Supplementary material for the manuscript: “Urban groundwater contamination by non–steroidal anti–inflammatory drugs”

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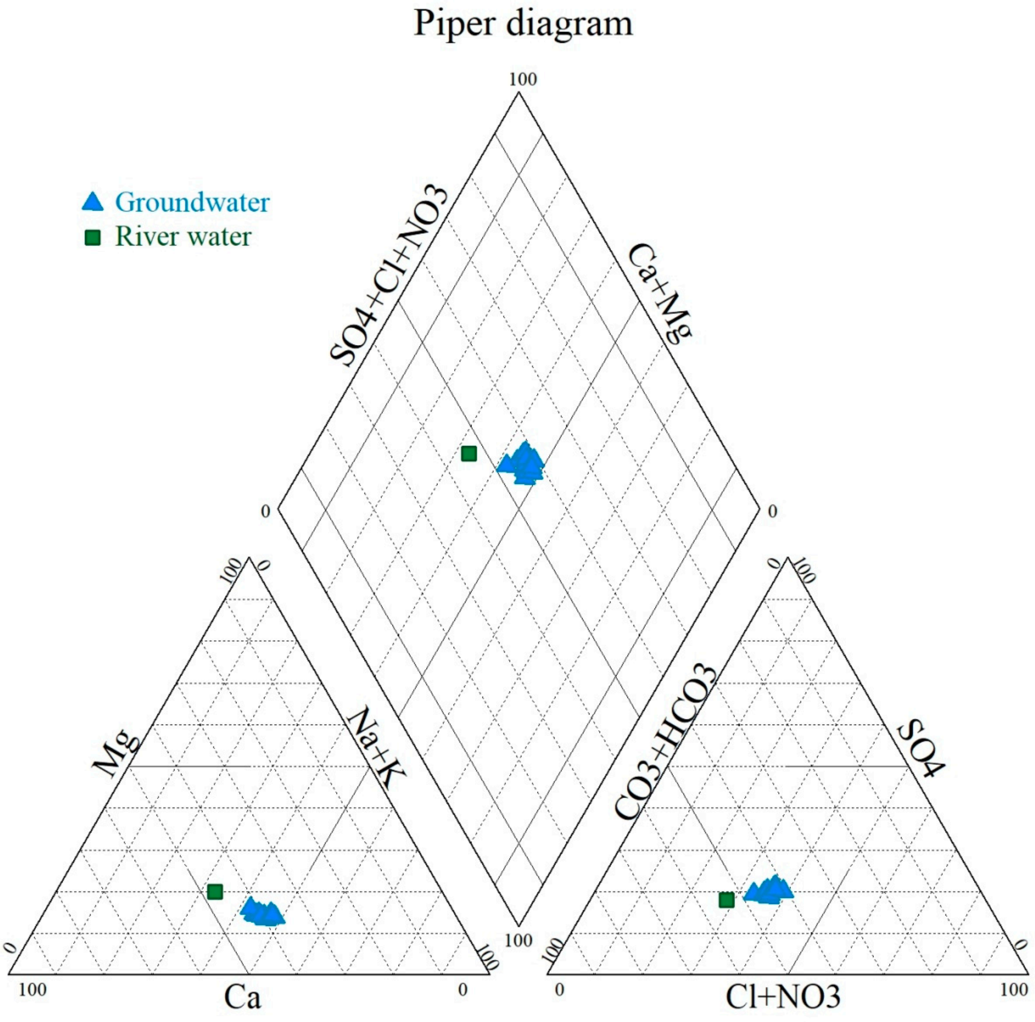

Figure S1. Piper diagram showing major ion chemistry of the groundwater (blue triangles) and river water (green squares) [1].

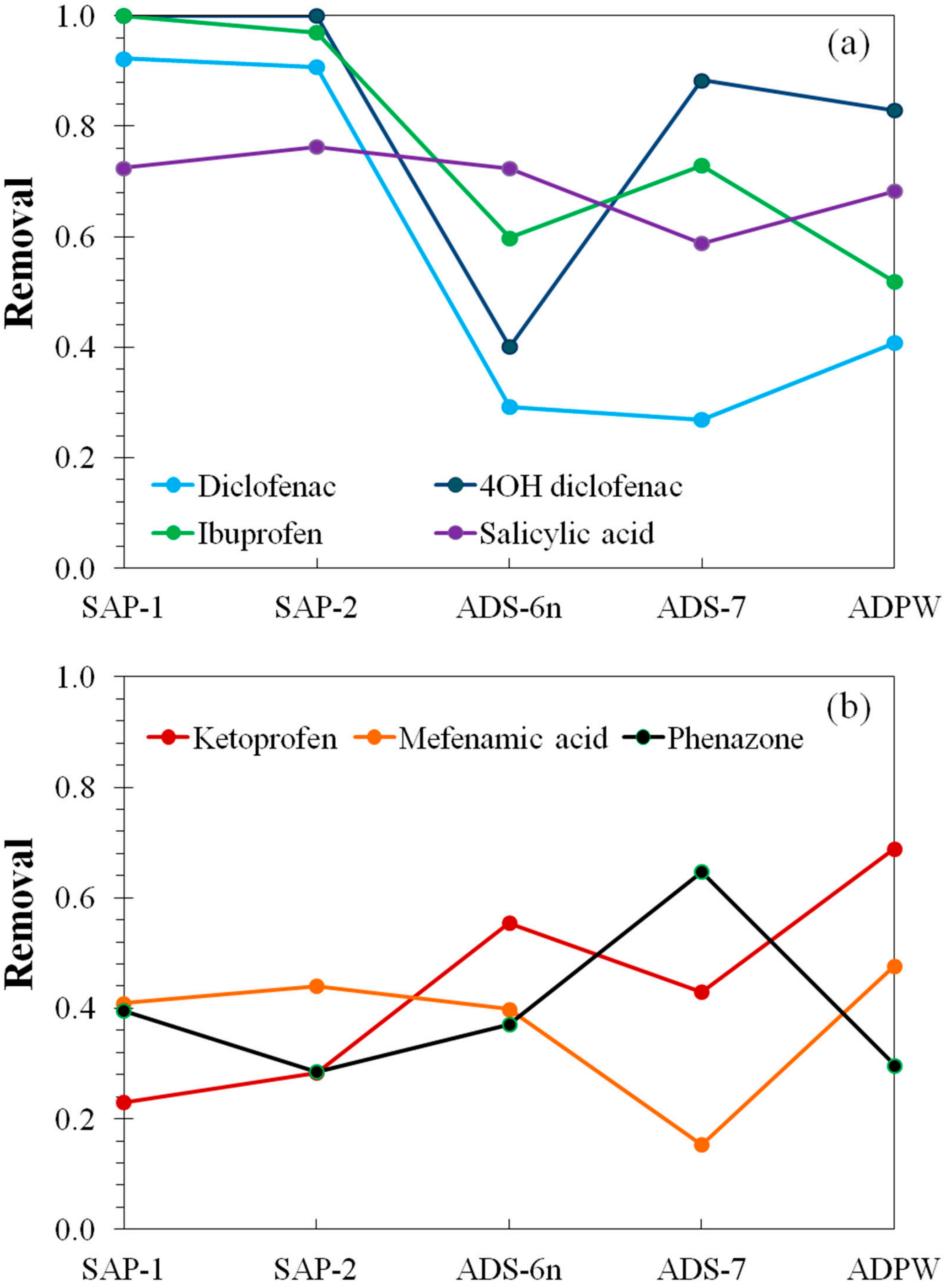

Figure S2. Removal of the NSAIDs along a linear ground water flow path (from SAP−2b to ADPW) for: **(a)** diclofenac, 4OH diclofenac, ibuprofen, and salicylic acid; and **(b)** ketoprofen, mefenamic acid, and phenazone. The removal was evaluated as follows: $1-(C_{GW-Obs}/C_{SAP-2b})$, where C_{GW-Obs} and C_{SAP-2b} are the concentrations of a given NSAID in the groundwater sampling points and at SAP−2b, respectively.

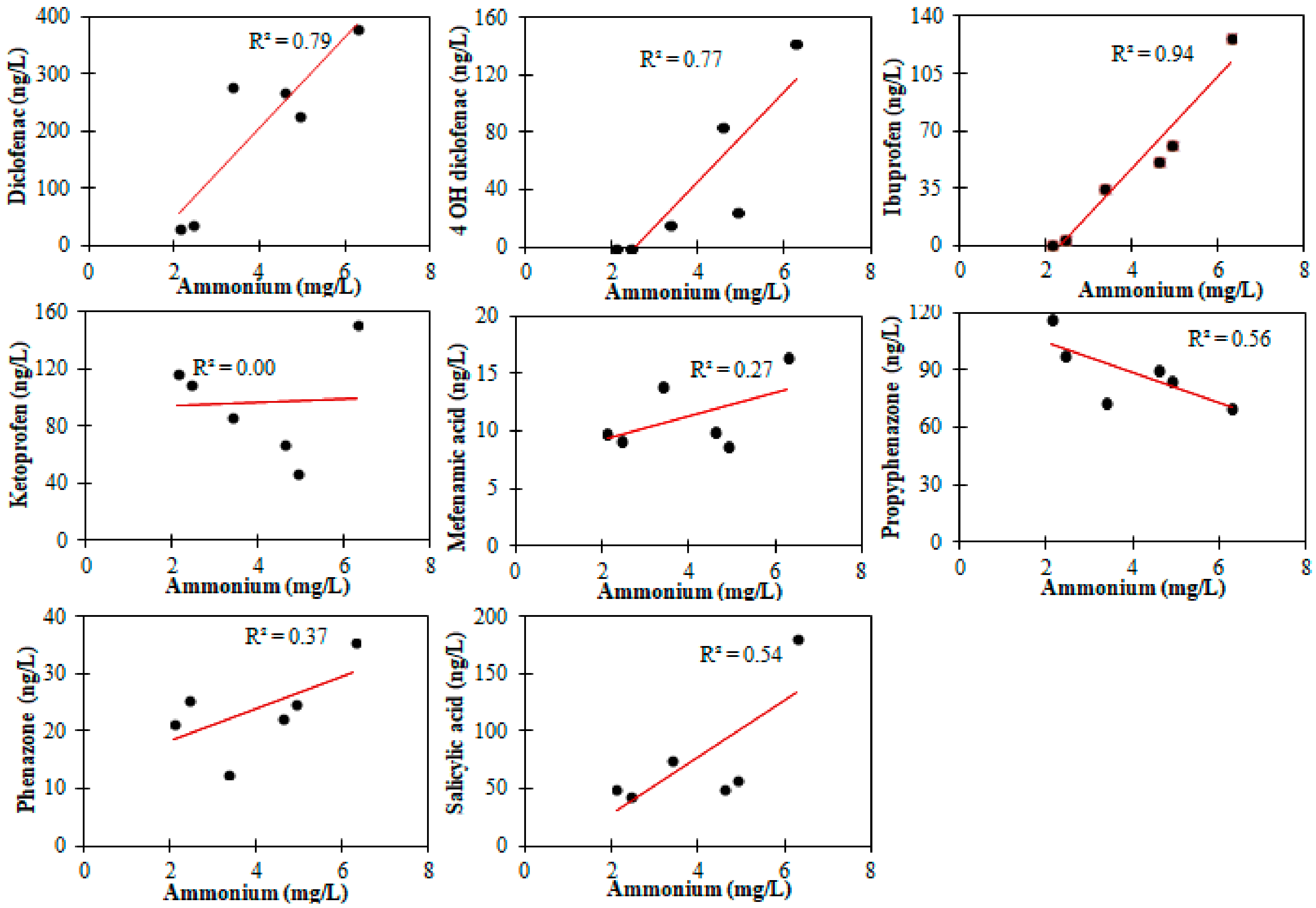

Figure S3. R–squared (R^2) values for the target NSAIDs (ng/L) vs. ammonium (mg/L).

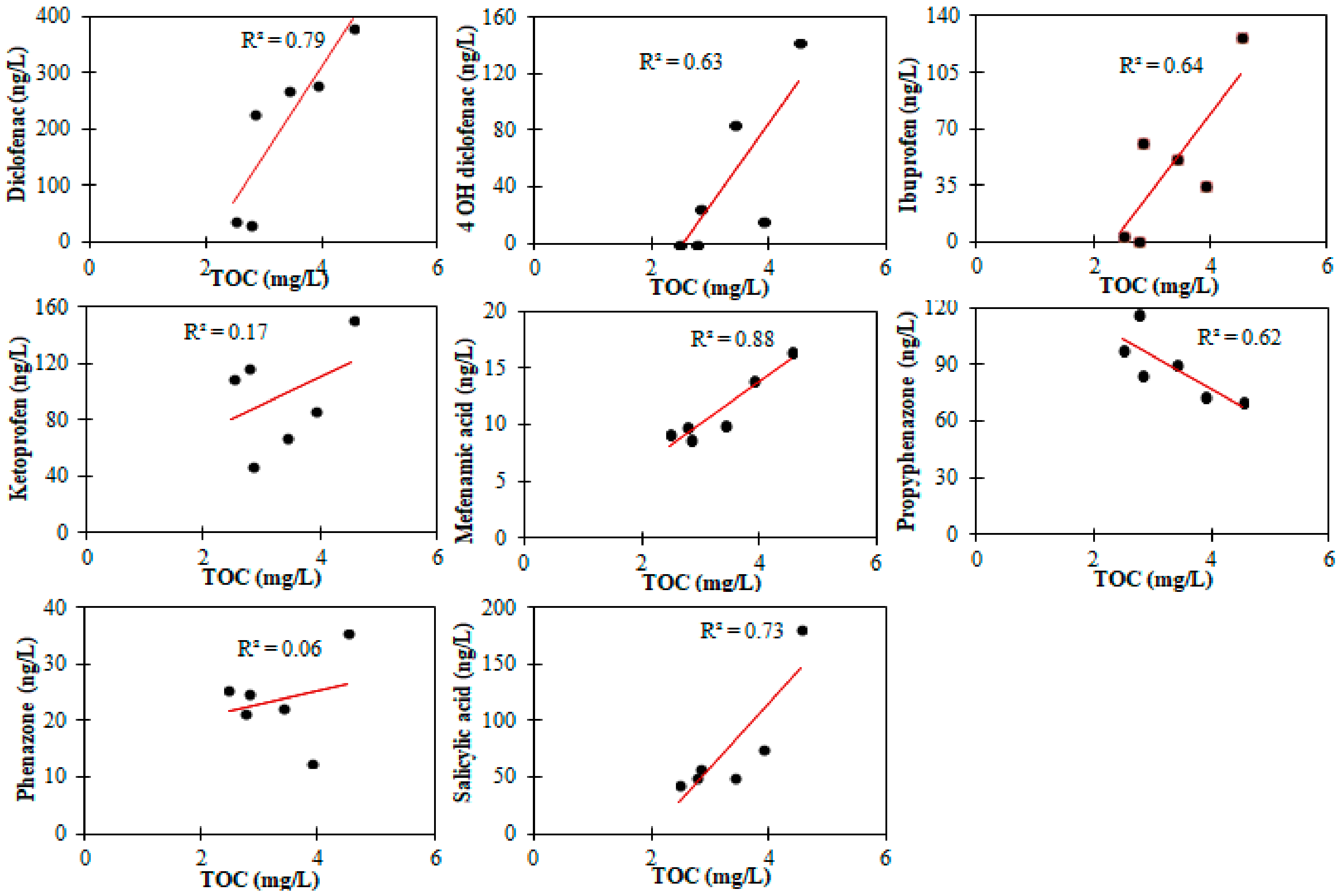

Figure S4. R–squared (R^2) values for the target NSAIDs (ng/L) vs. total organic carbon (TOC, mg/L).

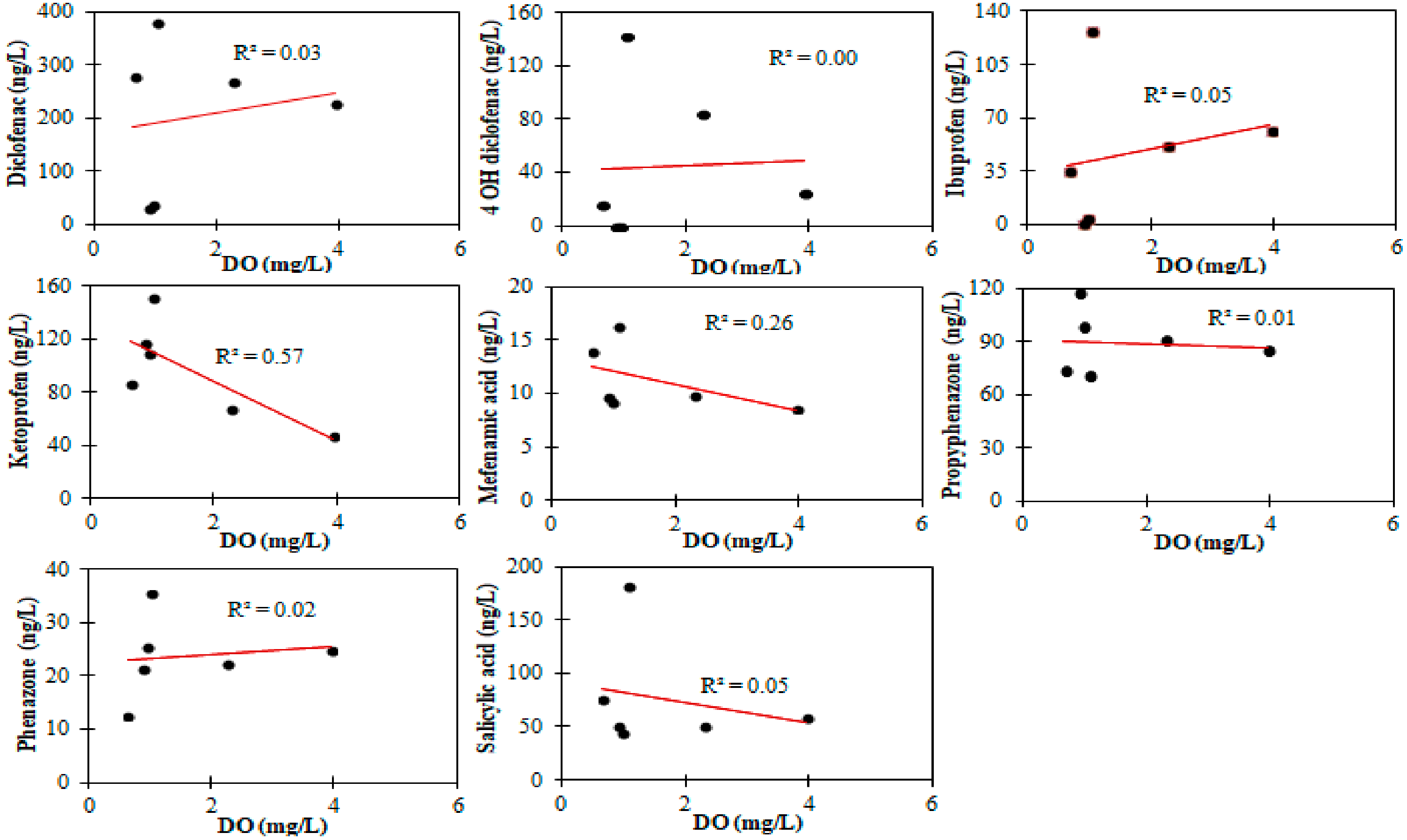

Figure S5. R–squared (R^2) values for the target NSAIDs (ng/L) vs. dissolved oxygen (DO, mg/L).

S1. Details of MIX Code and steps followed for the evaluation of the concentration of the NSAIDs and the mixing ratios.

The MIX code [2] was used to evaluate the concentrations of the NSAIDs and the mixing ratios in groundwater. MIX evaluates mixing ratios in the case of uncertain end−members, incorporating the uncertainty in the recharge sources and the observation point measurements. The uncertainty is quantified through covariance matrices and the results depend on the assumed standard deviations. Therefore, the standard deviations have to be selected carefully and are assigned depending on whether the tracers are conservative or not. For example, non−conservative tracers, such as dissolved oxygen or the NSAIDs, will have higher standard deviations assigned than that for chloride, as they can be affected by chemical processes.

The rationale of MIX Code is that n_i conservative species coming from n_e end−members mix, in variable proportion, in n_j wells. This methodology evaluates the mixing ratios, considering that the data samples contain errors. The mixing equation (Eq. S1) of a mixture j at each observation point can be written as:

$$\hat{X}_{ij} = \sum_e \lambda_{ej} \hat{Y}_{ie}, \qquad \text{Eq. (S1)}$$

where $\hat{X}_{ij}$ and $\hat{Y}_{ie}$ are the concentrations of species i in sample j and end−member e, respectively; and λ_{ej} is the proportion of end−member e in mixture j. The λ_{ej} have to satisfy the following constraints: (i) $0 \leq \lambda_{ej} \leq 1$ and (ii) $\sum_e \lambda_{ej} = 1$.

The ultimate goal is to compute the proportion in which uncertain end−members are mixed into a set of samples, using the concentrations of conservative and non−conservative tracers, whilst quantifying the concentrations of the NSAIDs in the river end−members. Therefore, the procedure involves the following tasks: (1) Identification of the recharge sources (end−members) and selection of the tracers (conservative and non−conservative) to be used, (2) evaluation of mixing ratios with the selected tracers, and (3) evaluation of mixing ratios, including the NSAIDs in the recharge sources. These steps are applied iteratively.

The identification of the recharge sources and the composition of the end−members was previously established by conducting an end−member mixing analysis and using the tracers chloride, electrical conductivity (EC), sodium, sulphate, bicarbonate, calcium, magnesium, potassium, and total nitrogen (Table S1a) [3]. Afterwards, these end−members were used to evaluate the groundwater mixing ratios. The aforementioned tracers were used to estimate the concentrations of the target NSAIDs in the end−members W1 and D2. A critical step is the assignment of the standard deviations, as the results depend on the assumed standard deviations. For major and minor ions and EC, the standard deviations assigned to the end−members and the sampling points were low, in order to avoid changing the composition of the end−members and the mixing ratios. Generally, the standard deviations for the NSAIDs in the river end−members might be higher than these of the sampling points, as they are a mixture of the samples. Nevertheless, the concentrations of the NSAIDs in the aquifer can be affected by geochemical processes and, thus, the assigned standard deviations have to be assigned carefully. For example, ibuprofen concentrations in the sampling points were not constant along the groundwater flow path. Therefore, the standard deviations of less conservative NSAIDs in the sampling points were high, in order to obtain the theoretical composition; however, this did not affect the results of the mixing ratios and the composition of the conservative tracers. The standard deviations of the river end−members and groundwater samples, accounting for the all the tracers and the target NSAIDs, are shown in Table S2.

Table S1. Initial concentrations of the river end−members for **(a)** major elements (mg/L) and EC (µS/cm) and **(b)** NSAIDs (ng/L). Metabolites are listed in bold. DCF, diclofenac; 4OH DCF, 4OH diclofenac; IBU, ibuprofen; KET, ketoprofen; MEF, mefenamic acid; PPZ, propyphenazone; PZ, phenazone; SA, salicylic acid.

(a) River end−members	**Concentration (mg/L, µS/cm)**						
	Cl	**EC**	**Na**	**SO4**	**HCO3**	**Ca**	**Mg**
W1	43.7	585.6	29.0	52.8	222.7	62.2	13.2
D2	315.8	1891.5	246.6	198.6	470.3	151.3	30.1

(b) River end−member	**Concentration (ng/L)**							
	KET	**IBF**	**DCF**	**4OH DCF**	**MEF**	**SA**	**PPZ**	**PZ**
W1	12	50	65	6	3	18	3	3
D2	94	250	299	30	10	330	15	41

Table S2. Standard deviations assigned to major ions, EC, and the target NSAIDs in the river and groundwater samples. Metabolites are listed in bold. R_{rw}, Average concentration in River Besòs end−members; R_{gw}, Average concentration in groundwater sampling points; DCF, diclofenac; 4OH DCF, 4OH diclofenac; IBU, ibuprofen; KET, ketoprofen; MEF, mefenamic acid; PPZ, propyphenazone; PZ, phenazone; SA, salicylic acid.

Tracers and NSAIDs	**Standard deviation**		
	River water		Groundwater
	W1	D2	
Cl	0.04 x R_{rw}		0.05 x R_{gw}
EC	0.03 x R_{rw}		0.07 x R_{gw}
Na	0.05 x R_{rw}		0.07 x R_{gw}
SO4	0.04 x R_{rw}		0.11 x R_{gw}
HCO3	0.07 x R_{rw}		0.1 x R_{gw}
Ca	0.06 x R_{rw}		0.16 x R_{gw}
Mg	0.1 x R_{rw}		0.28 x R_{gw}
KET	25 x R_{rw}	50 x R_{rw}	10 x R_{gw}
IBF	25 x R_{rw}	50 x R_{rw}	5−500 x R_{gw}
DCF	25 x R_{rw}	50 x R_{rw}	5−250 x R_{gw}
4OH DCF	25 x R_{rw}	50 x R_{rw}	5−250 x R_{gw}
MEF	25 x R_{rw}	50 x R_{rw}	10 x R_{gw}
SA	25 x R_{rw}	50 x R_{rw}	5−100 x R_{gw}
PPZ	25 x R_{rw}	50 x R_{rw}	10 x R_{gw}
PZ	25 x R_{rw}	50 x R_{rw}	10 x R_{gw}

Table S3. Maximum (max.), minimum (min.), and mean concentrations (ng/L) in the River Llobregat. Metabolites are listed in bold. −, no data available; n.d, not detected; LOQ, Limit of quantification.

NSAIDs	Concentration (ng/L)					
	Mean	**Mean**	**Max.**	**Mean**	**Min.**	**Max.**
Ketoprofen	12–38.4	n.d −3.20	10.4	38–93.8	14.1	258.5
Ibuprofen	2.2–49.5	135–187	191–277	248–404.6	10.8	502.9
Diclofenac	34.2–65.4	89.5–177	127–248	128.6–299.3	66.1	442.6
4OH diclofenac						
Mefenamic acid	n.d–2.74	n.d–6.80	9.5	<LOQ–3.4	<LOQ	9.5
Salicylic acid	10.3–18.2	208.2–333.2	229–676			
Propyphenazone	n.d −2.6	3.3–11.1	7.3–23.6	3.5–15.2	2	35
Phenazone	n.d −1.8	5.90–40.3	20.2–84.2	10.5–40.8	6.8	94
References	Köck–Schulmeyer et al. [4]	López–Serna et al. [5]		Osorio et al.[6]		

Table S4. Acceptable daily intake (ADI) values of the target NSAIDs in groundwater. −, ADI not available. Metabolites are listed in bold.

NSAIDs	ADI (μg/kg·day)	Reference
Ketoprofen	1	Khan and Nicell [7]
Ibuprofen	110	Schwab et al. [8]
Diclofenac	1.6	de Jesus Gaffney et al. [9]
4OH diclofenac	–	–
Mefenamic acid	4.3	Khan and Nicell [7]
Salicylic acid	26	Leung et al. [10]
Propyphenazone	21	de Jongh et al. [11]
Phenazone	36	de Jongh et al. [11]

Table S5. 50th percentile body weight and Drinking Water Intake (WHO, [12]) for selected age groups.

Age Groups	Body weight (kg)	DWI (L/day)
0–6 months	7.6	0.68
6–12 months	8.6	1
1–2 years	10.6	1.2
2–3 years	13	1.3
4–8 years	20.4	1.6
9–13 years	35.4	2
14–18 years	58	2.25
Adults	62	2.25

Table S6. Concentrations of major ions (mg/L) and some redox indicators (mg/L) in groundwater sampling points and river water (grey background).

Sampling point	Concentration (mg/L)										
	Chloride	Sodium	Sulphate	Bicarbonate	Calcium	Magnesium	Potassium	Nitrate	Ammonium	Dissolved oxygen	TOC
SAP–2b	206.4	146.3	142.5	433.9	130.7	28.0	21.3	0.60	6.3	1.0	4.5
SAP–1	210.4	157.4	163.2	419.3	135.4	28.4	15.3	0.0	2.1	0.88	2.8
SAP–2	211.8	156.9	165.1	414.4	131.1	28.7	14.9	0.0	2.4	0.95	2.5
SAP–3	208.5	180.8	162.3	413.2	142.9	30.9	15.5	0.80	1.5	1.0	2.1
SAP–4	146.6	119.2	116.5	360.8	111.8	25.9	18.3	0.40	6.3	1.5	4.1
ADS–6n	183.0	156.1	139.1	402.2	117.3	26.2	18.1	0.0	4.6	2.3	3.4
ADS–7	181.7	154.0	141.1	391.3	122.5	25.2	18.6	3.7	3.4	0.65	3.9
ADPW	203.5	165.4	150.9	410.8	132.0	27.5	17.3	0.50	4.9	4.0	2.8
ADPM	202.3	156.4	152.7	402.2	130.3	27.4	18.5	2.4	3.1	1.5	3.1
ADPQ	201.2	165.0	145.6	416.9	122.2	28.5	16.2	0.40	4.5	2.0	3.0
ADS–4	192.1	157.7	144.6	386.4	113.6	25.6	17.6	1.9	5.8	1.2	2.9
ADS–2	193.3	158.4	145.7	377.9	122.3	27.0	22.8	28.4	4.9	1.4	2.9
ADPR	204.3	167.5	153.1	402.2	123.9	28.1	18.2	3.5	5.7	1.5	2.8
River Besòs	96.9	70.8	90.0	345.1	96.7	24.7	11.4	15.6	5.7	8.0	6.6

Table S7. Removal (R_{abs}) of the NSAIDs in the groundwater sampling points. Metabolites are listed in bold.

Sampling point	**Removal (R_{abs})**							
	KET	IBF	DCF	**4OH DCF**	MEF	**SA**	PPZ	PP
SAP−2b	−0.30	1.00	0.92	1.00	0.16	0.43	−0.93	−0.12
SAP−1	−0.56	−3.01	−0.06	−0.37	−0.34	0.06	−0.67	−0.39
SAP−2	−0.56	−0.21	−0.05	−0.15	−0.49	−1.08	−0.22	−0.44
SAP−3	−0.17	1.00	0.92	1.00	0.13	0.44	−0.97	0.16
SAP−4	−0.09	0.96	0.90	1.00	0.18	0.52	−0.64	0.01
ADS−6n	0.27	0.50	0.23	0.29	0.08	0.40	−0.69	0.02
ADS−7	0.06	0.66	0.20	0.86	−0.29	0.11	−0.38	0.45
ADPW	0.52	0.42	0.39	0.80	0.23	0.35	−0.46	0.01
ADPM	−0.38	0.74	0.33	0.66	0.05	0.36	−0.34	0.19
ADPQ	0.32	0.33	0.28	0.36	−0.36	−6.04	−1.06	−0.60
ADS−4	−0.21	0.89	0.16	0.79	0.27	0.35	−0.45	0.20
ADS−2	0.22	0.84	0.17	0.88	0.11	0.01	−0.29	0.47
ADPR	0.57	0.89	0.32	0.83	0.05	0.62	−1.07	−0.01

Table S8. (a) DWEL (μg/L) and **(b)** risk quotients (RQs) of the target NSAIDs in groundwater for the selected life stages. Metabolites are listed in bold.

(a) NSAIDs	**DW × 10L (μg/L)**							
	0–6 months	**6–12 months**	**1–2 year**	**2–3 year**	**4–8 year**	**9–13 year**	**14–18 year**	**Adults**
Diclof × 10nac	$1.9 \times 10^{+01}$	$1.4 \times 10^{+01}$	$1.5 \times 10^{+01}$	$1.7 \times 10^{+01}$	$2.1 \times 10^{+01}$	$3.0 \times 10^{+01}$	$4.3 \times 10^{+01}$	$4.6 \times 10^{+01}$
Ibuprof × 10n	$1.3 \times 10^{+03}$	$9.9 \times 10^{+02}$	$1.0 \times 10^{+03}$	$1.1 \times 10^{+03}$	$1.5 \times 10^{+03}$	$2.0 \times 10^{+03}$	$3.0 \times 10^{+03}$	$3.2 \times 10^{+03}$
K × 10toprof × 10n	$1.2 \times 10^{+01}$	$9.0 \times 10^{+00}$	$9.2 \times 10^{+00}$	$1.0 \times 10^{+01}$	$1.3 \times 10^{+01}$	$1.8 \times 10^{+01}$	$2.7 \times 10^{+01}$	$2.9 \times 10^{+01}$
M × 10f × 10namic acid	$5.0 \times 10^{+01}$	$3.9 \times 10^{+01}$	$4.0 \times 10^{+01}$	$4.5 \times 10^{+01}$	$5.7 \times 10^{+01}$	$7.9 \times 10^{+01}$	$1.2 \times 10^{+02}$	$1.2 \times 10^{+02}$
Propyph × 10nazon × 10	$2.4 \times 10^{+02}$	$1.9 \times 10^{+02}$	$1.9 \times 10^{+02}$	$2.2 \times 10^{+02}$	$2.8 \times 10^{+02}$	$3.9 \times 10^{+02}$	$5.6 \times 10^{+02}$	$6.0 \times 10^{+02}$
Ph × 10nazon × 10	$4.2 \times 10^{+02}$	$3.2 \times 10^{+02}$	$3.3 \times 10^{+02}$	$3.8 \times 10^{+02}$	$4.8 \times 10^{+02}$	$6.6 \times 10^{+02}$	$9.7 \times 10^{+02}$	$1.0 \times 10^{+03}$
Salicylic acid	$3.0 \times 10^{+02}$	$2.3 \times 10^{+02}$	$2.4 \times 10^{+02}$	$2.7 \times 10^{+02}$	$3.5 \times 10^{+02}$	$4.8 \times 10^{+02}$	$7.0 \times 10^{+02}$	$7.5 \times 10^{+02}$

(b) NSAIDs	**RQ**							
	0–6 months	**6–12 months**	**1–2 year**	**2–3 year**	**4–8 year**	**9–13 year**	**14–18 year**	**Adults**
Diclof × 10nac	2.0×10^{-02}	2.6×10^{-02}	2.6×10^{-02}	2.3×10^{-02}	1.8×10^{-02}	1.3×10^{-02}	8.8×10^{-03}	8.3×10^{-03}
Ibuprof × 10n	3.0×10^{-04}	3.8×10^{-04}	3.7×10^{-04}	3.3×10^{-04}	2.6×10^{-04}	1.9×10^{-04}	1.3×10^{-04}	1.2×10^{-04}
K × 10toprof × 10n	1.3×10^{-02}	1.7×10^{-02}	1.7×10^{-02}	1.5×10^{-02}	1.1×10^{-02}	8.2×10^{-03}	5.7×10^{-03}	5.3×10^{-03}
M × 10f × 10namic acid	3.3×10^{-04}	4.3×10^{-04}	4.1×10^{-04}	3.7×10^{-04}	2.9×10^{-04}	2.1×10^{-04}	1.4×10^{-04}	1.3×10^{-04}
Propyph × 10nazon × 10	4.9×10^{-04}	6.4×10^{-04}	6.3×10^{-04}	5.5×10^{-04}	4.3×10^{-04}	3.1×10^{-04}	2.1×10^{-04}	2.0×10^{-04}
Ph × 10nazon ×	9.5×10^{-05}	1.2×10^{-04}	1.2×10^{-04}	1.1×10^{-04}	8.3×10^{-05}	6.0×10^{-05}	4.1×10^{-05}	3.8×10^{-05}

10								
Salicylic acid	2.0×10^{-03}	2.7×10^{-03}	2.6×10^{-03}	2.3×10^{-03}	1.8×10^{-03}	1.3×10^{-03}	8.9×10^{-04}	8.3×10^{-04}
Mixtur × 10	4.5×10^{-02}	5.8×10^{-02}	5.6×10^{-02}	5.0×10^{-02}	3.9×10^{-02}	2.8×10^{-02}	1.9×10^{-02}	1.8×10^{-02}

References

1. Simler, R. *DIAGRAMMES: Logiciel d'hydrochimie Multilangage En Distribution Libre*; Laboratoire d'Hydrogéologie d'Avignon: Paris, France **2009**.
2. Carrera, J.; Vázquez-Suñé, E.; Castillo, O.; Sánchez-Vila, X. A Methodology to Compute Mixing Ratios with Uncertain End-members. *Water Resour. Res.* **2004**, *40*.
3. Tubau, I.; Vàzquez−Suñé, E.; Jurado, A.; Carrera, J. Using EMMA and MIX Analysis to Assess Mixing Ratios and to Identify Hydrochemical Reactions in Groundwater. *Sci. Total Environ.* **2014**, *470–471*, 1120–1131, doi:10.1016/j.scitotenv.2013.10.121.
4. Köck−Schulmeyer, M.; Ginebreda, A.; Postigo, C.; López−Serna, R.; Pérez, S.; Brix, R.; Llorca, M.; de Alda, M.L.; Petrović, M.; Munné, A. Wastewater Reuse in Mediterranean Semi−Arid Areas: The Impact of Discharges of Tertiary Treated Sewage on the Load of Polar Micro Pollutants in the Llobregat River (NE Spain). *Chemosphere* **2011**, *82*, 670–678.
5. López−Serna, R.; Postigo, C.; Blanco, J.; Pérez, S.; Ginebreda, A.; de Alda, M.L.; Petrović, M.; Munné, A.; Barceló, D. Assessing the Effects of Tertiary Treated Wastewater Reuse on the Presence Emerging Contaminants in a Mediterranean River (Llobregat, NE Spain). *Environ. Sci. Pollut. Res. Int.* **2012**, *19*, 1000–1012.
6. Osorio, V.; Pérez, S.; Ginebreda, A.; Barceló, D. Pharmaceuticals on a Sewage Impacted Section of a Mediterranean River (Llobregat River, NE Spain) and Their Relationship with Hydrological Conditions. *Environ. Sci. Pollut. Res. Int.* **2012**, *19*, 1013–1025.
7. Khan, U.; Nicell, J. Human Health Relevance of Pharmaceutically Active Compounds in Drinking Water. *The AAPS J.* **2015**, *17*, 558–585.
8. Schwab, B.W.; Hayes, E.P.; Fiori, J.M.; Mastrocco, F.J.; Roden, N.M.; Cragin, D.; Meyerhoff, R.D.; D'Aco, V.J.; Anderson, P.D. Human Pharmaceuticals in US Surface Waters: A Human Health Risk Assessment. *Regul. Toxicol. Pharm.* **2005**, *42*, 296–312, doi:10.1016/j.yrtph.2005.05.005.
9. de Jesus Gaffney, V.; Almeida, C.M.; Rodrigues, A.; Ferreira, E.; Benoliel, M.J.; Cardoso, V.V. Occurrence of Pharmaceuticals in a Water Supply System and Related Human Health Risk Assessment. *Water Res.* **2015**, *72*, 199–208.
10. Leung, H.W.; Jin, L.; Wei, S.; Tsui, M.M.P.; Zhou, B.; Jiao, L.; Cheung, P.C.; Chun, Y.K.; Murphy, M.B.; Lam, P.K.S. Pharmaceuticals in Tap Water: Human Health Risk Assessment and Proposed Monitoring Framework in China. *Environ. Health Perspect.* **2013**, *121*, 839–846.
11. de Jongh, C.M.; Kooij, P.J.; de Voogt, P.; ter Laak, T.L. Screening and Human Health Risk Assessment of Pharmaceuticals and Their Transformation Products in Dutch Surface Waters and Drinking Water. *Sci. Total Environ.* **2012**, *427*, 70–77.
12. EFSA, N. Scientific Opinion on Dietary Reference Values for Water. *EFSA J.* **2010**, *8*, 1459.