no previously established biofilm on pipe surfaces or sludge layer. Test sewers were previously in operation for > 6 months to establish biofilm and sludge layer. Key: a, metformin; b, carbamazepine; c, carbamazepine 10,11 epoxide; d, propranolol, e, venlafaxine; f, desmethylvenlafaxine; g, citalopram; h, desmethycitalopram; i, clarithromycin; j, desmethylclarithromycin.

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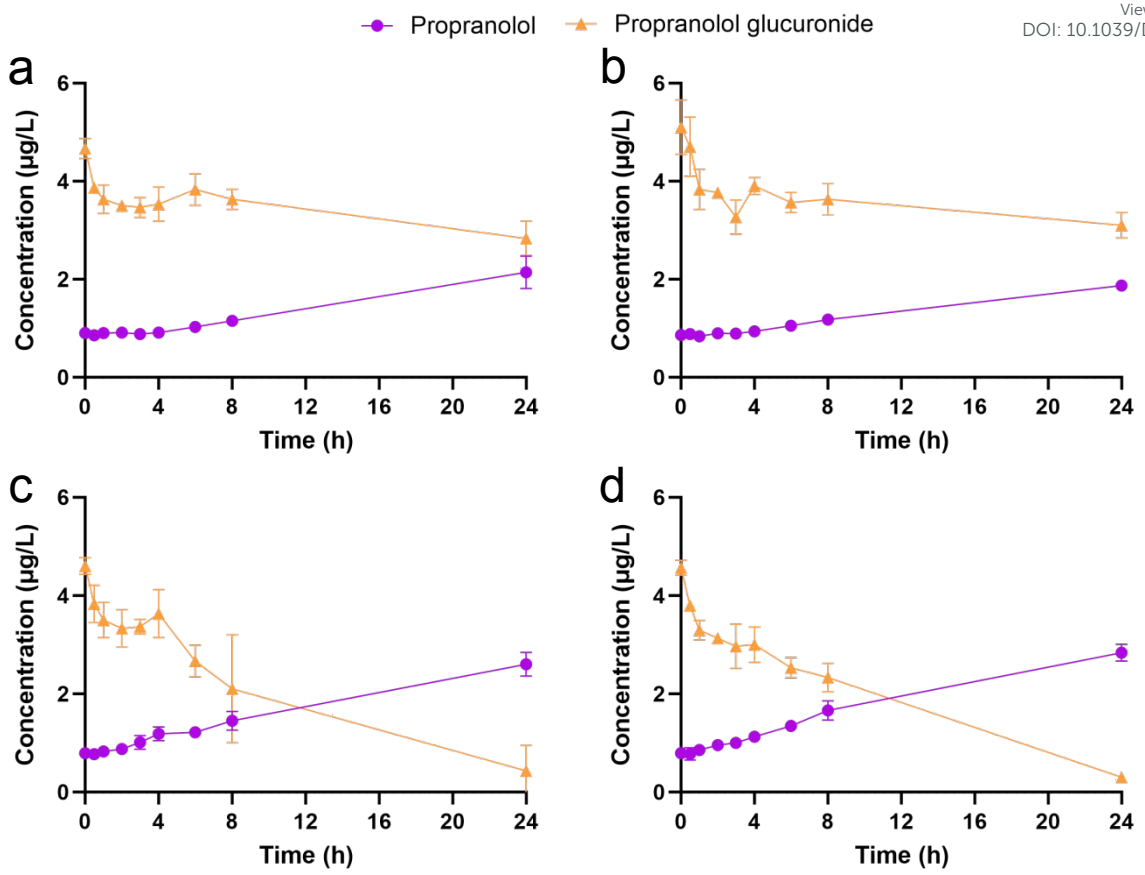

Figure 2. Propranolol and propranolol β-D-glucuronide concentrations in wastewater of laboratory-scale control and test gravity sewers during 24 hours (n = 3). Control sewers have no previously established biofilm on pipe surfaces or sludge layer. Propranolol β-D-glucuronide was initially spiked at a concentration of 5 µg/L. Test sewers were previously in operation for > 6 months to establish biofilm and sludge layer. Key: a, control – vitrified clay; b, control – plastic (PVC); c, test – vitrified clay; d, test – plastic (PVC).

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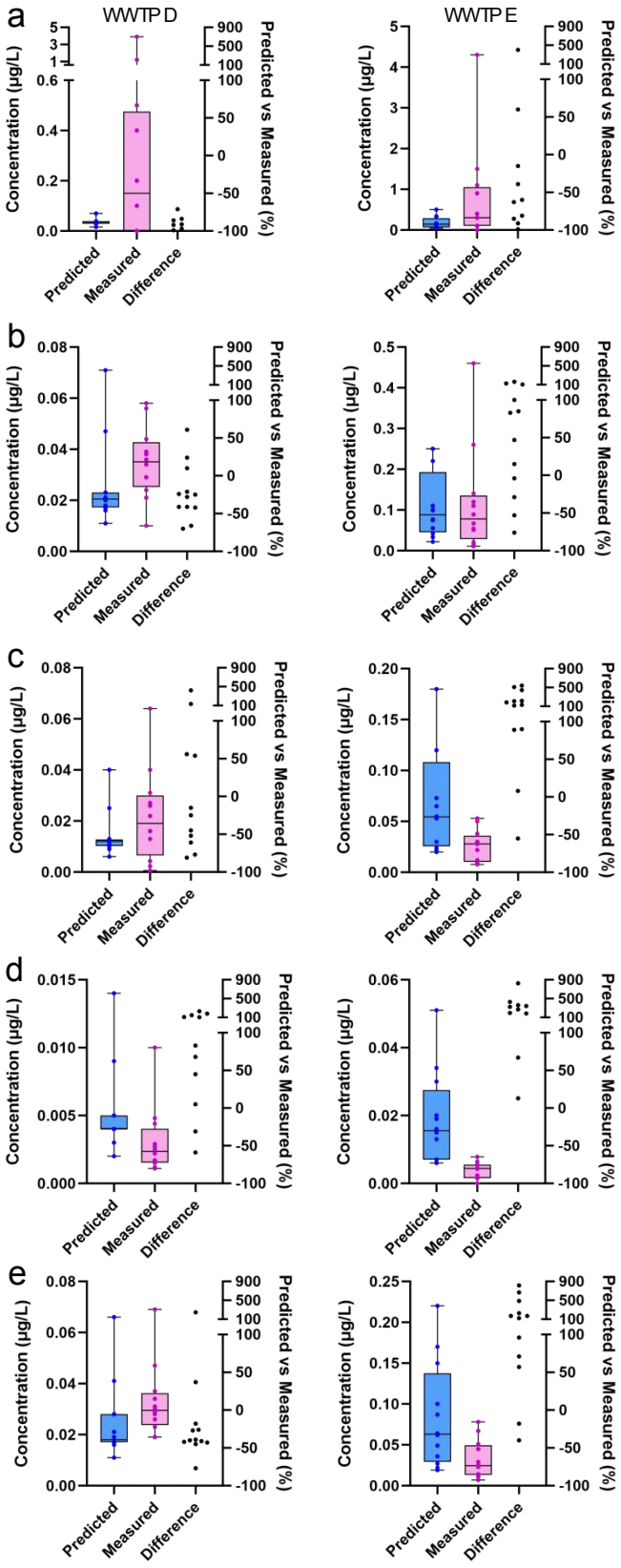

Figure 3. Predicted and measured concentration increase in river water from effluent discharge of WWTP D and E, and difference between predicted and measured concentrations (%, n = 12 where there is sufficient measured data available. See *Tables S8 – 12*). Key: a, metformin; b, carbamazepine, c, propranolol; d, fluoxetine; e, clarithromycin. Note: one data point for WWTP D and one data point for WWTP E is > 900 % difference and not shown on graph.

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Table 1. List of pharmaceuticals previously identified as a possible risk to the Scottish environment, their selected metabolites and isotopically labelled surrogates studied in three WWTPs in North-east Scotland.

Analyte		Risk to Scottish environment?[16,17]	Metabolite?	Isotopically labelled surrogate?
No.	**Name**			
1	Metformin	✓		
2	Carbamazepine	✓		
3	Carbamazepine-10,11-epoxide		✓	
4	Propranolol	✓		
5	Venlafaxine	✓		
6	Desmethylvenlafaxine		✓	
7	Fluoxetine	✓		
8	Norfluoxetine		✓	
9	Citalopram	✓		
10	Desmethylcitalopram		✓	
11	Ranitidine	✓		
12	Ranitidine-N-oxide		✓	
13	Clarithromycin	✓		
14	Desmethylclarithromycin		✓	
15	Metformin-d_6			✓
16	Carbamazepine-d_{10}			✓
17	Propranolol-d_7			✓
18	Venlafaxine-d_6			✓
19	Fluoxetine-d_6			✓
20	Norfluoxetine-d_6			✓
21	Citalopram-d_6			✓
22	Clarithromycin-^{13}C-d_3			✓

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Table 2. Information on WWTP A, B and C including flow, population equivalent numbers and sewer type.

WWTP	$Flow_{WW}$ (L/d)[a]	NH_4^+ (mg/L)[a]	Population equivalent numbers			CF_{pop}	Sewer residence time (h)[d]	Sewer type (%)[e]		Pipe material (%)[e]		
			Theo.[b]	Pred.[c]	Diff. (%)			Gravity	Rising main	Clay	Plastic	Concrete
A	7.93×10^7	26.4	2.5×10^5	2.6×10^5	+1	1.01	3.5	95	5	68	9	18
B	1.23×10^7	32.8	4.6×10^4	5.0×10^4	+8	1.08	1.5	99	1	71	8	21
C	6.53×10^6	35.7	2.4×10^4	2.8×10^4	+19	1.19	1.7 & 2.7	89	11	61	26	11

[a]Flow and NH_4^+ is the average of five days

[b]Household population equivalent number and does not include non-household, tourist or trade effluent contributions

[c]$Pred. = \frac{NH_4^+ \times Flow_{WW}}{8{,}100\ (= NH_4^+\ excreted\ per\ day\ in\ mg/d)^{10}}$

[d]Average sewer residence time at peak flow during dry weather conditions, WWTP C has two residence times as it receives wastewater from two major sub-catchments.

[e]sewer type and pipe material are based on length.

Key: WWTP, wastewater treatment plant; $Flow_{WW}$, wastewater flow; NH_4^+, ammonium; Theo., theoretical; Pred., predicted; CF_{pop}, correction factor for difference between theoretical and predicted population.

Table 3. Measured and predicted pharmaceutical and metabolite concentrations in influent wastewater at WWTP A, B and C (n = 5 for each WWTP). Those highlighted green represent ± 50 %, orange ± 51 – 75 %, and red > ± 75 % difference between predicted and measured concentrations.

Pharmaceutical	WWTP	Measured (µg/L)	Prescribed (g/d)		Daily dose (g)	Toilet flushes (/d)[a]	Human excretion prediction approach			Numerical correction factor prediction approach				
			Community	Hospital			CF_{exc}[b]	Predicted (µg/L)	Diff. (%)[c]	NF_{Inf}	Predicted (µg/L)	Diff. (%)[c]	Rem_{AS} (%)[d]	NF_{AS}
Metformin	A	73 ± 9.8	7,269	113	0.78	47,324	0.91	86 ± 8.6	+17	0.86	80 ± 5.8	+11	99	0.0087
	B	1.3×10^2 ± 15	878	-		5,626		70 ± 6.3	-44		62 ± 5.0	-50		
	C	97 ± 11	752	5.3		4,853		1.3×10^2 ± 15	+32		1.0×10^2 ± 19	+6		
Carbamazepine	A	0.42 ± 0.059	400	17.0	0.80	2,608	0.012	0.064 ± 0.0064	-85	0.090	0.48 ± 0.034	+17	0	0.090
	B	0.52 ± 0.068	43.4	-		271		0.046 ± 0.0041	-91		0.32 ± 0.026	-37		
	C	0.64 ± 0.44	48.7	0.54		308		0.11 ± 0.013	-83		0.70 ± 0.13	+35		
Carbamazepine 10,11 epoxide	A	0.075 ± 0.0070	-	-	-	2,608	0.011	0.059 ± 0.0059	-21	0.027[g]	0.14 ± 0.010	+92	-	-
	B	0.10 ± 0.013	-	-		271		0.042 ± 0.0038	-59		0.10 ± 0.0078	-6		
	C	0.21 ± 0.045	-	-		308		0.010 ± 0.012	-52		0.21 ± 0.039	+2		
Propranolol	A	0.45 ± 0.15	264	3.4	0.16	8,473	0.0040	0.013 ± 0.0010	-97	0.14	0.48 ± 0.034	+17	18	0.12
	B	0.61 ± 0.10	36.5	-		1,156		0.012 ± 0.0010	-98		0.42 ± 0.034	-30		
	C	0.61 ± 0.10	31.3	0		991		0.022 ± 0.0030	-96		0.69 ± 0.13	+14		
Venlafaxine	A	0.75 ± 0.14	291	9.8	0.15	10,016	0.049	0.19 ± 0.019	-75	0.25	0.95 ± 0.068	+30	-	-
	B	1.2 ± 0.12	49.3	-		1,643		0.21 ± 0.019	-83		1.0 ± 0.082	-18		
	C	0.89 ± 0.080	24.2	0		807		0.22 ± 0.026	-75		0.95 ± 0.18	+7		
Desmethylvenlafaxine	A	1.2 ± 0.10	-	-	-	10,016	0.25	0.98 ± 0.098	-15	0.42	1.6 ± 0.12	+39	-	-
	B	1.9 ± 0.30	-	-		1,643		1.1 ± 0.10	-43		1.7 ± 0.14	-11		
	C	1.6 ± 0.21	-	-		807		1.1 ± 0.14	-27		1.6 ± 0.30	+2		
Fluoxetine	A	0.18 ± 0.028	97.5	1.3	0.018	27,631	0.025	0.032 ± 0.0030	-83	0.18	0.22 ± 0.016	+24	48	0.093
	B	0.28 ± 0.020	13.6	-		3,810		0.030 ± 0.0030	-89		0.20 ± 0.016	-29		
	C	0.33 ± 0.031	11.9	0		3,315		0.055 ± 0.0070	-83		0.33 ± 0.062	+4		
Norfluoxetine	A	0.087 ± 0.0090	-	-	-	27,631	0.085	0.11 ± 0.011	+24	0.074	0.092 ± 0.0066	+7	-	-
	B	0.12 ± 0.0040	-	-		3,810		0.10 ± 0.0090	-16		0.082 ± 0.0067	-33		
	C	0.12 ± 0.013	-	-		3,315		0.19 ± 0.022	+61		0.14 ± 0.025	+19		
Citalopram	A	0.35 ± 0.033	76.8[f]	0.6[f]	0.016	24,170	0.16	0.16 ± 0.016	-55	0.37[g]	0.36 ± 0.026	+3	-	-
	B	0.50 ± 0.071	8.9[f]	-		2,777		0.13 ± 0.011	-75		0.27 ± 0.022	-46		
	C	0.45 ± 0.054	12.8[f]	<0.1[f]		4,000		0.38 ± 0.045	-14		0.74 ± 0.14	+67		
Desmethylcitalopram	A	0.19 ± 0.017	-	-	-	24,170	0.16	0.15 ± 0.015	-20	0.20[g]	0.20 ± 0.014	+3	-	-
	B	0.24 ± 0.022	-	-		2,777		0.12 ± 0.011	-50		0.14 ± 0.012	-41		
	C	0.22 ± 0.019	-	-		4,000		0.37 ± 0.044	+64		0.40 ± 0.074	+79		
Ranitidine	A	0.053 ± 0.020	0	0	-	-	0.29	-	-	-	-	-	-	-
	B	0.037 ± 0.016	0	-		-		-	-		-	-		
	C	0.018 ± 0.011[e]	0	0		-		-	-		-	-		
Ranitidine-N-oxide	A	nd	-	-	-	-	0.040	-	-	-	-	-	-	-
	B	nd	-	-		-		-	-		-	-		
	C	nd	-	-		-		-	-		-	-		

Clarithromycin	A	0.36 ± 0.040	65.8	21.3	0.50	871	0.30	0.34 ± 0.033	-7	0.34	0.38 ± 0.027	+6	56	0.15
	B	0.47 ± 0.11	10.3	-		103		0.27 ± 0.025	-42		0.29 ± 0.23	-36		
	C	0.65 ± 0.23	13.0	0		130		0.73 ± 0.087	+12		0.70 ± 0.13	+18		
Desmethylclarithromycin	A	0.068 ± 0.025	-	-	-	871	0.056	0.063 ± 0.0060	-15	0.094	0.10 ± 0.0075	+46	-	-
	B	0.14 ± 0.032	-	-		103		0.051 ± 0.0050	-64		0.079 ± 0.0065	-40		
	C	0.19 ± 0.025	-	-		130		0.14 ± 0.016	-30		0.19 ± 0.036	-1		

[a] $Toilet\ flushes\ (/d) = \frac{Daily\ prescription \times 5\ (= average\ daily\ number\ of\ toilet\ flushes\ per\ person)^{11}}{Daily\ dose}$

[b] $CF_{excretion} = \frac{Median\ total\ excretion\ (\%)}{100}$ – data taken from *Table S5*

[c] $Difference = \frac{(Predicted\ conc. - Measured\ conc.)}{Measured\ conc.} \times 100\ \%$

[d] Taken from Comber *et al*[18]

[e] Detected in two of five samples therefore detection limit (0.01 µg/L) used to determine average concentration

[f] Sum of prescribed citalopram and escitalopram

[g] Did not provide predicted analyte concentrations within ± 50 % of their measured concentration at all three WWTPs

Key: WWTP, wastewater treatment plant; CF_{exc}, correction factor for human excretion; NF_{Inf}, numerical correction factor for influent wastewater; Rem_{AS}, removal by activated sludge treatment; NF_{AS}, numerical correction factor for activated sludge treated wastewater; nd, not detected

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Data availability

The data supporting this article have been included as part of the Supplementary Information.