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1 **Supplementary Information**

2

3 Table S1: Sampling locations and background information

<i>Location</i>	<i>X-Y coordinate</i>	<i>Time (date)</i>	<i>pH</i>	<i>Temperature °C</i>	<i>Conductivity μS/m</i>
Meuse, Eijsden (@ Dutch-Belgian Border)		13:00 (23/11)	7.6	10.4	698
		9:30 (30/11)	7.8	9.2	728
		13:00 (7/12)	8.1	9.2	726
		11:25 (12/12)	7.9	10.9	375
Jeker, Maastricht	x 176,748 y 317,332	12:30 (23/11)	5.4	8.3	1098
		10:00 (30/11)	6.8	7.6	1206
		12:30 (7/12)	6.2	6.9	966
		10:45 (12/12)	7.1	7.0	1101
Geul, Meerssen	x 178,831 y 322,432	12:00 (23/11)	5.5	7.2	636
		10:30 (30/11)	6.8	7.2	693
		12:00 (7/12)	5.4	6.2	527
		10:15 (12/12)	6.8	6.4	603
Geleenbeek, Oud Roosteren	x 186,165 y 343,274	11:00 (23/11)	5.3	10.1	752
		11:00 (30/11)	6.5	8.7	742
		11:00 (7/12)	6.3	9.3	618
		9:15 (12/12)	6.7	8.4	646
Slijbeek, Heel	x 191,564 y 354,642	10:00 (23/11)	5.5	9.1	747
		12:00 (30/11)	6.3	8.3	769
		10:00 (7/12)	6.2	7.6	518
		12:45 (12/12)	6.5	8.4	637

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6 Table S2: Pharmaceuticals and TPs with their quantification limits (LOQ) and analytical recoveries

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Pharmaceutical or transformation product	CAS nr	LOQ (µg/L)	Recovery %	SD of recovery at 0.5 µg/L (n=8)	SD of recovery at LOQ (n=8)
10,11-trans-diol-carbamazepine ^c	35079-97-1	0.01	101.5	1.6	2.9
2-hydroxy carbamazepine ^c	68011-66-5	0.01	104	1.1	10
3-hydroxy carbamazepine ^c	68011-67-6	0.01	92.6	2.3	4.5
4-acetaminophen sulphate ^c	32113-41-0	0.025	66.2	2.4	10.9
4-formylaminoantipyrine ^c	1672-58-8	0.01	111.9	1.4	3.8
acetyl sulfadiazine ^d	127-74-2	0.01	93	3.5	3.4
α-hydroxy metoprolol ^c	56392-16-6	0.01	109.1	3	10.4
AMPH ^c	38604-70-5	0.01	92	1.7	4.4
erythromycine A ^c	23893-13-2	0.05	36.8	7.1	17.1
atenolol ^a	29122-68-7	0.01	96.5	2.7	4.7
bezafibrate ^a	41859-67-0	0.01	90.7	1.2	2.5
carbamazepine ^a	298-46-4	0.01	94.6	0.9	1.2
carbamazepine-10,11-epoxide ^c	36507-30-9	0.01	108.2	1.7	6.5
ciprofloxacin ^a	85721-33-1	0.50	99.1	1.7	6.1
clenbuterol ^a	37148-27-9	0.01	108.4	3.9	11.4
clindamycin	18323-44-9	0.01	76.1	2.9	9
clofibrac acid	882-09-7	0.01	80.9	3.6	10.5
cortisol ^a	50-23-7	0.025	92.9	2.9	12.1
cyclophosphamide ^a	50-18-0	0.01	52.8	5.8	18.8
diatrizoate (amidotrizoic acid) ^a	117-96-4	0.01	96.9	1.5	2.6
diclofenac ^a	15307-79-6	0.01	102	1.4	4
dimethylaminophenazone ^a	58-15-1	0.01	46.2	6.5	15.7
erytromycin A ^a	59319-72-1	0.025	89.9	3	5.9
phenazone ^a	60-80-0	0.01	105.9	6.2	9.5
fluoxetine ^a	59333-67-4	0.01	97.9	2	7
furosemide ^a	54-31-9	0.01	72.7	6.3	6.9
gemfibrozil ^a	25812-30-0	0.01	105.4	5.3	5.3
guanylurea ^c	141-83-3	0.05	103.6	1.4	7
hydroxy ibuprofen ^c	51146-55-5	0.50	99.7	1.2	4.6
ifosfamide ^a	3778-73-2	0.01	110.6	2	9.7
ketoprofen ^a	22071-15-4	0.01	78.8	1.4	1.9
lincomycin ^a	859-18-7	0.01	134.8	2.8	4.9
metformin ^a	657-24-9	0.05	96.3	2	3
metoprolol ^a	37350-58-6	0.01	103.2	1.9	6.7
metronidazole ^a	443-48-1	0.01	73.5	3.7	14.7
N4-acetyl sulfamethoxazole ^{c,d}	21312-10-7	0.01	104.2	2.2	4.2
naproxen ^a	22204-53-1	0.01	256.7	7.7	7.7
norfluoxetine ^c	83891-03-6	0.50	108.4	14	11.8
o-desmethyl metoprolol ^c	62572-94-5	0.01	85.9	3.1	3.4
o-desmethyl naproxen ^c	(R) 123050-98-6 / (S) 52079-10-4	0.05	111.4	2	9.4
o-Desmethyl tramadol ^c	73986-53-5	0.01	81.1	3.4	5.2
oxcarbamazepine ^{a(c)}	28721-07-5	0.01	93.6	1.1	21.5
paracetamol ^a	103-90-2	0.01	203	7.5	17.1
paroxetine ^a	61869-08-7	0.05	65.7	5.1	4
penicillin V ^{a,c}	132-98-9	0.01	97.9	2.7	5.1
pentoxifylline ^a	6493-05-6	0.01	103.6	2	3.3
pindolol ^a	13523-86-9	0.01	111.1	0.8	9.2
prednisolone ^a	50-24-8	0.05	89.9	3.2	4.8
propranolol ^a	525-66-6	0.01	107	2.9	3.4
propyphenazon ^a	479-92-5	0.01	104	1.1	5.7
salbutamol ^a	18559-94-9	0.01	86.6	2.2	5
salicylic acid ^c	69-72-7	< 5.0	79.2	146.4	4.6
sotalol ^a	3930-20-9	0.01	105.9	2.6	7.2
sulfachloropyridazine ^b	80-32-0	0.01	91.6	1.8	3
sulfadiazine ^{a,b}	68-35-9	0.01	110.3	0.9	8.2
sulfamethoxazole ^{a(b)}	723-46-6	0.01	98.2	1.6	7.2
sulfaquinoxalin ^b	59-40-5	0.01	102.1	1.5	10.2
terbutaline ^a	23031-32-5	0.01	73.2	5.5	2.1
tramadol ^a	27203-92-5	0.01	115	2.2	5.9
trimethoprim ^{a,b}	738-70-5	0.01	109	2.6	7.1
venlafaxine ^a	93413-69-5	0.01	113.6	3.3	2.9

^a human pharmaceutical^b (mainly) veterinary pharmaceutical^c transformation product of human pharmaceutical^d transformation product of (mainly) veterinary pharmaceutical

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11 Table S3: Consumption of pharmaceuticals in Belgium and the Netherlands obtained from RIZIV
 12 (Belgian National Institute for Health and Disability Insurance) and SFK (Dutch Foundation for
 13 Pharmaceutical Statistics), respectively

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Pharmaceutical	Additives	Belgian per capita annual consumption (g/Y)		Dutch per capita annual consumption (g/Y)	
metformin	HCl	16.288	12.702 ^c	14.454	11.272
furosemide		0.123		0.234	
propranolol	HCl	0.232	0.204 ^c	0.089	0.078 ^c
sotalol	HCl	0.295	0.260 ^c	0.245	0.216 ^c
metoprolol	tartrate / succinate	0.211	0.138 ^c	1.808	1.177 ^c
atenolol		0.155		0.193	
bezafibrate		0.010		0.025	
metronidazole		0.014		- ^e	
erythromycin A	stearate / ethylsuccinate	0.011	0.009 ^c	0.045	0.034 ^c
clindamicin	HCl·H ₂ O	0.131	0.116 ^c	0.066	0.059 ^c
lincomycin	HCl	0.006	0.006 ^c	- ^e	
diclofenac	Na / K	0.405	0.375 ^c	0.409	0.380 ^c
naproxen	Na ^a	0.661		0.800	
ketoprofen		0.014		0.007	
tramadol	HCl	0.595	0.523 ^c	0.287	0.252 ^c
paracetamol		1.143		- ^e	
carbamazepine		0.513		0.608	
oxcarbamazepine		0.054		- ^e	
venlafaxine	HCl	0.385	0.340 ^c	0.215	0.190 ^c
metronidazole		0.080		0.083	
gemfibrozil		0 ^d		0.305	
sulfamethoxazole	Trimethoprim ^b	- ^e		0.233	
trimethoprim	Sulfamethoxazole ^b	- ^e		0.030	

15 ^a Mass of additive not included in the Defined Daily Dose

16 ^b Cotrimoxazole is a combination of sulfamethoxazole and trimethoprim in a 5:1 mass ratio

17 ^c Consumption of pharmaceuticals corrected for additions to the formulation (e.g. HCl, Na, K, tartrate, succinate, stearate or
 18 ethylsuccinate)

19 ^d gemfibrozil is not prescribed in Belgium

20 ^e no data obtained

21 **Description of chemical analysis**

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23 **Internal standards**

24 0.5 µg/L internal standard is added to the sample, subsequently, the sample is filtered over a 0.20 µm
 25 filter and directly injected.

26

27 Internal standards are:

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<i>Internal standards</i>	<i>CAS nr.</i>	<i>Elemental composition</i>
Atenolol-d7	1202864-50-3	C ₁₄ D ₇ H ₁₅ N ₂ O ₃
Atrazine-d5	163165-75-1	C ₈ D ₅ H ₉ ClN ₅
Bentazone-d6	-	C ₁₀ D ₆ H ₆ N ₂ O ₃ S
Benzotriazol-d4	1185072-03-0-	C ₆ D ₄ HN ₃
Carbamazepine-d10	132183-78-9	C ₁₅ D ₁₀ H ₂ N ₂ O
Fluoxetine-d5	1173020-43-3	C ₁₇ D ₅ H ₁₃ F ₃ NO
Gemfibrozil-d6	1184986-45-5	C ₁₅ D ₆ H ₁₆ O ₃
Metformin-d6	1185166-01-1	C ₄ D ₆ H ₅ N ₅
Paracetamol-d3	60902-28-5	C ₈ D ₃ H ₆ NO ₂
Phenazone-d3	65566-62-3	C ₁₁ D ₃ H ₉ N ₂ O
Sulfamethoxazole-d4	1020719-86-1	C ₁₀ H ₇ D ₄ N ₃ O ₃ S

29

30 **Injection and liquid chromatographic separation**

31 Two LC separations and subsequent analysis are performed. Most compounds are separated by reversed
 32 phase chromatography while metformin and guanylurea are separated by normal phase chromatography.
 33 Details are given below.

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<i>Hypersil Gold - reversed phase</i>	
Flitration of the sample	Spartan 0.20 µm filter
UHPLC-pump	Accela
Autosampler	Accela
Autosampler washing liquid	70 % acetonitrile, 15 % methanol, 15 % Milli-Q
Analytical column	Hypersil Gold 1.9 µm 100 x 2.1 mm
Guardcolumn	Krudkatcher Ultra HPLC in-line Filter 0.5 µm
Column thermostate	Accela 25 °C
Vials	1.8 ml; afmetingen 12 x 32 mm
Tray temperature	15 °C
Divert valve (heart-cutting)	0.5 - 14 min

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<i>ZIC HILIC - normal phase (aberrations of the previous separation are given)</i>	
Autosampler washing liquid	70 % acetonitrile, 30 % Milli-Q
Analytical column	ZIC HILIC 3.5 µm 100A 100 x 2.1 mm
Guardcolumn	Guard column ZIC HILIC 14 x 1,0 mm, 5µm
Injection loop volume	50 µl
Divert valve (heart-cutting)	3 - 9 min

36

<i>Separation gradient program UPLC - Hypersil Gold column</i>				
Step	Time (m)	Milli-Q + 0.05 % acetic acid (%)	Acetonitrile + 0.05 % acetic acid (%)	Flow (µl/min)
0	0	95	5	300
1	1	95	5	300
2	15	0	100	300
3	17	0	100	300
4	17	95	5	300
5	20	95	5	300

37

Separation gradient program UPLC - ZIC HILIC column				
Step	Time (m)	Milli-Q + 5 mM ammonium formate pH 3.2 (%)	Acetonitrile (%)	Flow (µl/min)
0	0	5	95	300
2	6	90	10	300
4	8	5	95	300

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Analysis and mass spectrometric settings

Mass spectrometer	
Mass spectrometer	TSQ Vantage
Scan method	SRM
Pressure collision cell (Ar)	1.5 mTorr
LC/MS interface	ESI
Ionisation mode	positive/negative
Cycle time	0.50 s
Spray voltage	3.0/2.5 kV
Capillary temperature	275 °C
Vaporizer temperature	285 °C
Sheath gas (N ₂)	30 (Arb)
Auxilliary gas (N ₂)	10 (Arb)
Ion sweep gas (N ₂)	10 (Arb)
Resolution Q1	0,7 (FWHM)
Resolution Q3	0,7 (FWHM)

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All samples were analysed within one analytical run in order to reduce variability of the analytical procedure. Blanks and external standards were measured once every ~10 samples. Additionally both the blank matrix and sample matrices were spiked with the test chemicals to determine matrix dependent differences in sensitivity. The recoveries of the external standards and matrix effects did not exceed the range of 75% to 125%, so no corrections were made for the different samples.