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Urban Groundwater Contamination by Non-Steroidal Anti-Inflammatory Drugs

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Abstract: Pharmaceuticals, such as non-steroidal anti-inflammatory drugs (NSAIDs) and their metabolites, have become a major concern due to their increasing consumption and their widespread occurrence in the environment. In this paper, we investigate the occurrence of NSAIDs and their metabolites in an urban aquifer, which may serve as a potential resource for drinking water, and propose a methodology to assess the removal of these substances in the river–groundwater interface. Then, risk quotients (RQs) are computed, in order to determine the risk posed by the single NSAIDs and their mixture to human health. To this end, six NSAIDs and two metabolites were collected from an urban aquifer located in the metropolitan area of Barcelona (NE, Spain), in which the major pollution source is a contaminated river. All of the target NSAIDs were detected in groundwater samples, where the concentrations in the aquifer were higher than those found in the river water (except for ibuprofen). Diclofenac, ketoprofen, propyphenazone and salicylic acid were detected at high mean concentrations (ranging from 91.8 ng/L to 225.2 ng/L) in the aquifer. In contrast, phenazone and mefenamic acid were found at low mean concentrations (i.e., lower than 25 ng/L) in the aquifer. According to the proposed approach, the mixing of river water recharge into the aquifer seemed to some extent to promote the removal of the NSAIDs under the sub-oxic to denitrifying conditions found in the groundwater. The NSAIDs that presented higher mean removal values were 4OH diclofenac (0.8), ibuprofen (0.78), salicylic acid (0.35) and diclofenac (0.28), which are likely to be naturally attenuated under the aforementioned redox conditions. Concerning human health risk assessment, the NSAIDs detected in groundwater and their mixture do not pose any risk for all age intervals considered, as the associated RQs were all less than 0.05. Nevertheless, this value must be taken with caution, as many pharmaceuticals might occur simultaneously in the groundwater.

Keywords: water management; urban aquifer; redox conditions; pharmaceuticals; metabolites; human health risk assessment

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1. Introduction

Sharp urban growth has raised several problems, which tend to endanger the environmental, economic, and social sustainability of cities [1]. As a result, sustaining healthy living conditions in urban areas is a tremendous challenge; central to this mission is the provision of freshwater resources [2]. However, climate change is expected to have impacts on water resources—specifically in the Mediterranean region—which are already limited and often used at unsustainable rates [3]. Hence, potential water shortages have encouraged research into alternative water resources such as urban groundwater. Often, urban areas must pump groundwater as strategic resource to cover demand at specific times and to prevent damage to underground structures (e.g., building basements, underground car parks, and tunnels). This observation raises the question whether urban groundwater can be used as tap water, as urban aquifers may contain a vast array of pollutants [4].

Pharmaceuticals, such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), and their metabolites, have become a major concern due to their high and increasing consumption [5]. NSAIDs are used for inflammatory reduction, and as painkillers and, at

present, they include more than one hundred compounds [6]. NSAIDs can be delivered to urban groundwater through different pollution sources. The main contamination source is excretion via urine and feces in wastewater, containing non-metabolized or conjugated and transformed forms [7,8]. In most cases, these substances are detected in the effluents of wastewater treatment plants (WWTPs) at concentrations ranging from ng/L to µg/L, and are discharged into the aquatic environment reaching groundwater systems [9,10]. Such inefficient removal of the NSAIDs in WWTPs has encouraged research into new technologies and materials, in order to improve their removal rates [11,12]. Additional pollution sources compromise leakage from sewerage [13] and drinking water supply systems [14], as well as waters used in managed aquifer recharge techniques, such as river bank filtration, infiltration ponds, and/or injection wells [15–17]. While some of these substances seem to be naturally attenuated during the sub-surface transport, others can persist in groundwater [18,19].

The prediction of pharmaceutical concentrations in groundwater requires a sound knowledge of the concentrations of these substances in the aquifer pollution sources, the dilution factor in the aquifer, the residence times and, most importantly the biogeochemical processes that might control the fate of pharmaceuticals in the sub-surface. In groundwater, the attenuation of pharmaceuticals seems to occur mainly through microbial degradation, as adsorption is reversible and only retards the transport of these contaminants [20]. Biodegradation of some microcontaminants has been described as a redox-dependent process [19,21]; however, the redox state of groundwater has not been described in many field studies. Moreover, most research has been performed at the laboratory scale [19,22–24], thus missing the complex hydrochemical conditions that are inherent to urban aquifers. In addition, transferring laboratory experiments to field conditions can be unsuccessful due to scale dependencies [25]. For instance, laboratory experiments frequently use concentrations of pharmaceuticals that are higher than naturally occurring ones, which can result in degradation rate constants that might not be representative of field conditions. In this context, considering the raising demand of secure freshwater, understanding the fate of the NSAIDs and the factors that most influence their efficient removal in urban aquifers at field scale are of paramount importance, in order to assure the adequate protection of human health and the environment.

The objectives of this work were: (i) To investigate the occurrence of the NSAIDs and their metabolites in an urban aquifer recharged by a polluted river; (ii) to quantify their removal and identify the potential geochemical processes that might control their fate in groundwater and (iii) to assess the human health risk of the NSAIDs detected in groundwater. A total of 6 NSAIDs and 2 metabolites were collected from an urban aquifer located in the metropolitan area of Barcelona (NE Spain), in which the groundwater might serves as potential resource for drinking water. Then, risk quotients (RQs) were evaluated, in order to investigate the risk posed by the single NSAIDs and their mixture to human health. The main outcome of this research is a methodology that allows for quantification of the removal of the NSAIDs, contributing to the identification of processes that these substances might undergo in the sub-surface, as well as to determine the most persistent ones.

2. Materials and Methods

2.1. Study Area

The Besòs basin extends approximately 1000 km^2 and is a relatively flat area, occupied by the alluvial deposits of the River Besòs, ending in a small delta located NE of the city of Barcelona, Spain (Figure 1). The study area corresponds to the aquifers of the lower part of the Besòs River Delta (Figure 1a). The climate is Mediterranean, with an important variation in average monthly temperatures: The coldest month is January with an average temperature of 7.5 °C, and the warmest is July with an average temperature of 23 °C [26]. The average annual precipitation is about 600 mm but has a great variability throughout the year, as up to 20% of the total annual precipitation can occur in certain months.

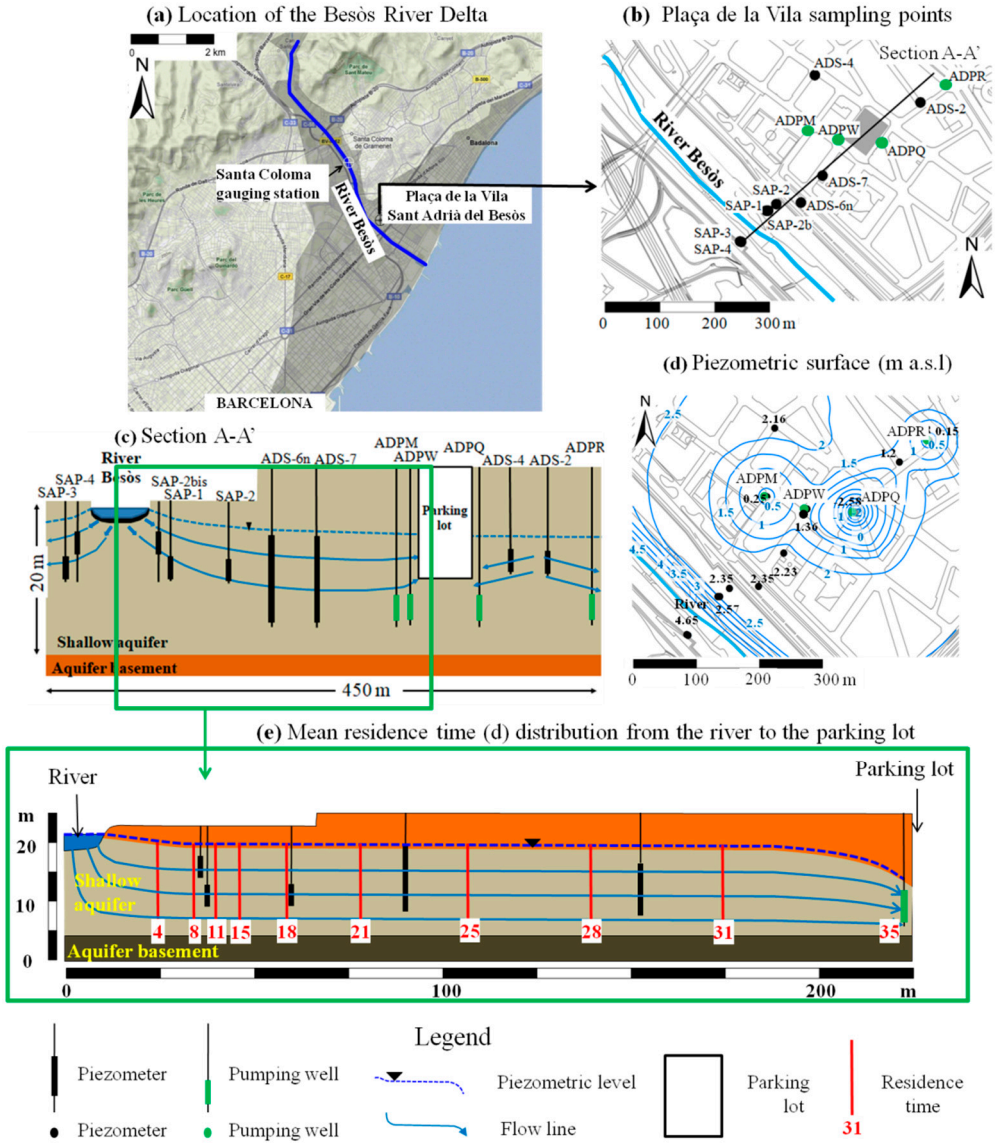


Figure 1. (**a**) Location of the Besòs River Delta (Barcelona, NE Spain); (**b**) spatial distribution of groundwater sampling points in the Plaça de La Vila of Sant Adrià del Besòs; (**c**) Section A–A' showing the screen depth of the sampling points and the major direction of groundwater flow; (**d**) piezometric surface at the surrounding of Plaça de la Vila; and (**e**) mean residence time (**d**) distribution from the river to the parking lot. Note that the piezometric level is in meters above sea level (m a.s.l.), the pumping wells are represented with green dots and the black line in Figure 1b shows the schematic cross-section in Figure 4 (section A–A'). The Catalan Water Agency (ACA) measures the river flow at the Santa Coloma gauging station.

From a hydrogeological point of view, the aquifers of the Besòs River Delta are assembled within Quaternary sediments that lie discordantly upon Pliocene and Paleozoic materials. In the lower valley, there is an accumulation of alluvial sands and gravels, which constitute two superposed aquifers that are separated by an aquitard composed of silts and clays. The unconfined shallow aquifer consists of sands and the main aquifer, which is the deep confined aquifer, consists of siliceous and carbonate sands. The shallow aquifer is hydraulically connected to the River Besòs, which is the major pollution source (Figure 1c) [27].

From a hydrological point of view, the Besòs is a Mediterranean river and its flow is characterized by high variability, which is controlled by seasonal rainfall. The average streamflow measured at the Santa Coloma gauging station varies from 2 to 4 m^3/s but it

has reached 100 m^3/s after heavy rain events (Figure 1a). The Besòs River controls the chemical characteristics of the unconfined shallow aquifer, due to its hydraulic connection. A previous study concluded that three river end-members are necessary to explain the chemical variability of the river: The wet end-member (W1), which is necessary to describe the intense but short rain events and two dry end-members (D1 and D2), which are used to explain the absence of rain or the low rain events that occur throughout most of the year, especially in summer [28]. In the conducted sampling campaign, the major contributor to the resident water of the shallow aquifer was the dry end-member D2, followed by W1, being on average 57.9% and 41.1%, respectively [28]. D1 represented less than 1% of the total groundwater recharge and, thus, it was not considered for further calculations in this study (see Sections 2.3 and 3.2).

Figure 1d shows the piezometric surface when three wells of the drainage system—which consists of four wells (ADPM, ADPQ, ADPR, and ADPW)—are pumping. This intensive pumping induced a drainage divide, where the groundwater flow around the parking is practically radial and only linear near the river (Figure 1d). Groundwater flows from the river to a parking lot with short residence times (i.e., about 1 month), due to the intensive pumping in the surroundings of the parking area [27] (Figure 1e). There is also a monitoring network of 16 observation points, along with the four pumping wells, that are used to monitor the piezometric head oscillations and to assess the groundwater quality. The 13 sampling points considered in this study were the four pumping wells and the piezometers of the series SAP-n (located close to the river) and ADS-n (Figure 1b,c). The screen depth intervals for the observation points are 9.5–11.5 m for SAP-1, SAP-2, and SAP-3; 4.5–6.5 m for SAP-2b and SAP-4; and 3–15 m for ADS-6n and ADS-7 (Figure 1c).

2.2. Sampling and Analytical Methods

One river water and 13 groundwater grab samples were collected for the analysis of NSAIDs, some redox indicators, and major ions, in May 2010. Groundwater samples were purged by pumping three well volumes to remove the stagnant water and collected, wearing globes, after the stabilization of the field parameters (i.e., dissolved oxygen; electrical conductivity (EC); pH; and temperature), which were measured within a flow cell. Water samples for chemical analyses were collected in high-density polyethylene bottles (25 mL for anion and 50 mL for cation samples). A volume of 30 mL was collected for Total organic carbon (TOC) analysis in glass bottles which had been previously muffled. Water samples collected for the NSAID analyses were gathered in 1 L pre-cleaned amber glass bottles, as this material has been recommended to avoid adsorption and photodegradation [29]. Water samples were stored in a portable refrigerator and shipped to the laboratory at the end of the day. Finally, water samples for the analysis of the NSAIDs were vacuum filtered at the laboratory using 1 µm glass fiber filters and 0.45 µm nylon membrane filters. Afterwards, they were stored at −20 °C in the dark until further analysis.

For the analysis of cations, samples were filtered, acidified with 1% (v/v) HNO_3, and centrifuged at 3500 rpm prior to the analysis, which was performed using the Inductively Coupled Plasma Mass Spectrometry method (ICP-MS). Anions were analyzed using ion chromatography (IC). TOC was measured using the 680 °C combustion catalytic oxidation method using a non-dispersive infra-red detector. Ammonium was quantified through spectrophotometry, based on the indophenol blue method. The analysis of the NSAIDs was performed by on-online Solid Phase Extraction–Liquid Chromatography–Electrospray–Tandem Mass Spectrometry (SPE–LC–ESI–MS/MS), following the methodology previously described by López-Serna et al. [30,31]. Samples, which were spiked with surrogate standards, and aqueous calibration solutions were analyzed in a fully online automated manner using a Symbiosis Pico system (Spark Holland, Emmen, The Netherlands) coupled to the LC–MS/MS system. The analytical procedure consisted of two sample injections (2.5 mL each) in the negative and positive ESI modes (ESI (-) and ESI (+), respectively). In each injection, the sample was pre-concentrated onto previously conditioned polymeric HySphere Resin GP cartridges from Spark Holland (Emmen, The Netherlands). Afterwards, the

cartridges were washed with HPLC water and the retained compounds were eluted to the LC-MS/MS system with the chromatographic mobile phase, with a gradient of acetonitrile (0.1%) in formic acid for ESI (+) and an acetonitrile:methanol (1:1, *v*/*v*)/water gradient for ESI (-). The chromatographic separation was performed using a Purospher® STAR RP-18 ec (125 × 2 mm, 5 µm) column, preceded by a pre-column of the same composition material. MS/MS detection was performed using a 4000 Q TRAP™ from Applied Biosystems-Sciex (Foster City, California, USA) and operated under selected reaction monitoring (SRM), registering the two most intense transitions. Quantification of all the target substances was carried out from the most intense SRM transition by the internal standard calibration approach, using the most suitable isotopically labeled compound for each analyte. This method allows for determining the target substances at concentrations ranging from 0.62–3.2 ng/L (i.e., the quantification limits) to 500 ng/L accurately.

2.3. Removal of the NSAIDs in Groundwater

The removal of the NSAIDs in groundwater was calculated as follows:

$$R_{abs} = 1 - \left(\frac{c_{gw-M}}{c_{gw-Riv}} \right) \quad (1)$$

where R_{abs} is the absolute removal of a given NSAID, $c_{gw\text{-}M}$ is the measured groundwater concentration of the NSAIDs (ng/L), and $c_{gw\text{-}Riv}$ is the computed groundwater concentration by the mixing of the River Besòs (ng/L). The removal efficiency was divided into three categories: efficient (>0.8), moderate (0.3–0.8), and poor (<0.3) [32].

The expected concentrations of the NSAIDs in the end-members W1 and D2 were evaluated using the code MIX, which allows for computing the mixing ratios and the compositions of the end-members [33]. Further details on the code and the steps followed to evaluate the concentrations of the NSAIDs in the river end-members are given in S1 (Supplementary Material).

2.4. Human Health Risk Assessment

The maximum concentrations of the NSAIDs in groundwater samples were used to assess the RQs for human health, in order to determine the "worst-case" scenario. The RQs were evaluated, for different age intervals, as follows:

$$RQ = \frac{c_{max}}{DWEL} \quad (2)$$

where c_{max} is the maximum concentration of a given NSAID in groundwater samples and DWEL is the corresponding age-dependent drinking water equivalent level. DWELs were computed using Equation (3) [34]:

$$DWEL \left(\frac{ng}{L} \right) = \frac{\text{ADI} \times \text{BW} \times \text{HQ}}{\text{DWI} \times \text{AB} \times \text{FOE}}, \quad (3)$$

where ADI is the Acceptable Daily Intake (µg/kg day), which were obtained from literature (Table S4); BW represents the 50th percentile values of body weight for the different life stages (kg); and DWI is the daily water ingestion rate (L/day), which is an age-specific value set by the European Food Safety Authority [35]. Values of BW and DWI for each life-stage considered are shown in Table S5. HQ is the hazard quotient, which was assumed to be 1 in this evaluation; generally, an HQ greater than 1 is likely to be toxic, whereas less than 1 is not toxic. AB is the gastrointestinal absorption, the value of which was taken to be 1, meaning that the adsorption rate was 100; while FOE is the frequency of exposure, which was assumed to be 0.96 (350 days over 365 days) [34].

Finally, the health risk posed by the mixture of detected NSAIDs in groundwater was evaluated by summing the individual RQs, as these substances were detected simultaneously in groundwater samples. The follow risk ranking criteria was applied for the

evaluated RQs: Substances with RQ lower than 0.1 indicate no risk, substances with RQ between 0.1 and 1 indicate median risk, and substances with RQ value higher than 1 can affect human health [36].

3. Results and Discussion

3.1. Hydrochemistry in the River Groundwater-Interface

3.1.1. General Hydrochemistry and Redox Conditions

The major ion composition of the shallow aquifer was classified as Cl-SO_4-Ca-Mg type, while the river water was of HCO_3-Ca-Mg type (Figure S1). The average major ion concentrations in groundwater were higher than those of the river for most of the tracers (Table S6; 195.8 vs. 96.9 mg/L for chloride, 147.9 vs. 90 mg/L for sulphate, 402.4 vs. 345.1 mg/L for bicarbonate, 125.9 vs. 96.7 mg/L for calcium, 27.5 vs. 24.7 mg/L for magnesium, 157 vs. 70.8 for sodium, and 17.9 vs. 11.4 mg/L for potassium). Only nitrate presented higher concentrations in river water than in groundwater, being 15.6 mg/L and 3.3 mg/L, respectively.

The redox state of groundwater has profound implications for the mobility and persistence of contaminants of emerging concern (CECs) in groundwater and, thus, it may serve as an important factor in determining the vulnerability of urban groundwater to contamination. The Besòs was in oxidizing conditions, as shown by the presence of dissolved oxygen and nitrate at concentrations of 8 mg/L and 15.6 mg/L, respectively. The electron donor (TOC) levels were 6.6 mg/L in the river. The average concentration of electron acceptors and donors in groundwater were lower than those of the river, being 1.5 mg/L for dissolved oxygen, 1.2 mg/L for nitrate (excluding the ADS-2 sampling point), and 3.1 mg/L for TOC (Table S6). This observation suggests the occurrence of redox reactions, such as aerobic respiration and denitrification, when river water mixed with the groundwater of the shallow aquifer. Consequently, the prevalent redox state of groundwater was a reducing environment, as also indicated by higher ammonium concentrations in the aquifer (average concentrations in the river and groundwater were 2 mg/L and 4.2 mg/L, respectively).

3.1.2. NSAIDs

NSAIDs and their metabolites have frequently been detected in groundwater samples of the Besòs River Delta. Six compounds—namely, ketoprofen, diclofenac, mefenamic acid, propyphenazone phenazone, and the metabolite salicylic acid—were ubiquitous in the aquifer. The detection frequencies of ibuprofen and the metabolite 4OH diclofenac were 92% and 77%, respectively. Figure 2 shows the box-plots of the NSAIDs and metabolites in groundwater samples. Several substances, such as diclofenac, ketoprofen, propyphenazone, and salicylic acid, were found at high mean concentrations (from 91.8 ng/L for propyphenazone to 225.2 ng/L for diclofenac). Conversely, phenazone and mefenamic acid were detected at low mean concentrations (11.1 ng/L and 24.1 ng/L, respectively). Generally, the highest concentrations of most NSAIDs were detected in the shallower sampling points located near the river (SAP-2b and SAP-4); for example, diclofenac and its metabolite 4OH diclofenac exceeded concentrations of 300 ng/L and 140 ng/L, respectively, at these sampling points. The maximum concentrations were, in descending order, observed for salicylic acid (620 ng/L at ADPQ), diclofenac (380 ng/L in SAP-2b), and ibuprofen (379 ng/L at SAP-4). Moreover, there were many NSAIDs that exceeded the concentration of 100 ng/L at different sampling points (77% for diclofenac, 54% for ketoprofen, 30% for propyphenazone, and 15% for ibuprofen, 4OH diclofenac, and salicylic acid).

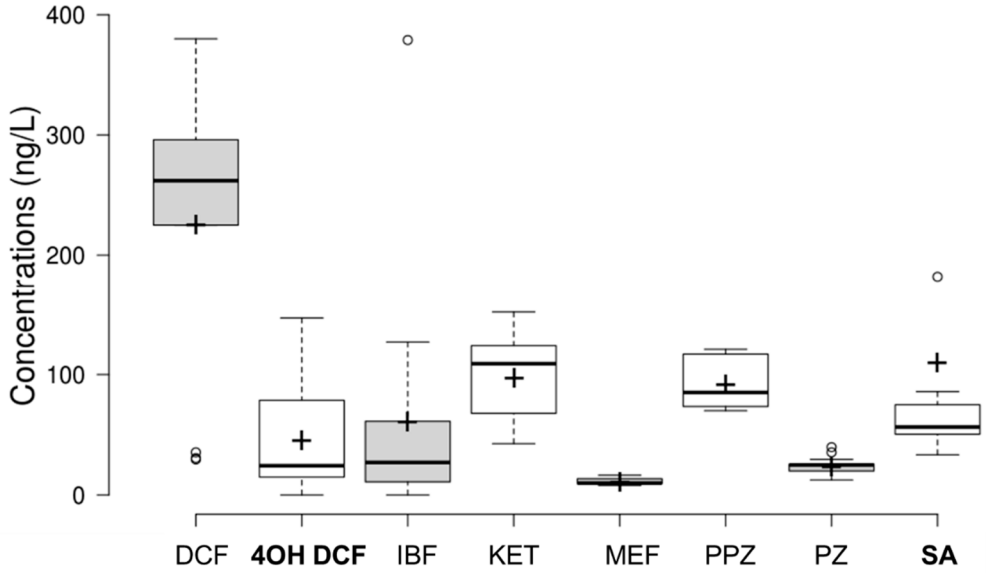


Figure 2. Boxplots showing the concentration of the NSAIDs and their metabolites (ng/L) in groundwater (GW, n = 13), including the non-detected values. The dots represent the outliers and the black crosses indicate the mean. There is one outlier not displayed, for SA (620 ng/L). Metabolites are highlighted in bold. DCF, diclofenac; 4OH DCF, 4OH diclofenac; IBU, ibuprofen; KET, ketoprofen; MEF, mefenamic acid; PPZ, propyphenazone; PZ, phenazone; SA, salicylic acid.

Concerning the presence of the NSAIDs in the River Besòs, all substances were detected, except 4OH diclofenac (Table 1 (a)). These substances were found in a wide range of concentrations, ranging from 9.3 ng/L for ketoprofen to 293 ng/L for ibuprofen. Salicylic acid and diclofenac were detected at concentrations near to 110 ng/L, while the remaining compounds were detected at concentrations below 30 ng/L. When comparing the mean concentrations in groundwater samples with those in the river water, mefenamic acid, phenazone, and salicylic acid presented similar concentrations in both aqueous matrices, while diclofenac, 4OH diclofenac, ketoprofen, and propyphenazone presented higher concentrations in groundwater. In contrast, the mean concentration of ibuprofen was higher in the river water than in groundwater. Such distinct behavior of the NSAIDs suggests that they may be affected by different processes, such as redox and sorption processes, when river water infiltrates the aquifer. Nevertheless, the concentrations reported in the river water might not be representative, due to the irregular flow pattern of the Besòs River.

Table 1. (a) Measured and computed concentrations of the NSAIDs (ng/L) in the River Besòs and (b) computed concentrations in the end-members W1 and D2. Metabolites are highlighted in bold. DCF, diclofenac; 4OH DCF, 4OH diclofenac; IBU, ibuprofen; KET, ketoprofen; MEF, mefenamic acid; PPZ, propyphenazone; PZ, phenazone; SA, salicylic acid.

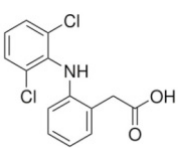
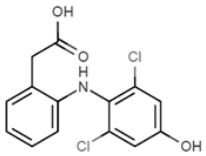
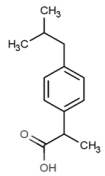
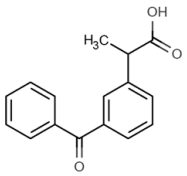
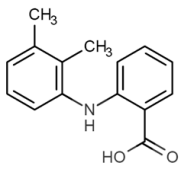
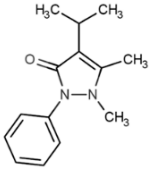
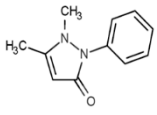
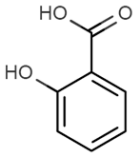
(a) Besòs River	**Concentration of the NSAIDs (ng/L)**							
	KET	**IBF**	**DCF**	**4OH DCF**	**MEF**	**SA**	**PPZ**	**PP**
Measured	9.3	293	113	0	9.5	110	28	15.7
Computed	60.8	83.6	254.0	91.0	9.1	65.2	29.0	11.4
(b) Besòs River	**Concentration of the NSAIDs (ng/L)**							
	KET	**IBF**	**DCF**	**4OH DCF**	**MEF**	**SA**	**PPZ**	**PP**
End-member W1	41.9	72.6	197.8	74.4	8.1	53.7	14.4	4.6
End-member D2	133.3	125.8	469.4	154.5	13.0	109.4	84.8	37.4

3.2. Fate of the NSAIDs in Groundwater

3.2.1. Physicochemical Properties

The physicochemical properties of the target NSAIDs are summarized in Table 2. These properties are used for scoring the mobility of these substances in groundwater [37]. For instance, the octanol–water partition coefficient (expressed as log K_{ow}) is used to predict the hydrophobicity of the micropollutants. In general, substances with a log K_{ow} (i.e., less than 1) are highly hydrophilic and are likely to be mobile, while substances with a log K_{ow} above 4 are classified as low-mobility substances. Intermediate log K_{ow} values (i.e., 1 to 4) are ranked as medium mobility substances [37]. However, log K_{ow} may only represent the hydrophobicity of neutral substances but most of the target NSAIDs are ionizable substances and, thus, the log D_{ow}, which is the pH-dependent n-octanol–water distribution, is more appropriate for ascertaining the mobility of the ionized substances in groundwater [38].

Table 2. Physicochemical properties of the target NSAIDs. These properties are from ChemAxon (© 1998–2021, Budapest, Hungary). Note that log D_{ow} is evaluated at pH = 7.3. pK_a, acid dissociation constant; (a), Strongest acidic pK_a; (b), Strongest basic pK_a. Metabolites are highlighted in bold.

NSAIDs	Diclofenac	**4OH Diclofenac**	Ibuprofen	Ketoprofen
Molecular formula	$C_{14}H_{11}Cl_2NO_2$	$C_{14}H_{11}Cl_2NO_3$	$C_{13}H_{18}O_2$	$C_{16}H_{14}O_3$
Chemical structure and molecular weight (g/mol)	 296.15	 312.15	 206.29	 254.28
CAS	15307-86-5	64118-84-9	15687-27-1	22071-15-4
S (mg/L)	15	42	59	36
Log K_{ow}	4.26	3.96	3.84	3.61
p*Ka* (a,b)	4 (a)	3.76 (a), 8.61 (a)	4.85 (a)	3.88 (a)
Log D_{ow} (pH = 7.3)	1.16	0.7	1.43	0.44
NSAIDs	Mefenamic acid	Propyphenazone	Phenazone	**Salicylic acid**
Molecular formula	$C_{15}H_{15}NO_2$	$C_{14}H_{18}N_2O$	$C_{11}H_{12}N_2O$	$C_7H_6O_3$
Chemical structure and molecular weight (g/mol)	 241.29	 230.31	 188.23	 138.12
CAS	61-68-7	479-92-5	60-80-0	69-72-7
S (mg/L)	21	403	4911	11,734
Log K_{ow}	5.4	2.35	1.22	1.98
p*Ka* (a,b)	3.89 (a)	0.87 (b)	0.49 (b)	2.79 (a), 13.23 (a)
Log D_{ow} (pH = 7.3)	2.23	2.35	1.22	−1.51

The NSAIDs propyphenazone and phenazone are neutral substances at the average pH of 7.3 of the shallow aquifer of the Besòs River Delta; further, their log K_{ow} and log D_{ow} values are equivalent (Table 2). These two NSAIDs are therefore moderate mobility substances. The remaining NSAIDs are negatively charged substances at pH 7.3 and, consequently, different values of log K_{ow} were observed, with respect to log D_{ow} (Table 2). Diclofenac, ibuprofen, and mefenamic acid can be classified as moderate mobility substances (log D_{ow} ranging from 1.16 to 2.23), whereas 4OH dicofenac, ketoprofen, and sal-

icylic acid presented high mobility, as their log D_{ow} values were lower than 1. Concerning the solubility in water (S) values (Table 2), the NSAIDs were considered to have medium to high solubility. The NSAIDS with high solubility were propyphenazone (403 mg/L), phenazone (4911 mg/L), and salicylic acid (11,734 mg/L).

In summary, NSAIDs are substances with moderate to high mobility based on their physicochemical properties (Table 2); however, the local environmental conditions (i.e., redox conditions of the aquifer, potential aquifer pollution sources and groundwater residence time, among others) must also be considered, in order to gain reliable insight into the fate of these substances in groundwater.

3.2.2. Concentration of the NSAIDs in the Recharge Sources

The main contamination source of the shallow aquifer is the River Besòs, which represents 91% of the total resident water [39]. However, the sample of the River Besòs may not has been representative, as it was collected after a rainy period and, so, it is expected that the dilution capacity of the river was increased, reducing the concentrations of the NSAIDs in the collected sample (Table 1 (a)). Water quality changes in the river water clearly influence the groundwater quality [27] and, therefore, it was required to assess the compositions of the River Besòs end-members (W1 and D2) using Mix Code [33] (Table S1), because there was a lack of previous data concerning these substances in the River Besòs. Nonetheless, the River Besòs has some similarities with the River Llobregat, which is located in SW Barcelona, with its mouth about 15 km from the study area. Both rivers have been impacted by anthropogenic pressure (i.e., discharges coming from WWTPs) and are characterized as having irregular flow regimes controlled by rainfall events. Hence, the NSAIDs concentrations might be similar in both rivers; furthermore, some previous studies reported the presence of the NSAIDs in the Llobregat (Table S3).

The evaluated concentrations of the NSAIDs in the River Besòs end-members are summarized in Table 1 (b). The concentrations in W1 were always lower than those in D2 for all of the substances. There were some substances, such as diclofenac and its metabolite 4OH diclofenac, ibuprofen, ketoprofen, and salicylic acid, that exceeded the threshold of 100 ng/L in the river end-member D2. The highest concentrations corresponded to diclofenac and its metabolite, which were 469.4 ng/L and 154.5 ng/L, respectively. The D2 concentrations of mefenamic acid and phenazone were low (13 ng/L and 37.4 ng/L, respectively), compared to the other NSAIDs. Concerning the NSAID concentrations in the river end-member W1, only diclofenac presented a concentration close to 200 ng/L and 4OH diclofenac and ibuprofen exceeded the threshold of 70 ng/L. The remaining compounds presented concentrations for this end-member that were below 55 ng/L (Table 1 (b)).

The evaluated concentrations of the River Besòs end-members were on the same order of magnitude as those reported in the lower part of the Llobregat River Basin (Table S3). Overall, mean concentrations of the NSAIDs did not exceed 100 ng/L, but some substances were detected at high concentrations; for example, ibuprofen and diclofenac were detected at maximum concentrations of 502.9 ng/L and 442.6 ng/L, respectively, in the River Llobregat [40]. Similarly, López-Serna et al. [41] have reported a wide range of NSAID concentrations in the lower section of the River Llobregat, salicylic acid being the one detected at a maximum concentration of 676 ng/L, while ketoprofen and mefenamic acid were found at concentrations close to 10 ng/L (Table S3).

3.2.3. Removal of the NSAIDs in the Aquifer

The presented methodology allows for evaluating the percentage of the target NSAIDs that could be naturally removed in the river–groundwater interface. First of all, it was necessary to evaluate the concentrations of the NSAIDs in the river water and groundwater using mixing ratios. The shallow aquifer is mainly recharged by the river, in which the flow rate and hydrochemistry vary greatly over time. Thus, the integration of the River Besòs end-members W1 and D2 was necessary to explain the composition of NSAIDs in the aquifer (Table 1 (b)). The major contributor to the groundwater recharge was the D2

end-member, representing 59% of the total recharge on average; however, W1 also had an important contribution to the resident water of the aquifer, comprising the remaining 41%. Finally, the computed concentrations were compared with the measured concentrations in groundwater samples using the term R_{abs} (Figure 3). Most of the target NSAIDs presented R_{abs} values above 0 (Figure 3), meaning that the measured concentrations were lower than those computed in groundwater by river water mixing. Some NSAIDs were easily and moderately removed when river water infiltrated the aquifer; namely, 4OH diclofenac, ibuprofen, and salicylic acid, with median R_{abs} values of 0.80, 0.74, and 0.35, respectively. This observation might indicate that the reducing conditions of the groundwater might favor the natural attenuation, to some extent, of these NSAIDs in the aquifer. Median removals for diclofenac, mefenamic acid, and phenazone were poor ($R_{abs} < 0.3$; Figure 3). However, the median R_{abs} values were negative for ketoprofen and propyphenazone (−0.09 and −0.64, respectively). These negative R_{abs} values suggest that the computed concentrations of these NSAIDs in the river water might have been underestimated. The computed concentrations of the NSAIDs in the river was evaluated considering that the composition of the river water was 79.3% from W1 and 20.7% from D2 [28] (Table 1 (a and b)); for example, the estimated concentration of ketoprofen in the River Besòs was 29 ng/L, while the average estimated concentration in groundwater was 56.2 ng/L.

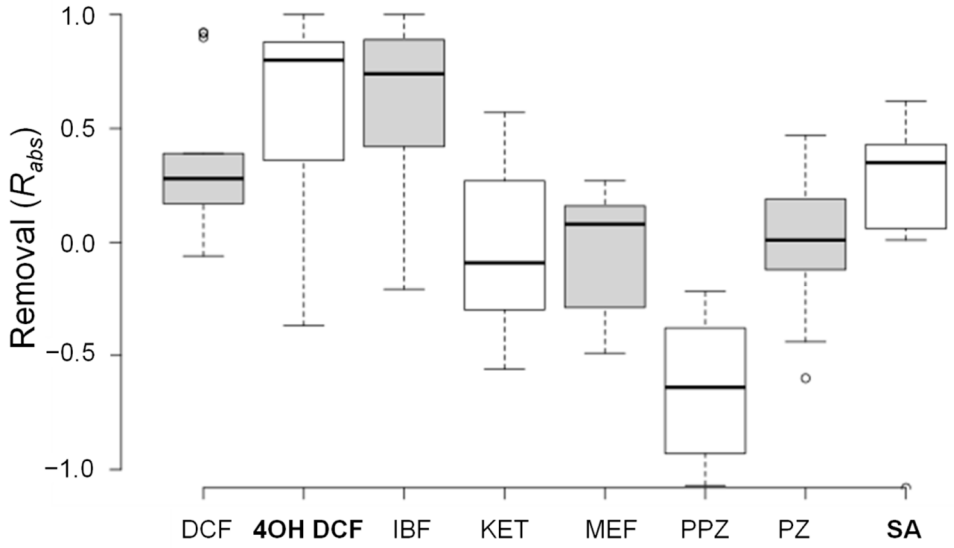


Figure 3. Boxplots showing the removal (R_{abs}, Equation (1)) of the NSAIDs and their metabolites in groundwater (GW, n = 13). The dots represent the outliers; there are two outliers which are not displayed for SA (−6.04) and IBF (−3.01). DCF, diclofenac; 4OH DCF, 4OH diclofenac; IBU, ibuprofen; KET, ketoprofen; MEF, mefenamic acid; PPZ, propyphenazone; PZ, phenazone; SA, salicylic acid.

One of the most important results of this research was the removal quantification of the NSAIDs at each groundwater sampling point (Table S7). As an example, Figure 4 shows the spatial distribution of the R_{abs} values for three NSAIDs with high (4OH diclofenac), moderate (salicylic acid), and low (mefenamic acid) median removals.

The extent of the removal differed in the groundwater sampling points and the following observations can be made:

- The shallow sampling points located close to the river (SAP-2b and SAP-4; Figure 4) presented negative R_{abs} values for almost all of the target NSAIDs (except for salicylic acid in SAP-4; Figure 4 and Table S7). Plausible reasons for the negative R_{abs} values are that: (i) The concentrations of the NSAIDs in the shallow sampling points were usually higher than those of the River Besòs; and (ii) the estimated river end-member concentrations for the NSAIDs were low, as the river sample was collected during rain events and, thus, the dilution capacity of the river was increased.

- The deep sampling points located close to the river (SAP-1, SAP-2 and SAP-3) displayed the highest R_{abs} values for ibuprofen, diclofenac and 4OH diclofenac, and salicylic acid. Salicylic acid presented R_{abs} values ranging from 0.43 to 0.52, whereas the other three substances had R_{abs} values above 0.90 at these sampling points (Figure 4 and Table S7). The R_{abs} values for these NSAIDs were somewhat low in the sampling points located in the surroundings of the parking area (Figure 4 and Table S7).
- R_{abs} values for ketoprofen, propyphenazone, and phenazone were negative at many groundwater sampling points (Table S7). This observation suggests that the computed concentrations for these substances by river water mixing were underestimated, likely as some rain events occurred during the sampling campaign.

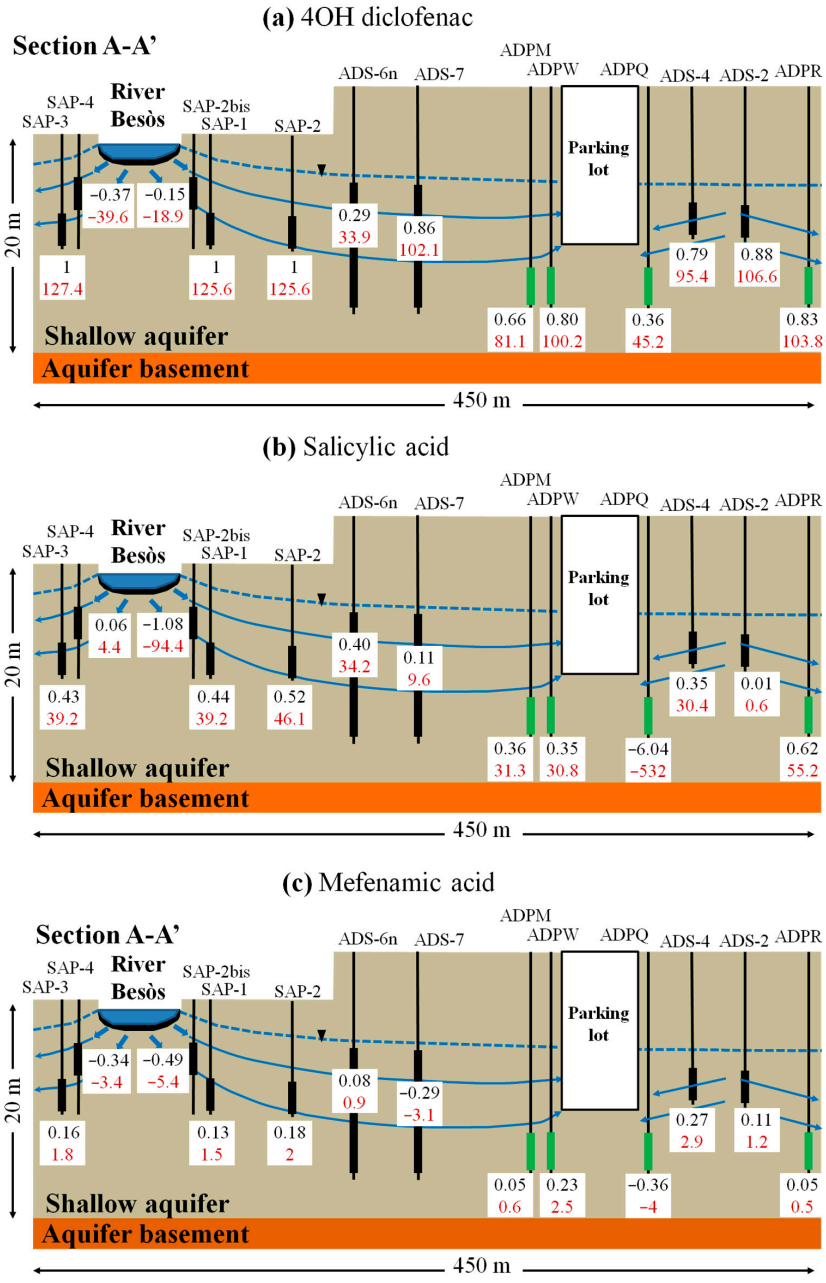


Figure 4. Spatial distribution of R_{abs} (Equation (1)) for three selected NSAIDs with (**a**) high (4OH diclofenac), (**b**) moderate (salicylic acid), and (**c**) poor (mefenamic acid) R_{abs}. The removal concentration (ng/L) of these NSAIDs is also shown (in red).

The potential natural removal of the NSAIDs was further explored by comparing the concentrations at SAP-2b and ADPW, as the flow regime between these two points was linear (Figure 1b,d). To this purpose, firstly, the mean degradation velocity for the NSAIDs was calculated using the decreases in concentrations between ADPW and SAP-2b and the mean residence time distribution shown in Figure 1e. Note that SAP-2b was selected as it had the highest concentration for the target NSAIDs (except for propyphenazone). The mean residence time distribution was obtained from a steady-state groundwater numerical model [42]. Afterwards, the computed mean degradation velocity was used to calculate the R_{abs} distribution along the linear groundwater flow path between the river and the parking area. As an example, Figure 5 shows the R_{abs} for 4OH diclofenac, diclofenac, and phenazone from the river to the parking area. Note that, in the absence of representative river concentrations, a R_{abs} of 0 was assumed in the river (Figure 5).

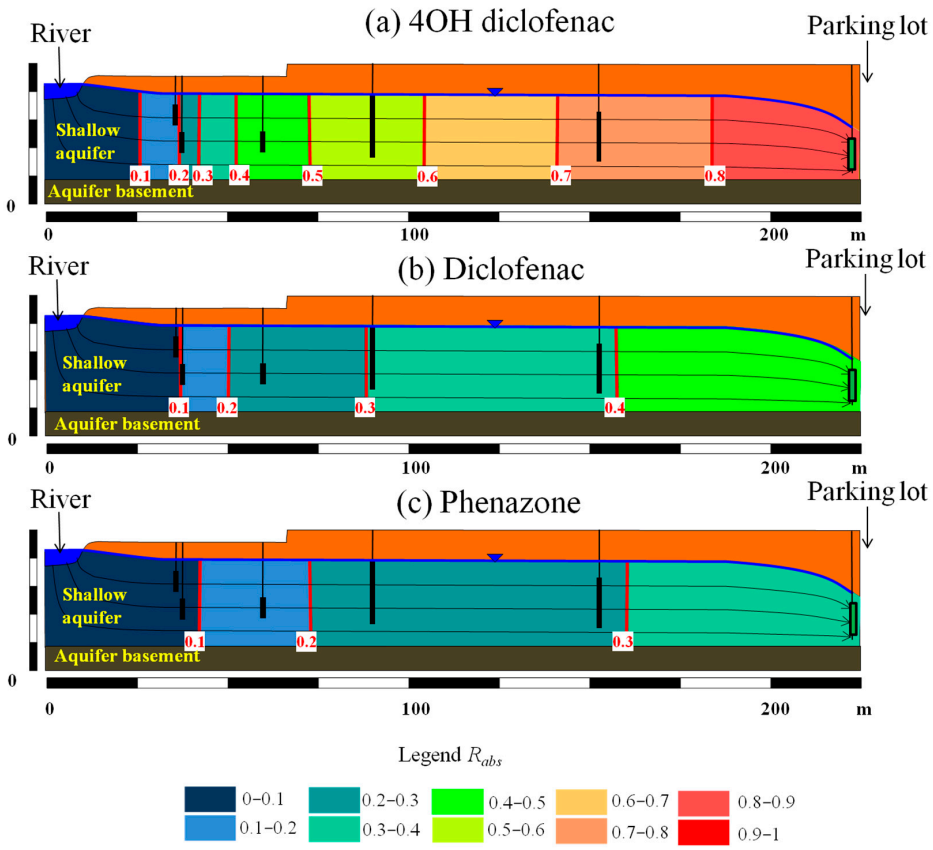


Figure 5. Graphical distribution of the R_{abs} values for (**a**) 4OH diclofenac, (**b**) diclofenac and (**c**) phenazone from the river to the parking area. R_{abs} was evaluated using the mean degradation velocity using the decrease in the concentrations between ADPW and SAP-2b and the mean residence time distribution shown in Figure 1e. Note that, in the absence of representative river concentrations, it was assumed that R_{abs} = 0 in the river.

All of the NSAIDs were removed, to some extent, from groundwater points SAP-2b to ADPW, ranging from 0.30 for phenazone and 0.83 for 4OH diclofenac (Figure 5 and Figure S2). In Figure S2, R_{abs} values are evaluated, comparing the NSAID concentrations at sampling points SAP-1, SAP-2, ADS-6n, ADS7, and ADPW with these at SAP-2b. It is important to mention that the removal in the sampling points SAP-1 and SAP-2 for diclofenac, 4OH diclofenac, and ibuprofen did not follow a linear decay, as their R_{abs} values varied from 0.9 to 1 (Figure S2a vs. Figure 5). High values of R_{abs} were also evaluated for salicylic acid, being above 0.7 at these sampling points (Figure S2a). This observation suggests that some processes may occur that deplete these NSAIDs at these sampling points, which deserves further investigation. Ketoprofen presented removal rates that

increased from the points located to the river to the parking area, whereas phenazone and mefenamic acid had similar removal efficiencies (Figure S2b).

All the NSAIDs seemed to be partially attenuated under the sub-oxic and nitrate reducing conditions of the groundwater resulting from the mixing of oxic river water recharged into the aquifer, driving redox reactions such as denitrification and aerobic respiration [43]. Presumably, this may be the case for diclofenac, 4OH diclofenac, and ibuprofen and, to a lesser extent, for salicylic acid, mefenamic acid, and phenazone. This observation was supported by the positive correlation (R^2) of these substances with two redox indicators—ammonium and TOC (Figures S3 and S4)—and the lack of correlation with dissolved oxygen (Figure S5). Previous studies have suggested that ibuprofen is biodegradable under oxic conditions in groundwater [44]; however, Carr et al. [45] found that the most efficient biological degradation occurred under reduced oxygen conditions (half-life of 41.2 days vs. 121.9 days in aerobic soils). No retardation was observed in column and field experiments for ibuprofen [17,46]. In contrast, high retardation values of diclofenac and 4OH diclofenac have been observed at a bank filtration site in Berlin, Germany, reaching values of up to 80.3 and 13.3, respectively [47,48]. The strong sorption of diclofenac has also been reported in other German river bank filtration systems in the Flehe—Rhine River (aerobic to denitrifying conditions) and Torgau-Elbe River (denitrifying conditions) [49]. Moreover, diclofenac also appeared to biodegrade at the bank filtration site in Berlin, with a half-life of 36 days. Concerning phenazone, previous studies have reported that redox conditions in groundwater have an influence on its degradation [50], as it was found to be highly degradable under the presence of oxygen [19,47]. However, this substance may also degrade under sub-oxic conditions, as Sanz-Prat et al. [48] reported a decline of concentration along the flow path at low dissolved oxygen concentrations in a river bank filtration site in Berlin, Germany. Retardation of phenazone was observed neither in field [48] nor laboratory experiments [51]. In this study, a negative correlation was observed among propyphenazone and ammonium and TOC and no correlation with dissolved oxygen (Figures S3–S5) was observed. Previous studies have reported that the natural attenuation of propyphenazone was enhanced under oxic conditions in groundwater at field scale [52]; whereas, in this study, it was also observed under sub-oxic conditions (average dissolved oxygen concentration 1.5 mg/L).

To conclude, when surface water infiltrates through the soil, the aquifer sediments act as a natural filter and the concentrations of most of the NSAIDs were partly reduced, likely due to physical and chemical processes such as sorption, mixing, and biodegradation, which may provide substantial improvements in water quality. The redox state of the shallow aquifer of the Besòs River Delta has to be regarded as the key factor driving the removal of the target NSAIDs, as the residence time from the river to the parking area is somewhat short (about a month; Figure 1e).

3.3. Human Health Risk Assessment

The occurrence of pharmaceuticals in urban aquifers has raised many questions about their risk to human health, as groundwater is the main source of drinking water in many European countries. In this study, the quantification of threat that the NSAIDs pose to human health was assessed by comparing the highest concentration of individual NSAIDs in groundwater to DWEL values. The DWEL values were always at least two or three orders of magnitude higher than the highest concentration of each individual NSAID in groundwater (Table S8). Consequently, these substances do not pose any risk to human health, in the case that the groundwater of the shallow aquifer of the Besòs River Delta is used as drinking water, as life-stage RQs for the 8 age intervals ranged from 0.027 to 0.000038. The NSAIDs that had the highest RQs were diclofenac followed, by ketoprofen. Among the assessed life stages, infants (6 to 12 months) and children (age 1 to 3 years) were the age intervals that presented the highest RQs (Figure 6). This observation suggests that early life stages are the most sensitive to exposure to NSAIDs from groundwater, as

they ingest a higher amount of water per body weight. One limitation of the assessment of RQs was that there exists no information on the DWI and BW of the inhabitants of Spain.

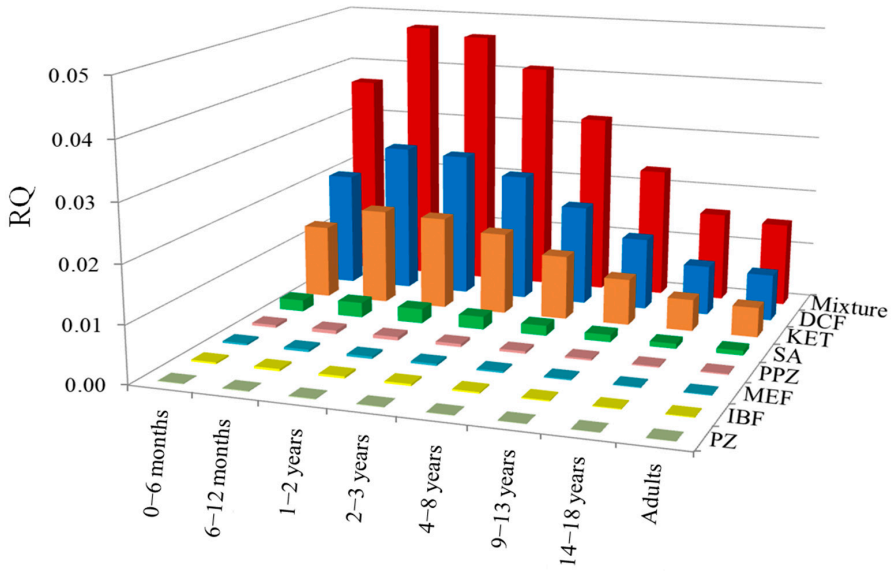


Figure 6. Human health life-stage RQ profile for the target NSAIDs and their mixture (sum of the target NSAIDs) in the shallow aquifer of the Besòs River Delta. DCF, diclofenac; IBU, ibuprofen; KET, ketoprofen; MEF, mefenamic acid; PPZ, propyphenazone; PZ, phenazone; SA, salicylic acid.

The evaluation of the risk of individual NSAIDs might have been underestimated, as these substances were detected simultaneously in groundwater samples. Thus, it was considered important to compute the RQ for the mixture of these substances (Figure 6). The mixture of NSAIDs seemed to represent a minimal risk to human health, as the RQs for all age intervals considered were far less than 0.1.

4. Conclusions

Water scarcity has encouraged research into alternative water resources, such as urban groundwater; however, the continuous input of pharmaceutical compounds, such as NSAIDs, may limit its potential uses and pose a tremendous risk to human health, particularly if safe drinking water is to come from groundwater sources. With this purpose in mind, this study investigated the occurrence of NSAIDs and their metabolites in an urban aquifer, proposed a methodology to quantify the removal of these substances from groundwater and, finally, demonstrated that the NSAIDs would not pose any risk to human health if the urban groundwater was used as potential source for drinking water. A total of six NSAIDs and two metabolites were investigated in river and 13 groundwater samples, coupled with major ions and redox indicators, in an urban aquifer located in Barcelona (Spain).

Six of the target NSAIDs were ubiquitous (ketoprofen, diclofenac, mefenamic acid, propyphenazone, phenazone, and the metabolite salicylic acid), while the remaining two were frequently detected (>75%) in groundwater. The highest average concentrations in the aquifer were 225.2 ng/L for diclofenac, 110.2 ng/L for salicylic acid, 97.7 ng/L for ketoprofen, and 91.7 ng/L for propyphenazone. Overall, the higher concentrations of the NSAIDs were detected at the shallow sampling points located near the river (SAP-2b and SAP-4). The maximum individual concentrations were, in descending order: 620 ng/L for salicylic acid (ADPQ), 380 ng/L for diclofenac (SAP-2b), and 379 ng/L for ibuprofen (SAP-4). All of the target substances were detected in the River Besòs, except 4OH diclofenac, with concentrations ranging from 9.3 ng/L (for ketoprofen) to 293 ng/L (for ibuprofen). The average concentrations in groundwater samples were higher than those detected in river water for all of the NSAIDs, expect for ibuprofen; however, the concentrations

reported in the river water—which is the main pollution source of the aquifer—may not be representative, due to the irregular flow pattern of the River Besòs.

We proposed a methodology to evaluate the percentage of the NSAIDs that were naturally removed in the river–groundwater interface by the term R_{abs}, which compares the expected concentrations of these substances by river water mixing in groundwater with those measured in the groundwater in the sampling campaign. Most of the NSAIDs presented R_{abs} above 0 and the substances that were easily and moderately removed were 4OH diclofenac, ibuprofen, and salicylic acid with median R_{abs} values of 0.80. 0.74 and 0.35, respectively. This observation suggests that the reducing conditions in the aquifer might favor the natural attenuation of the NSAIDs. Median removals for diclofenac, mefenamic acid, and phenazone were poor ($R_{abs} < 0.3$). The innovative aspect of the proposed approach is the quantification of the removal capacity of these substances in the subsurface at each groundwater sampling point.

Finally, RQs were estimated, in order to assess the human health risks posed by the considered NSAIDs in groundwater, as this resource might serve as an alternative source for drinking water provision. Individual NSAIDs and their mixture posed a minimum risk for human health, for all life stages, as associated RQs values were all less than 0.05. Nevertheless, the evaluation of the risk posed by the sum of different pharmaceuticals should be evaluated, as these substances can be detected simultaneously in groundwater.

This preliminary research can help to set groundwater quality standards for CECs, such as pharmaceuticals, as this freshwater is expected to be used as a drinking water source in semi-arid regions, such as Spain. There exist some knowledge gaps regarding the fate and risk assessment of NSAIDs in groundwater, which deserve further investigation in the near future. First, it is necessary to better understand the dynamics of the NSAIDs (and CECs in general) in groundwater over long periods of time (e.g., hydrogeological year), including a wide range of flow conditions. Moreover, it is of paramount importance to quantify the hydrochemical processes (i.e., transport and redox processes and adsorption) that control the behavior of the NSAIDs in groundwater, by means of numerical modelling. This additional research will help to better characterize the variability of the NSAID concentrations in the river water, to properly define the potential uses of urban groundwater, and to implement solutions for its management in urban areas. Secondly, as the consumption of pharmaceuticals has been increasing sharply and urban groundwater is expected to constitute a source of drinking water more frequently in the future, evaluating the human risk posed by these substances is a major issue, as their effect on human health is not yet well-understood.

Supplementary Materials: The following are available online at https://www.mdpi.com/2073-4441/13/5/720/s1, Figure S1: Piper diagram showing major ion chemistry of the groundwater (blue triangles) and river water (green squares), Figure S2: Removal of the NSAIDs along linear groundwater 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-($C_{GW\text{-}Obs}/C_{SAP\text{-}2b}$), where $C_{GW\text{-}Obs}$ and $C_{SAP\text{-}2b}$ 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), Table S1. Details of MIX Code and steps followed for the evaluation of the concentration of the NSAIDs and the mixing ratios, 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, 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, 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, Table S4: Acceptable daily intake (ADI) values of the target NSAIDs in groundwater. ADI not available. Metabolites are listed in bold, Table S5: 50th percentile body weight and Drinking Water Intake (WHO) for selected age groups, Table S6: Concentrations of major ions (mg/L) and some redox indicators (mg/L) in groundwater sampling points and river water, **Table S7**: Removal (R_{abs}) of the NSAIDs in the groundwater sampling points Metabolites are listed in bold, 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.

Author Contributions: Conceptualization, A.J. and E.P.; methodology, A.J. and E.P.; investigation, A.J., E.P. and E.V-S.; data curation, A.J. and E.P.; writing—original draft preparation, A.J.; writing—review and editing, A.J., E.P. and E.V-S.; visualization, A.J. and E.P.; project administration, A.J. and E.V-S.; funding acquisition, A.J. and E.V-S. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Data supporting the reported results can be found in the Supplementary Materials.

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