

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

Bruce Petrie^{a*}, Elise Cartmell^b

^aSchool of Pharmacy, Applied Sciences and Public Health, Robert Gordon University, Aberdeen, AB10 7GJ, UK

^bScottish Water, 55 Buckstone Terrace, Edinburgh EH10 6XH, UK

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

The supplementary information contains three figures and 12 tables with images of laboratory-scale sewers, analyte stability in collected wastewaters, relationship between prediction error and analyte excretion, molar concentration of propranolol and propranolol glucuronide during sewer studies, wastewater flow information, the UPLC gradient and MRM information, instrument and method performance detail, literature excretion data for analytes, trueness vales for the analytical method, the range of numerical correction factors for individual WWTPs and data from river water predictions.

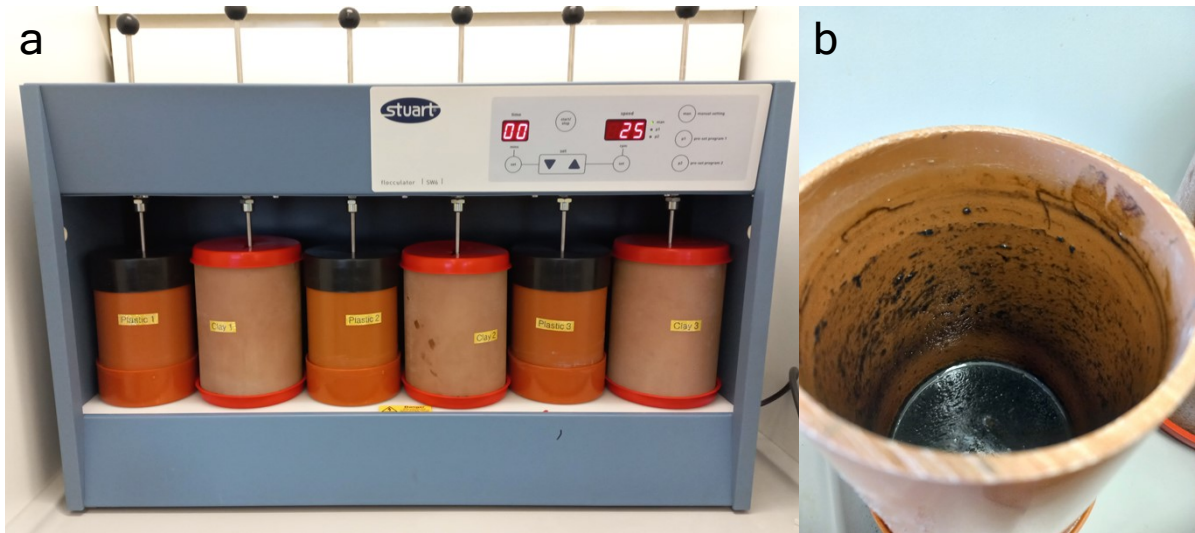


Figure S1. Laboratory-scale gravity sewers (a) and biofilm on pipe surface observed during wastewater change (b).

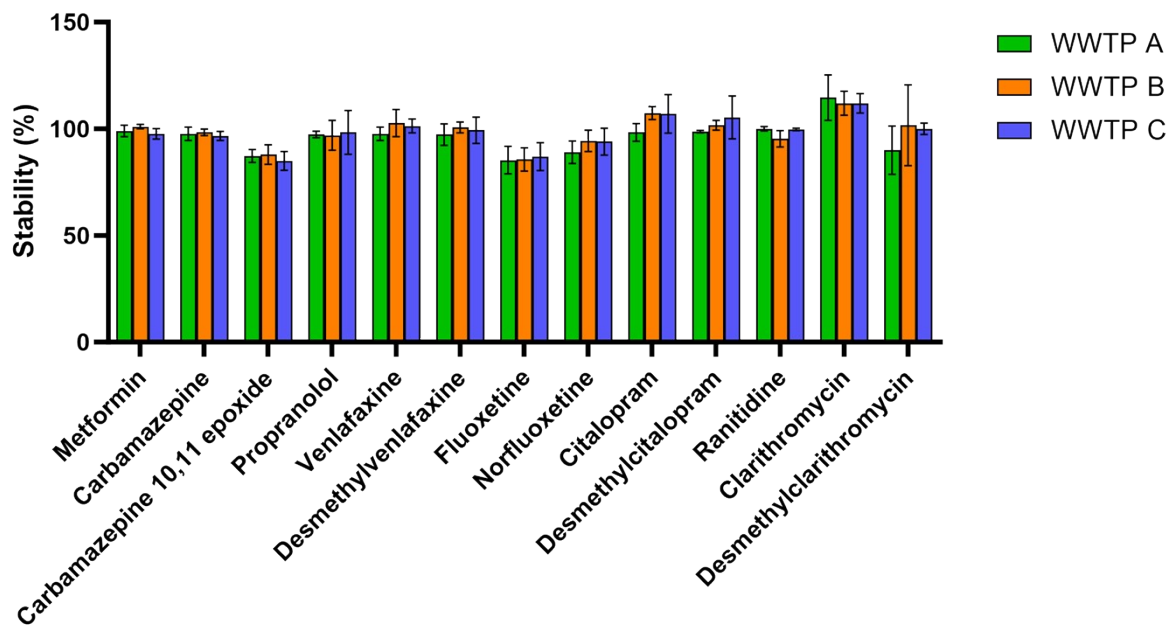


Figure S2. Analyte stability in collected wastewater from WWTP A, B and C during 12 hours. Note: a stability value of 100 % demonstrates no change in concentration.

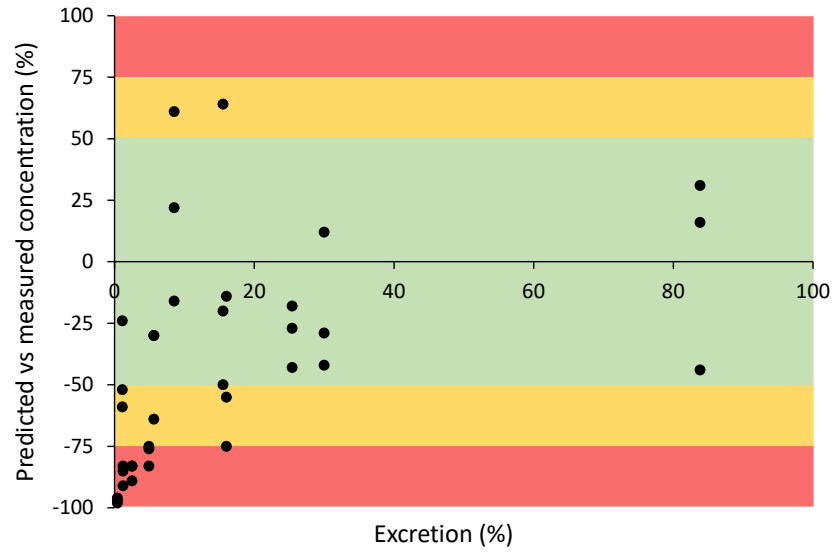


Figure S3. Relationship between median analyte excretion rate (*Table S5*) and concentration difference between predicted and measured analyte concentrations for WWTP A, B and C. Results from each WWTP is plotted as an individual data point. Area shaded green represent $\pm 50\%$, orange $\pm 51 - 75\%$, and red $> \pm 75\%$ difference between the predicted and measured concentrations.

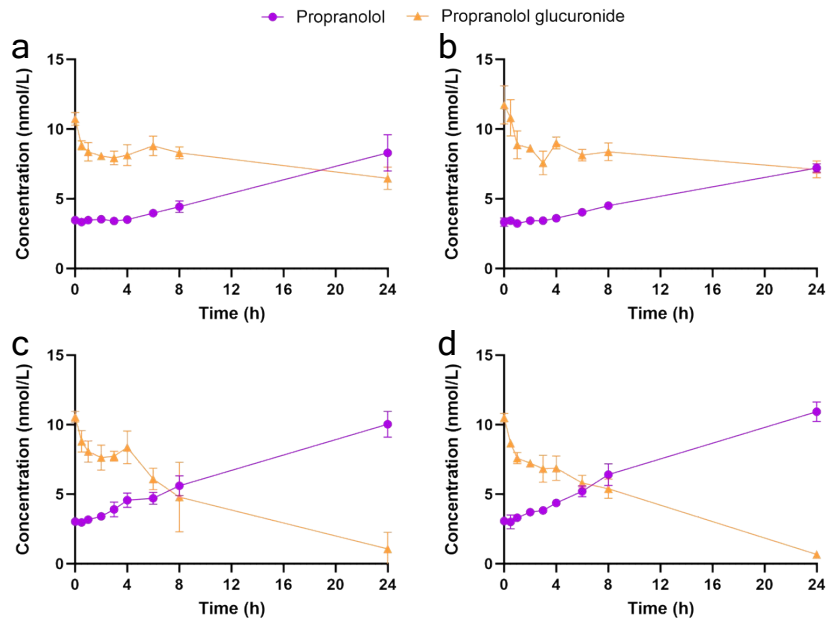


Figure S4. Propranolol and propranolol β -D-glucuronide molar concentrations in wastewater of laboratory-scale control and test gravity sewers during 24 hours ($n = 3$). Control sewers have no previously established biofilm on pipe surfaces or sludge layer. Test sewers were previously in operation for > 6 months to establish biofilm and sludge layer. Key: a, control – vitrified clay; b, control – plastic (PVC); c, test – vitrified clay; d, test – plastic (PVC).

Table S1. Wastewater flow data for individual sampling dates of WWTP A, B and C

WWTP	Sampling date	Flow (L/d)
A	21/08/23 – 22/08/23	7.69×10^7
	22/08/23 – 23/08/23	7.31×10^7
	23/08/23 – 24/08/23	8.44×10^7
	28/08/23 – 29/08/23	7.56×10^7
	29/08/23 – 30/08/23	8.64×10^7
B	22/08/23 – 23/08/23	1.16×10^7
	23/08/23 – 24/08/23	1.32×10^7
	28/08/23 – 29/08/23	1.13×10^7
	29/08/23 – 30/08/23	1.36×10^7
	30/08/23 – 31/08/23	1.18×10^7
C	21/08/23 – 22/08/23	5.53×10^6
	23/08/23 – 24/08/23	5.36×10^6
	28/08/23 – 29/08/23	6.00×10^6
	29/08/23 – 30/08/23	8.22×10^6
	30/08/23 – 31/08/23	7.56×10^6

Table S2. Mobile phase composition and gradient programme for UPLC analysis

Time (min)	Flow rate (mL/min)	Mobile phase A % (5 mM ammonium formate + 0.1 % formic acid in ultrapure water)	Mobile phase B % (5 mM ammonium formate + 0.1 % formic acid in methanol)
0	0.35	95	5
0.5		95	5
9		20	80
11		20	80
11.1		95	5
14		95	5

Table S3. Retention times and multiple reaction monitoring parameters for studied analytes

Analyte	Time (min)	Precursor (m/z)	Cone (V)	Quantifier (m/z)	Collision energy (eV)	Qualifier (m/z)	Collision energy (eV)
Metformin	0.86	130.2	27	60.1	12	71.2	17
Carbamazepine	6.89	237.2	33	194.2	18	179.2	32
Carbamazepine-10,11-epoxide	5.83	253.1	20	180.1	20	210.2	14
Propranolol	5.83	260.2	50	116.1	16	183.1	18
Venlafaxine	5.61	278.3	36	260.3	10	215.2	16
Desmethylvenlafaxine	4.25	264.3	29	246.3	12	107.1	30
Fluoxetine	7.37	310.2	34	44.1	10	148.1	10
Norfluoxetine	7.39	296.2	10	134.2	5	-	-
Citalopram	5.93	325.2	24	262.2	20	116.1	25
Desmethylcitalopram	5.97	311.2	22	109.1	20	262.2	17
Ranitidine	2.36	315.2	31	176.1	16	130.1	25
Ranitidine-N-oxide	2.52	331.2	20	176.1	17	102.1	33
Clarithromycin	7.76	748.5	29	158.2	32	558.4	24
Desmethylclarithromycin	7.76	734.6	28	144.2	30	576.5	18
Propranolol β -D-glucuronide ^a	5.85 & 6.17	436.6	15	260.6	21	116.6	31
Metformin- <i>d</i> ₆	0.86	136.3	28	60.1	13	-	-
Carbamazepine- <i>d</i> ₁₀	6.82	247.1	33	204.2	20	-	-
Propranolol- <i>d</i> ₇	5.78	267.1	22	189.2	18	-	-
Venlafaxine- <i>d</i> ₆	5.58	284.3	34	266.3	12	-	-
Fluoxetine- <i>d</i> ₆	7.34	316.1	19	154.2	9	-	-
Norfluoxetine- <i>d</i> ₆	7.36	302.3	10	140.2	6	-	-
Citalopram- <i>d</i> ₆	5.93	331.2	24	109.1	31	-	-
Carbamazepine- <i>d</i> ₁₀	6.82	247.1	33	204.2	20	-	-
Clarithromycin- ¹³ C- <i>d</i> ₃	7.76	752.6	25	162.2	29	-	-

^aTwo propranolol β -D-glucuronide peaks were combined for data reporting purposes

Note: electrospray ionisation mode = positive, capillary voltage = 2.6 kV, nebulising and desolvation gas = nitrogen, collision gas = argon, gas temperature = 400 °C, desolvation gas flow = 550 L/min, nebulising pressure = 7.0 bar, and cone gas flow = 150 L/h.

Table S4. Analytical method and performance detail for studied pharmaceuticals and metabolites.

Pharmaceutical	Isotopically labelled surrogate	Linear range (µg/L)	r^2	MLQ (µg/L)
Metformin	Metformin- d_6	0.10-200	0.997	0.10
Carbamazepine	Carbamazepine- d_{10}	0.01-5	0.998	0.01
Carbamazepine-10,11-epoxide	Carbamazepine- d_{10}	0.01-5	0.999	0.01
Propranolol	Propranolol- d_7	0.01-20	0.997	0.01
Venlafaxine	Venlafaxine- d_6	0.01-7.5	0.999	0.01
Desmethylvenlafaxine	Venlafaxine- d_6	0.01-7.5	1.000	0.01
Fluoxetine	Fluoxetine- d_6	0.01-5	1.000	0.01
Norfluoxetine	Norfluoxetine- d_6	0.01-5	0.998	0.01
Citalopram	Citalopram- d_6	0.01-5	1.000	0.01
Desmethylcitalopram	Citalopram- d_6	0.01-5	1.000	0.01
Ranitidine	Carbamazepine- d_{10}	0.01-5	1.000	0.01
Ranitidine-N-oxide	Carbamazepine- d_{10}	0.01-20	1.000	0.01
Clarithromycin	Clarithromycin- $^{13}C-d_3$	0.01-5	0.997	0.01
Desmethylclarithromycin	Clarithromycin- $^{13}C-d_3$	0.01-5	0.998	0.01
Propranolol β -D-glucuronide	Propranolol- d_7	0.05-10	0.997	0.05

Key: MLQ, method quantitation limit

Table S5. Excretion data for pharmaceuticals and metabolites from studies reporting oral medicine consumption and urine collected for a sufficient length of time considering drug half-life.

Pharmaceutical/metabolite	Excretion (%)			Reference	Median total excretion (%)
	Urine	Faeces	Total		
Metformin	99	-	99	1	90.5
	-	-	90.5	2	
	50	27	77	3	
Carbamazepine	2	12.5	14.5	4	1.2
	2	-	2	5	
	0.52	-	0.52	6	
	0.48	-	0.48	7	
	1.19	-	1.19	8	
	0.4	-	0.4	9	
	3.0	-	3	10	
Carbamazepine-10,11-epoxide	0.5	-	0.5	1	1.1
	1	-	1	4	
	1.1	-	1.1	6	
	1.45	-	1.45	7	
	2.6	-	2.6	8	
	1.1	-	1.1	9	
	1.1	-	1.1	11	
1.3	-	1.3	12		
Propranolol	13.6	-	13.6	13	0.4
	0.4	-	0.4	14	
	0.37	-	0.37	15	
	12.26	-	12.26	16	
	0.2	-	0.2	17	
	0.25	-	0.25	18	
Venlafaxine	4.025	-	4.025	19	4.9
	5.1	-	5.1	20	
	4.7	-	4.7	21	
	5.2	-	5.2	22	
Desmethylvenlafaxine	22.35	-	22.35	19	25.4
	20.00	-	20	20	
	29.4	-	29.4	21	
	28.5	-	28.5	22	
Fluoxetine	1.25	-	1.25	1	2.5
	2.5	-	2.5	23	
	11	-	11	24	
Norfluoxetine	10	-	10	23	8.5
	7	-	7	24	
Citalopram	26	-	26	25	16.0
	18.7	-	18.7	26	
	14.9	-	14.9	27	
	16	-	16	28	
	8	-	8	29	
Desmethylcitalopram	19	-	19	25	15.5
	16.6	-	16.6	28	
	9.6	-	9.6	29	
	14.3	-	14.3	26	
Ranitidine	30	-	30	1	28.5
	26	-	26	30	
	60	-	60	31	
	27	-	27	32	

Ranitidine-N-oxide	4	-	4	30	4.0
Clarithromycin	35	-	35	1	30.0
	30	-	30	33	
	48.4	-	48.4	34	
	14.5	-	14.5	35	
	22.55	-	22.55	36	
	18	4	22	37	
	23.9	7.5	31.4	38	
N-desmethylclarithromycin	0.9	4.7	5.6	38	5.6

Key: -, not reported or investigated

Table S6. Determined trueness of the direct injection UHPLC-MS/MS method applied to influent wastewaters from WWTP A, B and C (n = 3)

Analyte	Method trueness (%)		
	WWTP A	WWTP B	WWTP C
Metformin	91 ± 7	95 ± 14	91 ± 4
Carbamazepine	107 ± 4	110 ± 3	104 ± 5
Carbamazepine-10,11-epoxide	126 ± 7	119 ± 3	130 ± 7
Propranolol	101 ± 3	103 ± 7	97 ± 2
Venlafaxine	106 ± 3	104 ± 6	102 ± 4
Desmethylvenlafaxine	113 ± 5	97 ± 3	95 ± 5
Fluoxetine	101 ± 5	100 ± 4	103 ± 4
Norfluoxetine	102 ± 9	110 ± 6	110 ± 2
Citalopram	106 ± 5	109 ± 6	110 ± 5
Desmethylcitalopram	96 ± 4	99 ± 8	96 ± 4
Ranitidine	93 ± 9	102 ± 4	132 ± 17
Ranitidine-N-oxide	77 ± 7	87 ± 3	97 ± 8
Clarithromycin	117 ± 1	115 ± 3	114 ± 7
Desmethylclarithromycin	100 ± 1	101 ± 4	99 ± 8

Table S7. Range of individual influent wastewater numerical correction factors (NF_{inf}) determined for pharmaceuticals at WWTP A, B and C

Analyte	WWTP A (n=5)	WWTP B (n=5)	WWTP C (n=5)
Metformin	0.66 – 0.86	1.62 – 1.82	0.68 – 0.95
Carbamazepine	0.063 – 0.091	0.11 – 0.17	0.050 – 0.17
Carbamazepine-10,11-epoxide	0.013 – 0.015	0.027 – 0.031	0.020 – 0.031
Propranolol	0.074 – 0.19	0.17 – 0.23	0.092 – 0.14
Venlafaxine	0.16 – 0.25	0.29 – 0.32	0.18 – 0.29
Desmethylvenlafaxine	0.29 – 0.32	0.43 – 0.54	0.34 – 0.49
Fluoxetine	0.11 – 0.17	0.24 – 0.26	0.12 – 0.24
Norfluoxetine	0.057 – 0.074	0.080 – 0.12	0.047 – 0.080
Citalopram	0.33 – 0.38	0.58 – 0.76	0.18 – 0.25
Desmethylcitalopram	0.18 – 0.20	0.32 – 0.35	0.091 – 0.13
Clarithromycin	0.31 – 0.33	0.41 – 0.65	0.20 – 0.43
Desmethylclarithromycin	0.046 – 0.083	0.11 – 0.22	0.085 – 0.12

Table S8. Measured and predicted concentrations of metformin inputs into river water from WWTP D and WWTP E. Those highlighted green represent ± 50 %, orange $\pm 51 - 75$ %, and red $> \pm 75$ % difference between predicted and measured concentrations.

WWTP	Date	Average prescribed (g/d)	River flow (m ³ /s)	Predicted (µg/L)	Measured (µg/L)	Difference (%)
D	30/01/17	8758	25.2	0.035	0	-
	06/02/17	9436	56.5	0.017	0.20	-92
	27/03/17	9020	28.9	0.031	1.2	-97
	25/04/17	8929	13.0	0.070	0.50	-86
	08/05/17	9535	8.70	0.11	-	-
	05/06/17	9560	31.3	0.031	3.9	-99
	03/07/17	8708	24.9	0.035	0.40	-91
	07/08/17	9454	29.9	0.032	0.20	-84
	04/09/17	9457	35.5	0.027	0	-
	09/10/17	9211	36.3	0.026	0	-
	06/11/17	9487	32.6	0.029	0.10	-71
	04/12/17	9593	29.3	0.033	0	-
	E	18/01/17	499	0.292	0.17	1.1
15/02/17		492	0.359	0.14	1.5	-91
08/03/17		531	0.933	0.057	0.30	-81
26/04/17		440	0.134	0.33	0.90	-63
17/05/17		543	0.109	0.50	0.10	+400
14/06/17		462	0.284	0.16	0.10	+60
12/07/17		492	0.146	0.34	0.40	-15
16/08/17		496	0.407	0.12	0.30	-60
13/09/17		497	0.814	0.061	0.10	-39
18/10/17		521	0.742	0.070	0	-
15/11/17		501	0.320	0.062	0	-
13/12/17		530	0.854	0.062	4.3	-99

Table S9. Measured and predicted concentrations of carbamazepine inputs into river water from WWTP D and WWTP E. Those highlighted green represent $\pm 50\%$, orange $\pm 51 - 75\%$, and red $> \pm 75\%$ difference between predicted and measured concentrations.

WWTP	Date	Average prescribed (g/d)	River flow (m ³ /s)	Predicted (µg/L)	Measured (µg/L)	Difference (%)
D	30/01/17	532	25.2	0.023	0.029	-21
	06/02/17	594	56.5	0.011	0.010	+10
	27/03/17	517	28.9	0.020	0.034	-41
	25/04/17	556	13.0	0.047	0.038	+24
	08/05/17	562	8.70	0.071	0.044	+61
	05/06/17	567	31.3	0.020	0.058	-66
	03/07/17	526	24.9	0.023	0.039	-41
	07/08/17	563	29.9	0.021	0.036	-42
	04/09/17	540	35.5	0.017	0.056	-70
	09/10/17	548	36.3	0.016	0.021	-24
	06/11/17	534	32.6	0.018	0.024	-25
	04/12/17	556	29.3	0.021	0.029	-28
E	18/01/17	26.7	0.292	0.10	0.054	+85
	15/02/17	34.7	0.359	0.10	0.14	-29
	08/03/17	19.7	0.933	0.022	0.011	+100
	26/04/17	31.8	0.134	0.25	0.11	+127
	17/05/17	26.1	0.109	0.25	0.26	-4
	14/06/17	30.7	0.284	0.11	0.46	-76
	12/07/17	30.4	0.146	0.22	0.12	+83
	16/08/17	30.0	0.407	0.077	0.067	15
	13/09/17	25.9	0.814	0.033	0.016	+106
	18/10/17	39.3	0.742	0.055	0.021	+162
	15/11/17	23.2	0.320	0.075	0.051	+47
	13/12/17	34.8	0.854	0.042	0.089	-53

Table S10. Measured and predicted concentrations of propranolol inputs into river water from WWTP D and WWTP E. Those highlighted green represent $\pm 50\%$, orange $\pm 51 - 75\%$, and red $> \pm 75\%$ difference between predicted and measured concentrations.

WWTP	Date	Average prescribed (g/d)	River flow (m ³ /s)	Predicted (µg/L)	Measured (µg/L)	Difference (%)
D	30/01/17	241	25.2	0.013	0.027	-52
	06/02/17	258	56.5	0.0061	0.00060	+917
	27/03/17	265	28.9	0.012	0.0023	+422
	25/04/17	239	13.0	0.025	0.016	+56
	08/05/17	262	8.70	0.040	0.026	+54
	05/06/17	272	31.3	0.012	0.064	-81
	03/07/17	232	24.9	0.012	0.022	-45
	07/08/17	276	29.9	0.012	0.031	-61
	04/09/17	249	35.5	0.0093	0.040	-77
	09/10/17	269	36.3	0.010	0.0043	+133
	06/11/17	268	32.6	0.011	0.013	-15
	04/12/17	265	29.3	0.012	0.016	-25
E	18/01/17	11.1	0.292	0.053	0.028	+89
	15/02/17	14.0	0.359	0.054	0.050	+8
	08/03/17	13.7	0.933	0.020	0.0087	+130
	26/04/17	12.0	0.134	0.12	0.022	+445
	17/05/17	14.1	0.109	0.18	0.028	+543
	14/06/17	14.9	0.284	0.073	0.012	+508
	12/07/17	12.7	0.146	0.12	0.038	+216
	16/08/17	16.0	0.407	0.055	0.029	+90
	13/09/17	12.6	0.814	0.022	0.0077	+186
	18/10/17	15.9	0.742	0.030	0.0097	+209
	15/11/17	15.0	0.320	0.065	0.030	+117
	13/12/17	14.9	0.854	0.024	0.053	-55

Table S11. Measured and predicted concentrations of fluoxetine inputs into river water from WWTP D and WWTP E. Those highlighted green represent $\pm 50\%$, orange $\pm 51 - 75\%$, and red $> \pm 75\%$ difference between predicted and measured concentrations.

WWTP	Date	Average prescribed (g/d)	River flow (m ³ /s)	Predicted (µg/L)	Measured (µg/L)	Difference (%)
D	30/01/17	109	25.2	0.0046	0.0022	+109
	06/02/17	115	56.5	0.0022	0.0012	+83
	27/03/17	112	28.9	0.0042	0.0025	+68
	25/04/17	107	13.0	0.0089	0.0027	+230
	08/05/17	113	8.70	0.014	0.0011	+1,173
	05/06/17	119	31.3	0.0041	0.010	-59
	03/07/17	108	24.9	0.0046	0.0044	+5
	07/08/17	116	29.9	0.0042	0.0029	+45
	04/09/17	110	35.5	0.0033	0.0048	-31
	09/10/17	117	36.3	0.0035	0.0017	+106
	06/11/17	120	32.6	0.0040	0.0016	+150
	04/12/17	115	29.3	0.0042	0.0015	+180
E	18/01/17	4.4	0.292	0.016	0.0043	+272
	15/02/17	4.9	0.359	0.015	0.0053	+183
	08/03/17	6.0	0.933	0.0069	0.0015	+360
	26/04/17	3.7	0.134	0.030	0	-
	17/05/17	5.2	0.109	0.051	0.0055	+827
	14/06/17	5.0	0.284	0.019	0.0017	+1,018
	12/07/17	4.6	0.146	0.034	0.0064	+431
	16/08/17	5.0	0.407	0.013	0.0078	+67
	13/09/17	4.8	0.814	0.0064	0.0015	+327
	18/10/17	4.7	0.742	0.0068	0.0023	+196
	15/11/17	5.9	0.320	0.020	0.0045	+344
	13/12/17	4.9	0.854	0.0062	0.0055	+13

Table S12. Measured and predicted concentrations of clarithromycin inputs into river water from WWTP D and WWTP E. Those highlighted green represent $\pm 50\%$, orange $\pm 51 - 75\%$, and red $> \pm 75\%$ difference between predicted and measured concentrations.

WWTP	Date	Average prescribed (g/d)	River flow (m ³ /s)	Predicted (µg/L)	Measured (µg/L)	Difference (%)
D	30/01/17	330	25.2	0.028	0.034	-18
	06/02/17	298	56.5	0.011	0.019	-42
	27/03/17	279	28.9	0.021	0.037	-43
	25/04/17	246	13.0	0.041	0.030	+37
	08/05/17	266	8.70	0.066	0.019	+247
	05/06/17	237	31.3	0.016	0.069	-77
	03/07/17	198	24.9	0.017	0.028	-39
	07/08/17	240	29.9	0.017	0.029	-41
	04/09/17	280	35.5	0.017	0.031	-45
	09/10/17	279	36.3	0.017	0.023	-26
	06/11/17	290	32.6	0.019	0.026	-27
	04/12/17	386	29.3	0.028	0.047	-40
E	18/01/17	14.6	0.292	0.087	0.051	+71
	15/02/17	13.2	0.359	0.064	0.078	-18
	08/03/17	19.4	0.933	0.036	0.011	+227
	26/04/17	11.7	0.134	0.15	0.067	+124
	17/05/17	13.5	0.109	0.22	0.024	+817
	14/06/17	15.9	0.284	0.10	0.013	+669
	12/07/17	14.4	0.146	0.17	0.029	+486
	16/08/17	11.5	0.407	0.049	0.025	+96
	13/09/17	10.2	0.814	0.022	0.014	+57
	18/10/17	8.0	0.742	0.019	0.0070	+171
	15/11/17	11.5	0.320	0.062	0.023	+170
	13/12/17	13.3	0.854	0.027	0.045	-40

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