

Article

An Initial Approach to the Presence of Pharmaceuticals in Wastewater from Hospitals in Colombia and Their Environmental Risk

Efraím A. Serna-Galvis ^{1,2}, Ana M. Botero-Coy ³, Milton Rosero-Moreano ⁴, Judy Lee ⁵, Félix Hernández ^{3,*}
and Ricardo A. Torres-Palma ^{1,*}

- ¹ Grupo de Investigación en Remediación Ambiental y Biocatálisis (GIRAB), Facultad de Ciencias Exactas y Naturales, Instituto de Química, Universidad de Antioquia UdeA, Calle 70 No. 52-21, Medellín 050010, Colombia; efrain.serna@udea.edu.co
 - ² Grupo de Investigaciones Biomédicas Uniremington, Facultad de Ciencias de la Salud, Corporación Universitaria Remington (Uniremington), Calle 51 No. 51-27, Medellín 050010, Colombia
 - ³ Environmental and Public Health Analytical Chemistry, Research Institute for Pesticides and Water (IUPA), University Jaume I (UJI), Avda. Sos Baynat, S/N, 12071 Castellón, Spain; botero@uji.es
 - ⁴ Grupo de Investigación en Cromatografía y Técnicas Afines GICTA, Departamento de Química, Facultad de Ciencias Exactas y Naturales, Universidad de Caldas, Calle 65 No. 26-10, Manizales 170004, Colombia; milton.rosero@ucaldas.edu.co
 - ⁵ Department of Chemical and Process Engineering, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford GU2 7XH, UK; j.y.lee@surrey.ac.uk
- * Correspondence: hernandf@uji.es (F.H.); ricardo.torres@udea.edu.co (R.A.T.-P.)



Citation: Serna-Galvis, E.A.; Botero-Coy, A.M.; Rosero-Moreano, M.; Lee, J.; Hernández, F.; Torres-Palma, R.A. An Initial Approach to the Presence of Pharmaceuticals in Wastewater from Hospitals in Colombia and Their Environmental Risk. *Water* **2022**, *14*, 950. <https://doi.org/10.3390/w14060950>

Academic Editor: Carmen Teodosiu

Received: 15 January 2022

Accepted: 7 March 2022

Published: 18 March 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Hospital wastewater (HWW) from three different cities in Colombia was characterized. Wastewater quality indicators and 38 relevant pharmaceuticals were examined. The HWW had pH from 6.82 to 8.06, chemical oxygen demand was between 235.5 and 1203 mg L⁻¹, and conductivity ranged from 276.5 to 717.5 μS cm⁻¹. Additionally, most of the target pharmaceuticals (20 of 38) had 100% occurrence frequency in the samples due to their high and continuous consumption in the hospitals. Indeed, acetaminophen, diclofenac, azithromycin, ciprofloxacin, sulfamethoxazole, losartan, metoprolol, and omeprazole were present in all samples at concentrations from one up to some hundreds of μg L⁻¹. Once pharmaceuticals are discharged into local sewage systems or rivers, because of the high dilution of HWW, the individual environmental hazards are low (i.e., risk quotients, RQ < 0.1 were determined). The action of conventional treatments on HWW also decreased the individual environmental risks of pharmaceuticals (RQ values < 0.1). However, the mixture of pharmaceuticals in the HWW had potential environmental risks (as RQ > 0.1 were found), remarking the need for efficient processes to eliminate pharmaceuticals from HWW. This work provides an initial view on the characterization of diverse Colombian HWW, which could be useful for the understanding of the current situation of pollution by pharmaceuticals in Latin America.

Keywords: contaminants of emerging concern; Colombian wastewater; hospital sewage; risk quotient; water characterization; water pollution

1. Introduction

Hospital effluents have been the object of study and research worldwide in the last two decades. Special attention has been paid to improving the knowledge about the chemical and physical characteristics of such wastewater. Thus, conventional quality parameters (e.g., chemical oxygen demand—COD or pH) and the presence of contaminants of emerging concern (CECs, such as pharmaceuticals) are typically analyzed [1–3].

Hospital wastewater (HWW) contains hazardous pharmaceuticals, and these matrices can cause severe environmental pollution. Hence, it is paramount that hospital wastewater must be characterized and treated before being released to sewers and the aquatic

environment [4]. HWW is considered a hot spot in terms of a load of pharmaceuticals, prompting the scientific community to question the acceptability of the general practice of discharging HWW into public sewers or direct disposal into the environmental water. Indeed, HWW may harm environmental and human health by disseminating antibiotics and antibiotic-resistant bacteria in rivers. Hence, the proper management and disposal of HWW is of increasing international interest [5].

In many developing countries, there is no safe management of hospital waste. Most hospitals in these countries have poor waste segregation and disposal practices, leading to occupational and environmental risks [6]. The environmental risks associated with pharmaceuticals in hospital effluents must be assessed. Nowadays, it is recognized that the knowledge of pollutants in the HWW and their concentration levels is necessary for scientists to evaluate their risks and impacts on the environment. This is also relevant information for administrators and decision-makers for regulatory purposes and the implementation of solution alternatives [7].

When HWW is discharged into the municipal sewage systems, CECs (e.g., pharmaceuticals) enter the wastewater treatment plants (WWTP). A WWTP is mostly composed of physical processes (primary treatments) and conventional activated sludge—CAS (secondary treatments), which are ineffective at removing CECs. Additionally, from the WWTP, the pollutants that are not eliminated can be released within the treated effluents or accumulate in sludges. Therefore, CAS often needs revamping with innovative systems such as membrane bioreactors (MBR) or up-flow anaerobic sludge blankets (UASB), or even the combination with advanced oxidation processes (AOP) to improve its removal efficiencies towards emerging CECs [8].

The occurrence, concentrations, and sources of pharmaceuticals in surface water, municipal wastewater, and treated wastewater in Latin America, in addition to the associated environmental impact from the release of pharmaceuticals, have been previously analyzed and discussed [9]. Indeed, some works on the characterization of HWW from Mexico and Brazil have been published [10–12], and such reports present valuable information on HWW from a single hospital. However, additional studies in other countries considering effluents from various hospitals are necessary to widen the panorama about HWW in Latin America.

This research was focused on the characterization of HWW in Colombia from three different hospitals, considering a high number of pharmaceuticals (specifically 38) simultaneously. The main aim of our research was to provide an initial view on the pharmaceuticals load in Colombian HWW and their potential risks, which can be used as a starting point for future works on the pollution by CECs in Colombia and other Latin American countries.

2. Materials and Methods

2.1. Reagents and Samples

For liquid chromatography-tandem mass spectrometry (LC-MS/MS) analyses, pharmaceutical reference standards were acquired from Sigma-Aldrich, LGC Promochem, Toronto Research Chemicals, Across Organics, Bayer Hispania, and Aventis Pharma. More details on reagents and chemicals used in the analyses can be found in reference [11]. Potassium dichromate and sulfuric acid were purchased from Merck. Silver sulfate was obtained from Carlo Erba. Target pharmaceuticals were selected based on prior findings in a work performed in Colombian wastewaters [13] and our previous experience on the analytical determinations of pharmaceuticals in hospital wastewater samples [11].

HWW samples collection was performed in two campaigns: one in the dry season (February–March months) and the other one in the rainy season (November–December months) in Colombia. The considered samples were taken from a hospital from a large-size city (Medellín, ~2,600,000 people), and two hospitals from medium-size towns (Manizales, ~401,000 people; and Tumaco, ~230,000 people) in Colombia. HWW from the hospital in Medellín is discharged into the municipal sewage system, whereas the HWW from the hospital in Tumaco ends up in the local river. In turn, the HWW from the hospital

in Manizales is pre-treated before they are discharged into the corresponding municipal sewage system. The pre-treatment system consisted of an aerobic activated sludge tank, followed by a clarification tank and a chlorination step.

2.2. Analyses

Determination of pharmaceuticals was performed by LC-MS/MS with triple quadrupole. Briefly, aliquots of the sample were centrifuged and diluted 5-folds with ultrapure water, adding a mixture of 12 isotope-labeled internal standards (ILIS) for matrix effect correction. The final solution (50 μL) was then injected into the LC-MS/MS apparatus (Waters Acquity UPLC interfaced to a triple quadrupole mass spectrometer Xevo TQS) equipped with electrospray ionization—ESI and operated in positive mode. The chromatographic separation was performed using an Acquity UPLC BEH C18 column (1.7 μm , 100 mm \times 2.1 mm), with a gradient mobile phase consisting of $\text{H}_2\text{O}/\text{MeOH}$, and both solvents with 0.01% HCOOH and 1 mM ammonium acetate, at 0.4 mL min^{-1} .

Three MS/MS transitions were acquired for each compound for accurate quantification and reliable identification of the pharmaceuticals detected in the samples. Confirmation of the identity of the compound was based on the ion ratio between the confirmation (q_1 and q_2) and quantification (Q) transitions, and by chromatographic retention time compliance in comparison with the reference standards injected in the calibration (tolerance ranges $\pm 30\%$ for ion ratio and ± 0.1 min for retention time) [14].

Quality control (QCs) samples, consisting of wastewater spiked with the target pharmaceuticals at 0.1 and 1 $\mu\text{g L}^{-1}$, were included in every sample sequence to ensure the reliability of the concentration data reported. At the two tested concentrations, the wide majority of QCs recoveries were satisfactory (60–140%), and most were within the range of 70–120%. More information on analytical conditions can be found elsewhere [13].

Frequency of occurrence (FO) was calculated for each pharmaceutical as the number of samples with a concentration higher than the limit of detection divided by the total number of samples.

Chemical oxygen demand (COD) of the samples was established using the closed reflux colorimetric procedure based on the Standard Methods for Examination of Water and Wastewater 5220, as described in [15]. The pH was directly measured using a pH 93 pH-meter. Conductivity was also determined by direct measurement using a Lab945 SI Analytics conductimeter.

2.3. Environmental Risk Assessment

The environmental risk assessment was evaluated through the determination of risk quotients (RQ). The RQ values can be calculated as the ratio between measured concentrations (MEC) and predicted no-effect concentration (PNEC) (Equation (1), RQ measured, expressed as RQ_m). The other option to determine the quotient uses predicted environmental concentration (PEC) instead of MEC (Equation (2), RQ predicted, expressed as RQ_p) for the individual pharmaceuticals [16]. The PNEC values for the determination of RQ values were taken from literature, and such values are summarized in Table S1 (in the Supplementary Materials). Moreover, it must be noted that the environmental risk is categorized according to the RQ values as follows: $\text{RQ} \leq 0.1$: low risk; $0.1 < \text{RQ} \leq 1$: moderate risk, and $\text{RQ} > 1$: high risk.

$$\text{RQ}_m = \text{MEC}/\text{PNEC}, \quad (1)$$

$$\text{RQ}_p = \text{PEC}/\text{PNEC}, \quad (2)$$

The utilization of Equation (1) or Equation (2) depends on the scenario of the sample. According to Escher et al. [17], to evaluate the environmental risk linked to the target pharmaceuticals, we can consider the following scenarios: *Scenario a*) Risk potential of the HWW before discharge to the sewage system (i.e., full risk potential without any degradation or dilution); *Scenario b*) Risk potential at the inlet of a sewage system or an

environmental media such as rivers (i.e., reduced risk potential through dilution); and *Scenario c*) Risk potential after a treatment (i.e., reduced risk potential through the action of a conventional process).

Nowadays, it is recognized that the single RQ is not sufficient to accurately evaluate the risk related to a complex mixture of pollutants that are non-independently affecting aquatic biota. Therefore, mixture risk quotients (RQ_{mix} , Equation (3)) are a good option to denote the potential environmental risk for a complex mixture of pollutants [18,19]. As HWW are mixtures of many pollutants, in addition to the RQ values for the individual pharmaceuticals, the RQ_{mix} was also estimated using Equation (3).

$$RQ_{mix} = \Sigma RQ_p \text{ or } \Sigma RQ_m, \quad (3)$$

3. Results and Discussion

3.1. Wastewater Quality Indicators of the Considered HWW

Initially, three relevant wastewater quality indicators (i.e., pH, COD, and conductivity) for the HWW samples were measured (Table 1). In the hospital from medium-size cities (i.e., Manizales and Tumaco), all facilities water is mixed as a whole wastewater effluent. Meanwhile, the hospital from the large-size city (i.e., Medellín) has different sewage systems for each facility. In this case, the individual sewages from the dialysis unit (DIA), intensive care unit (ICU), and hospitalization unit (HOS) were considered.

Table 1. Characterization of the samples through relevant wastewater quality indicators.

Hospital Campaign	Medellín						Manizales		Tumaco	
	1		2		1	2	1	2		
Notation	ICU ¹	DIA	HOS	ICU	DIA	HOS	W	W	W	W
pH	6.82	7.67	7.67	6.85	8.06	7.19	7.96 ²		7.45	6.82
Conductivity ($\mu\text{S cm}^{-1}$)	365	538	326	276.5	439	400	717.5		478.3	487.7
COD (mg L^{-1})	380.6	507.5	545.1	501.8	235.5	258.1	1203		382.23	342.67

¹ ICU: intensive care unit, DIA: dialysis unit; HOS: hospitalization unit, W: whole hospital wastewater. ² In the case of Manizales, average values were reported for the wastewater quality indicators.

The tested wastewater from Colombian hospitals had pH values ranging from 6.82 to 8.06. The COD parameter presented values between 235.5 and 1203 mg L^{-1} . Meanwhile, the conductivity of these HWW ranged from 276.5 to 717.5 $\mu\text{S cm}^{-1}$. The values for these wastewater quality indicators belong to the normal ranges reported in the literature for several HWW around the world [1,2,20–22]. It is important to mention that in the case of the two HWW from the medium-size cities, the samples correspond to mixtures of wastewater from toilets, kitchens, laundry, and health facilities. Thus, the COD content can be mainly associated with organic substances coming from both medical and non-medical activities within the hospitals [2,21]. The conductivity is related to the presence of ionic substances; particularly, chloride anion is the main contributor to this parameter in HWW [23].

Regarding the wastewater from the subunits in the hospital in the large-size city (Medellín), we should mention that the contents of COD and ionic substances are related to the activities performed therein. The sewages from the intensive care unit (ICU) and hospitalization facility (HOS) could contain organic compounds and ionic substances released through the toilets (e.g., excretions) and handwashing systems (e.g., soaps or disinfectants). In turn, the COD for the wastewater from the dialysis unit (DIA) would be linked to the presence of citric acid (substance typically used for washing the dialysis machines [24]) and some substances from the dialyzed bloodstreams [25]. Additionally, dialysis effluents are considered saline water [25], which was reflected in higher conductivity levels for DIA samples compared with samples from the ICU and HOS (Table 1).

3.2. Presence of the Target Pharmaceuticals in the HWW Samples

The target pharmaceuticals (38 compounds) were analyzed in the HWW samples. Table 2 summarizes the concentrations and frequency of occurrence (FO) of the pharmaceuticals in the evaluated samples. It was found that 31 of 38 target substances were above the limit of quantification (Table 2). Moreover, 20 of 38 target pharmaceuticals had an FO of 100%. These results are consistent with previous studies from other HWW that also report high FO for pharmaceuticals in this kind of matrix [23,26]. Due to the low number of sampling campaigns and the hospitals considered, the data in Table 2 represent an initial/flash approach to the content of pharmaceuticals in the Colombian HWW. Therefore, it is insufficient information to discuss trends, averages, and maximum or minimum concentrations. Such discussions require data from numerous sampling campaigns using composed samples from several days. Therefore, it is better to focus the discussion of this information on the presence of pharmaceuticals and any warnings associated with these substances.

Table 2 shows that in the tested HWW, pharmaceuticals such as acetaminophen, diclofenac, azithromycin, ciprofloxacin, sulfamethoxazole, losartan, metoprolol, and omeprazole were present in all samples at concentration levels ranging from one up to some hundreds of $\mu\text{g L}^{-1}$. It is important to mention that the content of pharmaceuticals in HWW depends on the number of beds, as well as the number and type of wards and units in the hospitals [26]. The remarkable presence of the above-mentioned pharmaceuticals in the HWW can be associated with their high and continuous consumption.

Acetaminophen (also called paracetamol) is the most consumed analgesic/antipyretic worldwide [27]. This pharmaceutical is very common in HWW at 10^1 to $10^3 \mu\text{g L}^{-1}$ levels [2]. This analgesic is also vastly consumed in Colombian hospitals; consequently, high concentrations of acetaminophen were found in the tested HWW (Table 2).

Additionally, diclofenac is another typical analgesic in HWW at concentrations ranging between 10^{-1} and $10^2 \mu\text{g L}^{-1}$ [2]. In addition to the analgesics, antibiotics groups such as lincosamides (e.g., clindamycin), macrolides (e.g., clarithromycin, azithromycin, and erythromycin), quinolones (e.g., ciprofloxacin and norfloxacin), and sulfonamides (e.g., sulfamethoxazole) belong to the highly consumed groups in Latin American countries [28]. Most of them are frequently found in wastewater samples from these countries [9,29,30]. The pharmaceuticals in the Colombian HWW are at concentration levels similar to those reported for HWW from Mexico and Brazil [10–12]. For the Mexican HWW (from Toluca city), the presence of acetaminophen ($2.66 \mu\text{g L}^{-1}$), diclofenac ($0.59 \mu\text{g L}^{-1}$), and metoprolol ($2.02 \mu\text{g L}^{-1}$) has been reported. In turn, for the Brazilian HWW, a literature review informed that in Sao Paulo, antiparasitic drugs were detected in concentrations up to $3.81 \mu\text{g L}^{-1}$. In Southern Brazil (Rio Grande do Sul), acetaminophen ($7.5 \mu\text{g L}^{-1}$) and enalapril ($1 \mu\text{g L}^{-1}$) were found in hospital sewage samples. Moreover, in other HWW (in Rio Grande), diclofenac was detected with concentrations from 0.83 to $3.59 \mu\text{g L}^{-1}$ [12]. In addition, a recent study revealed the presence of acetaminophen, clindamycin, metoprolol, metronidazole, sulfamethoxazole, trimethoprim, and tramadol in at least three of six samples from HWW in the city of Porto Alegre (South Brazil) [11].

It should be mentioned that the concentrations of some target pharmaceuticals (e.g., acetaminophen, ciprofloxacin, diclofenac, losartan, sulfamethoxazole, or trimethoprim) in HWW (the present work) were much higher than those in influents of municipal wastewater treatment plants in Colombia [13], which is in agreement with the literature reports [20]. This is associated with the effect of dilution in the municipal wastewater matrix. Indeed, the concentrations of pharmaceuticals in HWW can be 2–100 times higher than in influents of municipal wastewater treatment plants [2,20]. This is important because it marks the relevance of HWW as a significant source of pharmaceuticals in the sewage system. Furthermore, knowledge about the concentration levels of these pollutants in HWW and municipal wastewater is essential for scientists, practitioners, administrators, and decision-makers to evaluate their environmental impact [7].

Table 2. Measured concentration (MEC) of the target pharmaceuticals (in $\mu\text{g L}^{-1}$) in the considered HWW.

Hospital Campaign Notation	Medellín						Manizales		Tumaco		² FO (%)
	¹ ICU	1 DIA	HOS	2 ICU	DIA	HOS	1 W	2 W	1 W	2 W	
Acetaminophen	0.56	392.30	131.17	10.19	366.97	28.96	651.80	667.79	³ d	11.31	100
Alprazolam	⁴ -	-	-	-	-	-	-	-	-	-	0
Atorvastatin	d	d	1.36	-	-	-	6.79	-	0.15	0.82	60
Azithromycin	0.41	0.58	0.46	0.41	0.40	0.40	1.87	1.65	11.63	3.18	100
Carbamazepine	-	-	-	-	0.08	0.20	0.15	6.26	0.02	-	50
Ciprofloxacin	0.17	5.77	1.23	185.28	6.07	3.74	36.62	6.80	2.79	5.03	100
Clarithromycin	-	-	-	-	-	-	d	-	d	d	30
Clindamycin	d	0.07	0.28	0.12	0.02	d	2.23	0.34	32.09	12.04	100
Diclofenac	15.84	6.57	-	0.06	0.04	0.05	1.08	0.11	2.82	0.68	90
Enalapril	d	1.02	0.14	7.40	0.11	0.42	0.51	0.54	0.56	0.10	100
Erythromycin	-	-	-	0.93	-	-	0.12	-	-	0.11	30
Flumequine	d	d	d	d	d	d	d	d	d	d	100
Furaltadone	-	-	-	-	-	-	-	-	-	-	0
Gabapentin	-	-	0.20	0.15	-	-	17.83	-	-	-	30
Iopromide	d	d	-	-	0.02	d	1591.04	131.39	d	d	80
Irbesartan	-	-	-	-	-	0.03	0.03	0.01	0.05	0.03	50
Levamisole	-	-	-	-	1.02	-	3.09	-	0.12	-	30
Lincomycin	-	-	d	-	-	-	-	-	-	-	10
Lorazepam	-	-	-	-	-	-	0.02	0.03	-	-	20
Losartan	2.89	18.99	2.56	0.74	1399.65	5.87	2.46	34.81	14.98	9.70	100
Metoprolol	3.94	1.29	0.39	2.03	0.12	1.55	4.59	0.13	0.11	0.13	100
Metronidazole	1.01	0.38	1.08	0.20	0.07	0.72	0.96	1.14	0.02	0.02	100
Nalidixic acid	0.02	d	d	d	d	d	d	d	d	d	100
Norfloxacin	0.19	1.03	0.31	0.19	2.04	0.07	3.85	0.19	0.12	0.03	100
Omeprazole	0.07	0.49	0.07	5412.91	2124.97	30.29	5.06	2.63	0.17	0.56	100
Oxolinic acid	d	d	d	d	d	d	d	d	d	d	100
Pantoprazole	-	-	-	-	-	-	-	-	-	-	0
Phenazone	0.038	0.453	0.029	20.908	1.722	3.472	0.816	0.252	0.678	0.422	100
Primidone	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	100
Roxithromycin	-	-	-	-	-	-	-	-	-	-	0
Salbutamol	0.01	0.01	d	0.20	0.04	0.01	0.78	0.49	0.08	0.06	100
Sulfadiazine	0.01	0.01	0.01	0.01	0.01	0.25	0.11	0.01	0.01	0.01	100
Sulfamethoxazole	0.09	7.41	0.03	0.02	0.02	0.30	198.53	26.24	1.62	0.07	100
Tetracycline	-	-	-	-	-	-	d	-	-	-	10
Tramadol	1.22	2.90	0.69	6.95	3.38	0.13	16.63	1.16	14.24	4.44	100
Trimethoprim	2.14	8.98	0.24	0.04	d	0.47	>50	21.86	2.04	0.04	100
Valsartan	0.04	-	-	-	0.79	-	0.16	-	d	d	50
Venlafaxine	-	-	-	-	-	-	-	-	-	-	0

¹ ICU: intensive care unit, DIA: dialysis unit; HOS: hospitalization unit, W: whole hospital wastewater.
² FO: frequency of occurrence. ³ d: detected but not quantified. ⁴ -: not detected.

3.3. Environmental Risk Assessment for the Pharmaceuticals

It is well-known that HWW is a major contributor of pharmaceuticals into the environment when they are directly discharged into environmental water (e.g., rivers) or through effluents of municipal wastewater treatment plants (due to the persistence of pharmaceuticals to conventional wastewater treatments) [5,31]. After target contaminants were quantified in the HWW samples, the environmental risk assessment for the pharmaceuticals was performed using the risk quotient criteria (Equations (1)–(3)) and the scenarios analyses according to Escher et al. [17]. Table 3 presents the RQ_m values for *Scenario a* for all the HWW samples. *Scenario b* was also applied to the samples from Medellín and Tumaco, which experienced dilution due to their discharge into the sewage system and a local river, respectively; thus, Table 4 contains the RQ_p for these HWW samples.

Table 3. Risk quotients (RQ_m) for the pharmaceuticals in the hospital wastewaters under *Scenario a*.

Hospital Campaign Notation	Medellín						Manizales		Tumaco		Counting of RQ > 1
	1			2			1	2	1	2	
	ICU	DIA	HOS	ICU	DIA	HOS	W	W	W	W	
Acetaminophen	0.08	56.69	18.95	1.47	53.03	4.18	94.19	96.50	¹ –	1.63	8
Alprazolam	–	–	–	–	–	–	–	–	–	–	0
Atorvastatin	–	–	7.18	–	–	–	35.76	–	0.80	4.29	3
Azithromycin	21.80	30.43	24.42	21.45	21.17	20.95	98.59	86.90	611.90	167.11	10
Carbamazepine	–	–	–	–	0.04	0.10	0.07	3.13	0.01	–	1
Ciprofloxacin	0.34	11.54	2.46	370.57	12.14	7.47	73.25	13.60	5.59	10.06	9
Clarithromycin	–	–	–	–	–	–	–	–	–	–	0
Clindamycin	–	0.73	2.80	1.17	0.24	–	22.29	3.44	320.91	120.41	6
Diclofenac	792.21	328.56	–	2.98	1.76	2.25	53.81	5.73	141.23	33.99	9
Enalapril	–	0.05	0.01	0.35	0.01	0.02	0.02	0.03	0.03	0.00	0
Erythromycin	–	–	–	2.32	–	–	0.29	–	–	0.27	1
Flumequine	–	–	–	–	–	–	–	–	–	–	0
Furaltadone	–	–	–	–	–	–	–	–	–	–	0
Gabapentin	–	–	1.04	0.78	–	–	90.95	–	–	–	2
Iopromide	–	–	–	–	0.00	–	6.22	0.51	–	–	1
Irbesartan	–	–	–	–	–	0.00	0.00	0.00	0.00	0.00	0
Levamisole	–	–	–	–	1.02	–	3.09	–	0.12	–	2
Lincomycin	–	–	–	–	–	–	–	–	–	–	0
Lorazepam	–	–	–	–	–	–	0.01	0.01	–	–	0
Losartan	0.05	0.30	0.04	0.01	21.97	0.09	0.04	0.55	0.24	0.15	1
Metoprolol	39.44	12.89	3.86	20.26	1.16	15.53	45.91	1.35	1.06	1.33	10
Metronidazole	0.01	0.00	0.01	0.00	0.00	0.01	0.01	0.01	0.00	0.00	0
Nalidixic acid	0.22	–	–	–	–	–	–	–	–	–	0
Norfloxacin	115.99	646.51	190.67	118.52	1274.42	42.08	2404.29	116.21	75.78	20.34	10
Omeprazole	0.00	0.00	0.00	54.13	21.25	0.30	0.05	0.03	0.00	0.01	2
Oxolinic acid	–	–	–	–	–	–	–	–	–	–	0
Pantoprazole	–	–	–	–	–	–	–	–	–	–	0
Phenazone	0.14	1.64	0.10	75.75	6.24	12.58	2.96	0.91	2.46	1.53	7
Primidone	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0.22	0
Roxithromycin	–	–	–	–	–	–	–	–	–	–	0
Salbutamol	0.01	0.00	–	0.18	0.03	0.01	0.68	0.42	0.07	0.05	0
Sulfadiazine	0.01	0.01	0.01	0.01	0.01	0.35	0.16	0.01	0.01	0.01	0
Sulfamethoxazole	0.16	12.56	0.05	0.04	0.04	0.52	336.49	44.47	2.74	0.11	4
Tetracycline	–	–	–	–	–	–	–	–	–	–	0
Tramadol	1.27	3.03	0.72	7.25	3.52	0.13	17.34	1.21	14.85	4.63	8
Trimethoprim	368.10	1547.48	40.54	6.89	–	80.22	–	3768.52	351.29	7.04	8
Valsartan	0.01	–	–	–	0.20	–	0.04	–	–	–	0
Venlafaxine	–	–	–	–	–	–	–	–	–	–	0

¹ –: Not applicable.

Table 3 contains the individual RQ_m values in *Scenario a* for all the considered hospital wastewater samples. It can be noted that substances such as acetaminophen, azithromycin, ciprofloxacin, clindamycin, diclofenac, metoprolol, norfloxacin, phenazone, tramadol, and trimethoprim had RQ_m > 1 for more than five of the considered samples. These pharmaceuticals represent a high potential risk before the discharge of the HWW in the sewage system, environmental water, or the application of treatment. However, we should mention that samples from the hospital in Medellín are discharged into the municipal sewage system, whereas HWW from Tumaco is discharged into a local river. These two kinds of samples were diluted, and *Scenario b* was applied. The individual RQ_p values were calculated by taking into account the dilution factor for Colombia (which is 929.87 [32]) and are presented in Table 4.

Table 4. Risk quotients (RQ_p) of the pharmaceuticals in the hospital wastewaters under *Scenario b*.

Hospital Campaign	Medellín						Tumaco	
	1			2			1	2
	ICU	DIA	HOS	ICU	DIA	HOS	W	W
Acetaminophen	0.00	0.06	0.02	0.00	0.06	0.00	¹ –	0.00
Alprazolam	–	–	–	–	–	–	–	–
Atorvastatin	–	–	0.01	–	–	–	0.00	0.00
Azithromycin	0.02	0.03	0.03	0.02	0.02	0.02	² 0.66	0.18
Carbamazepine	–	–	–	–	–	0.00	0.00	–
Ciprofloxacin	0.00	0.01	0.00	0.40	0.01	0.01	0.01	0.01
Clarithromycin	–	–	–	–	–	–	–	–
Clindamycin	–	0.00	0.00	0.00	0.00	–	0.35	0.13
Diclofenac	0.85	0.35	–	0.00	0.00	0.00	0.15	0.04
Enalapril	–	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Erythromycin	–	–	–	–	–	–	–	0.00
Flumequine	–	–	–	–	–	–	–	–
Furaltadone	–	–	–	–	–	–	–	–
Gabapentin	–	–	0.00	0.00	–	–	–	–
Iopromide	–	–	–	–	0.00	–	–	–
Irbesartan	–	–	–	–	–	0.00	0.00	0.00
Levamisole	–	–	–	–	0.00	–	0.00	–
Lincomycin	–	–	–	–	–	–	–	–
Lorazepam	–	–	–	–	–	–	–	–
Losartan	0.00	0.00	0.00	0.00	0.02	0.00	0.00	0.00
Metoprolol	0.04	0.01	0.00	0.02	0.00	0.02	0.00	0.00
Metronidazole	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Nalidixic acid	0.00	–	–	–	–	–	–	–
Norfloxacin	0.12	0.70	0.21	0.13	1.37	0.05	0.08	0.02
Omeprazole	0.00	0.00	0.00	0.06	0.02	0.00	0.00	0.00
Oxolinic acid	–	–	–	–	–	–	–	–
Pantoprazole	–	–	–	–	–	–	–	–
Phenazone	0.00	0.00	0.00	0.08	0.01	0.01	0.00	0.00
Primidone	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Roxithromycin	–	–	–	–	–	–	–	–
Salbutamol	0.00	0.00	–	0.00	0.00	0.00	0.00	0.00
Sulfadiazine	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Sulfamethoxazole	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Tetracycline	–	–	–	–	–	–	–	–
Tramadol	0.00	0.00	0.00	0.01	0.00	0.00	0.02	0.00
Trimethoprim	0.40	1.66	0.04	0.01	–	0.09	0.38	0.01
Valsartan	0.00	–	–	–	0.00	–	–	–
Venlafaxine	–	–	–	–	–	–	–	–
RQ _{mix}	1.44	2.85	0.32	0.73	1.53	0.20	1.64	0.40

¹ –: Not applicable. ² Values in **bold** correspond to RQ > 0.1, moderate or high risk.

From Table 4, it can be observed that the individual risk quotient values for all pharmaceuticals were significantly diminished compared with the data in Table 3. In fact, most target pharmaceuticals showed low or moderate environmental risks. This indicates that despite the high concentration of the pharmaceuticals in the HWW samples from Medellin and Tumaco, they did not represent high environmental risks individually because of the very high dilution factor in Colombia. Nevertheless, the RQ_{mix} (based on the individual RQ_p values, Table 4) for four of six HWW samples was higher than one, indicating that the whole set of pharmaceuticals in the samples had environmental risk. We can note that all the pharmaceuticals contribute to an environmental risk caused by the whole effluent (i.e., RQ_{mix}). Those substances having the highest individual RQ values had a major contribution to the RQ_{mix} [18].

In the particular case of the wastewater from the hospital of Manizales city, *Scenario c* could be adequate because its wastewater was treated using a conventional treatment (composed of a biological process combined with a clarifier and a chlorination step). The target pharmaceuticals in the effluents coming from the conventional treatment were quantified, and the corresponding RQ_m values (under *Scenario c*) were calculated (Table 5). Most MECs of the pharmaceuticals after the conventional treatment were lower than in the raw HWW. Consequently, most RQ_m values were also lowered (Table 5). Additionally, it

must be mentioned that the organic matter (i.e., the COD) decreased by ~60% (data not shown), indicating the good performance of the treatment system. Additionally, it can be remarked that the concentration of acetaminophen was significantly low in the effluent of the treatment, and this may be associated with its high biodegradability (which is very dependent on the chemical structure of the compound [33]). Indeed, theoretical analyses indicate that aerobic biotransformation of acetaminophen involves pathways such as amide hydrolysis, amine oxidation, and cleavage of hydroquinone structures (see Figure S1, in the supplementary material). Besides, it is important to mention that the HWW also carries metabolites/conjugates substances, which act as a reservoir because they can release the parent pharmaceuticals [33]. For this reason, some compounds can be found in the effluents at higher concentrations than in the inlet of the process [13].

Table 5. Concentration of the target pharmaceuticals in the HWW from Manizales before and after the conventional treatment and their RQ_m values under *Scenario c*.

Condition Campaign	Before the Conventional Treatment				After the Conventional Treatment			
	1		2		1		2	
Notation	MEC ($\mu\text{g L}^{-1}$)	RQ _m	MEC ($\mu\text{g L}^{-1}$)	RQ _m	MEC ($\mu\text{g L}^{-1}$)	RQ _m	MEC ($\mu\text{g L}^{-1}$)	RQ _m
Acetaminophen	651.80	94.19	667.79	96.50	¹ d	³ -	d	-
Alprazolam	² -	-	-	-	-	-	-	-
Atorvastatin	6.79	35.76	-	-	1.09	5.75	0.56	2.95
Azithromycin	1.87	98.59	1.65	86.90	2.59	136.57	2.51	132.10
Carbamazepine	0.15	0.07	6.26	3.13	0.20	0.10	1.20	0.60
Ciprofloxacin	36.62	73.25	6.80	13.60	0.41	0.82	1.60	3.21
Clarithromycin	d	-	-	-	d	-	d	-
Clindamycin	2.23	22.29	0.34	3.44	1.88	18.81	0.69	6.87
Diclofenac	1.08	53.81	0.11	5.73	0.86	43.10	0.51	25.49
Enalapril	0.51	0.02	0.54	0.03	0.02	0.00	0.18	0.01
Erythromycin	0.12	0.29	-	-	0.08	0.20	0.10	0.26
Flumequine	d	-	d	-	d	-	d	-
Furaltadone	-	-	-	-	-	-	-	-
Gabapentin	17.83	90.95	-	-	2.85	14.54	-	-
Iopromide	1591.04	6.22	131.39	0.51	68.54	0.27	45.02	0.18
Irbesartan	0.03	0.00	0.01	0.00	0.01	0.00	0.01	0.00
Levamisole	3.09	3.09	-	-	0.03	0.03	-	-
Lincomycin	-	-	-	-	d	-	-	-
Lorazepam	0.02	0.01	0.03	0.01	0.06	0.03	0.10	0.05
Losartan	2.46	0.04	34.81	0.55	5.08	0.08	3.23	0.05
Metoprolol	4.59	45.91	0.13	1.35	1.22	12.15	0.44	4.39
Metronidazole	0.96	0.01	1.14	0.01	1.09	0.01	1.23	0.01
Nalidixic acid	d	-	d	-	d	-	-	-
Norfloxacin	3.85	2404.29	0.19	116.21	0.04	24.96	0.12	76.85
Omeprazole	5.06	0.05	2.63	0.03	0.53	0.01	0.36	0.00
Oxolinic acid	d	-	d	-	d	-	d	-
Pantoprazole	-	-	-	-	d	-	-	-
Phenazone	0.816	2.96	0.252	0.91	181.043	655.95	1.477	5.35
Primidone	0.02	0.22	0.02	0.22	0.01	0.09	0.01	0.09
Roxithromycin	-	-	-	-	-	-	-	-
Salbutamol	0.78	0.68	0.49	0.42	0.05	0.04	0.02	0.01
Sulfadiazine	0.11	0.16	0.01	0.01	0.00	0.00	0.01	0.02
Sulfamethoxazole	198.53	336.49	26.24	44.47	2.85	4.83	30.81	52.22
Tetracycline	d	-	-	-	d	-	-	-
Tramadol	16.63	17.34	1.16	1.21	5.54	5.78	2.22	2.31
Trimethoprim	>50	-	21.86	3768.52	6.46	1114.64	9.41	1621.99
Valsartan	0.16	0.04	-	-	d	-	d	-
Venlafaxine	-	-	-	-	d	-	-	-

¹ d: detected but not quantified. ² -: not detected. ³ -: Not applicable.

After the action of the conventional process, the effluent is discharged and diluted into the municipal sewage system in Manizales and by considering the dilution factor, the corresponding RQ_p should be determined (Table 6). Table 6 shows that almost all the target pharmaceuticals had RQ_p values lower than 0.1, which indicates that the environmental

risk associated with these compounds individually was very low. However, when we considered the RQ_{mix} (based on the individual values of RQ_p) for the effluent coming from the biological system, it was found that this risk quotient was higher than two, indicating that the whole set of pharmaceuticals in the samples had environmental risk.

Table 6. RQ_p values for the pharmaceuticals after the conventional treatment (*Scenario c*).

Pharmaceutical	Campaign	
	1	2
Acetaminophen	–	–
Alprazolam	–	–
Atorvastatin	0.01	0.00
Azithromycin	¹ 0.15	0.14
Carbamazepine	0.00	0.00
Ciprofloxacin	0.00	0.00
Clarithromycin	–	–
Clindamycin	0.02	0.01
Diclofenac	0.05	0.03
Enalapril	0.00	0.00
Erythromycin	0.00	0.00
Flumequine	–	–
Furaltadone	–	–
Gabapentin	0.02	–
Iopromide	0.00	0.00
Irbesartan	0.00	0.00
Levamisole	0.00	–
Lincomycin	–	–
Lorazepam	0.00	0.00
Losartan	0.00	0.00
Metoprolol	0.01	0.00
Metronidazole	0.00	0.00
Nalidixic acid	–	–
Norfloxacin	0.03	0.08
Omeprazole	0.00	0.00
Oxolinic acid	–	–
Pantoprazole	–	–
Phenazone	0.71	0.01
Primidone	0.00	0.00
Roxithromycin	–	–
Salbutamol	0.00	0.00
Sulfadiazine	0.00	0.00
Sulfamethoxazole	0.01	0.06
Tetracycline	–	–
Tramadol	0.01	0.00
Trimethoprim	1.20	1.74
Valsartan	–	–
Venlafaxine	–	–
RQ_{mix}	2.19	2.08

¹ Values in **bold** correspond to $RQ > 0.1$, moderate or high risk.

The above results (especially the RQ_{mix} values) reveal the need to develop and apply specific treatments within the hospitals for eliminating pharmaceuticals before the HWW are discharged in the environment or the municipal sewage systems. For instance, AOPs such as ozonation, Fenton-based processes, or sonochemical systems can degrade most CECs (e.g., pharmaceuticals) in water by producing hydroxyl radicals and their oxidative properties [34–38]. Thus, treatment technologies such as AOPs, MBRs, or combinations of these technologies could be evaluated to efficiently remove/degrade pharmaceuticals from HWW and decrease environmental risks associated with these compounds [33,34]. Even more relevant could be the treatment of primary pollution sources inside hospitals such as

the urine of patients loaded with pharmaceuticals, applying high-frequency ultrasound or electrochemical processes that have shown very high potential to eliminate drugs in urine [39,40].

4. Conclusions

The COD, conductivity, and pH parameters of tested samples belonged to the typical ranges reported in the literature for HWW worldwide. The pharmaceuticals in the Colombian HWW were at levels of concentration ($\mu\text{g L}^{-1}$) similar to those reported for HWW from Mexico and Brazil. Additionally, 20 of 38 target pollutants had a frequency of detection of 100%. Indeed, acetaminophen, diclofenac, azithromycin, ciprofloxacin, sulfamethoxazole, losartan, metoprolol, and omeprazole were present in all samples at concentrations levels from one up to some hundreds of $\mu\text{g L}^{-1}$, which can be associated with their elevated and continuous consumption in the considered hospitals. Due to the very high dilution of HWW, once they are discharged into sewage systems or local rivers, the individual environmental hazards of pharmaceuticals are significantly decreased. On the other hand, the action of a conventional treatment process on the HWW could diminish the concentration of some biodegradable pharmaceuticals in the effluents and subsequently decrease the environmental risks of such pollutants. However, this study revealed that the mixture of pharmaceuticals in HWW had potential environmental risks. Then, treatment technologies such as AOPs, MBRs, or combinations of these technologies to efficiently remove/degrade pharmaceuticals from HWW and decrease environmental risks are needed. Finally, future studies should consider several HWW and more sampling campaigns (or composed samples for several days/months) to provide more detailed data and wider information about the discharge of pharmaceuticals from hospitals effluents and their environmental risks.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/w14060950/s1>, Figure S1: Biotransformation pathway for acetaminophen, Table S1: PNEC values used for the RQ determination [41–48].

Author Contributions: Conceptualization, E.A.S.-G., A.M.B.-C., F.H., M.R.-M., J.L. and R.A.T.-P.; methodology, F.H. and A.M.B.-C.; validation, F.H. and A.M.B.-C.; formal analysis, E.A.S.-G. and M.R.-M.; investigation, E.A.S.-G., M.R.-M. and R.A.T.-P.; resources, F.H., J.L. and R.A.T.-P.; writing—original draft preparation, E.A.S.-G.; writing—review and editing, F.H., A.M.B.-C., M.R.-M., J.L. and R.A.T.-P.; project administration, J.L. and R.A.T.-P.; funding acquisition, F.H., J.L. and R.A.T.-P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by MINCIENCIAS COLOMBIA, grant No. 111577757323, ROYAL SOCIETY-UK through the project “Sound” methods of remediating emerging contaminants in hospital wastewater (ICA\R1\191053). Authors from UJI acknowledge the financial support from the MINISTRY OF SCIENCE INNOVATION AND UNIVERSITY, Spain (Ref. RTI2018-097417-B-I00) as well as Generalitat Valenciana (Research Group of Excellence, Prometeo 2019/040). Milton Rosero-Moreano thanks to Diana Castillo Gómez and Gustavo Sánchez Duque for their collaboration and support in the two sample campaigns. E.A. S-G. thanks to MINCIENCIAS COLOMBIA for his fellowship during July 2015–June 2019 (Convocation 647-2014). “The APC was funded by Universidad de Antioquia UdeA”.

Data Availability Statement: The data will be available by request through email to the corresponding authors.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AOP: advanced oxidation process, CAS: conventional activated sludge, CECs: contaminants of emerging concern, COD: chemical oxygen demand, DIA: dialysis unit, FO: frequency of occurrence, ESI: Electrospray ionization, HOS: hospitalization unit, HWW: hospital wastewater, ICU: intensive care unit, ILIS: isotope-labeled internal standards, LC-MS/MS: liquid chromatography-tandem mass spectrometry, MEC: measured concentrations, MBR: membrane bioreactors, PNEC: predicted no-

effect concentration, q_1 and q_2 : confirmation transitions, Q: quantification transitions QC: Quality control, RQ: risk quotient, UASB: up-flow anaerobic sludge blanket, UPLC: ultra-performance liquid chromatography, WWTP: wastewater treatment plants.

References

1. Verlicchi, P.; Aukidy, M.A.; Zambello, E. What have we learned from worldwide experiences on the management and treatment of hospital effluent?—An overview and a discussion on perspectives. *Sci. Total Environ.* **2015**, *514*, 467–491. [CrossRef] [PubMed]
2. Verlicchi, P.; Galletti, A.; Petrovic, M.; Barceló, D. Hospital effluents as a source of emerging pollutants: An overview of micropollutants and sustainable treatment options. *J. Hydrol.* **2010**, *389*, 416–428. [CrossRef]
3. Oliveira, T.S.; Al Aukidy, M.; Verlicchi, P. Occurrence of Common Pollutants and Pharmaceuticals in Hospital Effluents. In *Hospital Wastewaters—Characteristics, Management, Treatment and Environmental Risks*; Verlicchi, P., Ed.; Springer International Publishing: Berlin/Heidelberg, Germany, 2018; pp. 17–32. ISBN 978-3-319-62178-4.
4. DHI Group Hospital Wastewater from a Pollution Problem to New Water Resources. Available online: <https://www.dhigroup.com/global/news/2016/08/hospital-wastewater-from-a-pollution-problem-to-new-water-resources> (accessed on 1 August 2021).
5. Al Aukidy, M.; Al Chalabi, S.; Verlicchi, P. Hospital Wastewater Treatments Adopted in Asia, Africa, and Australia. In *Hospital Wastewaters—Characteristics, Management, Treatment and Environmental Risks*; Verlicchi, P., Ed.; Springer International Publishing: Berlin/Heidelberg, Germany, 2017; pp. 171–188.
6. Ali, M.; Wang, W.; Chaudhry, N.; Geng, Y. Hospital waste management in developing countries: A mini review. *Waste Manag. Res.* **2017**, *35*, 581–592. [CrossRef] [PubMed]
7. Verlicchi, P.; Zambello, E. Predicted and measured concentrations of pharmaceuticals in hospital effluents. Examination of the strengths and weaknesses of the two approaches through the analysis of a case study. *Sci. Total Environ.* **2016**, *565*, 82–94. [CrossRef] [PubMed]
8. Mainardis, M.; Cecconet, D.; Moretti, A.; Callegari, A.; Goi, D.; Freguia, S.; Capodaglio, A.G. Wastewater fertigation in agriculture: Issues and opportunities for improved water management and circular economy. *Environ. Pollut.* **2022**, *296*, 118755. [CrossRef] [PubMed]
9. Valdez-Carrillo, M.; Abrell, L.; Ramírez-Hernández, J.; Reyes-López, J.A.; Carreón-Diazconti, C. Pharmaceuticals as emerging contaminants in the aquatic environment of Latin America: A review. *Environ. Sci. Pollut. Res.* **2020**, *27*, 44863–44891. [CrossRef] [PubMed]
10. Pérez-Alvarez, I.; Islas-Flores, H.; Gómez-Oliván, L.M.; Barceló, D.; López De Alda, M.; Pérez Solsona, S.; Sánchez-Aceves, L.; SanJuan-Reyes, N.; Galar-Martínez, M. Determination of metals and pharmaceutical compounds released in hospital wastewater from Toluca, Mexico, and evaluation of their toxic impact. *Environ. Pollut.* **2018**, *240*, 330–341. [CrossRef]
11. Wielens Becker, R.; Ibáñez, M.; Cuervo Lumbaque, E.; Wilde, M.L.; Flores da Rosa, T.; Hernández, F.; Sirtori, C. Investigation of pharmaceuticals and their metabolites in Brazilian hospital wastewater by LC-QTOF MS screening combined with a preliminary exposure and in silico risk assessment. *Sci. Total Environ.* **2020**, *699*, 134218. [CrossRef]
12. Reichert, G.; Hilgert, S.; Fuchs, S.; Azevedo, J.C.R. Emerging contaminants and antibiotic resistance in the different environmental matrices of Latin America. *Environ. Pollut.* **2019**, *255*, 113140. [CrossRef]
13. Botero-Coy, A.M.; Martínez-Pachón, D.; Boix, C.; Rincón, R.J.; Castillo, N.; Arias-Marín, L.P.; Manrique-Losada, L.; Torres-Palma, R.; Moncayo-Lasso, A.; Hernandez, F. An investigation into the occurrence and removal of pharmaceuticals in Colombian wastewater. *Sci. Total Environ.* **2018**, *642*, 842–853. [CrossRef]
14. European Commission. *SANTE/12682/2019 Guidance Document on Analytical Quality Control and Method Validation for Pesticide Residues Analysis in Food and Feed*; European Commission: Brussels, Belgium, 2019.
15. Serna-Galvis, E.A.; Silva-Agredo, J.; Giraldo-Aguirre, A.L.; Torres-Palma, R.A. Sonochemical degradation of the pharmaceutical fluoxetine: Effect of parameters, organic and inorganic additives and combination with a biological system. *Sci. Total Environ.* **2015**, *524–525*, 354–360. [CrossRef] [PubMed]
16. Gros, M.; Petrović, M.; Ginebreda, A.; Barceló, D. Removal of pharmaceuticals during wastewater treatment and environmental risk assessment using hazard indexes. *Environ. Int.* **2010**, *36*, 15–26. [CrossRef] [PubMed]
17. Escher, B.I.; Baumgartner, R.; Koller, M.; Treyer, K.; Lienert, J.; McArdell, C.S. Environmental toxicology and risk assessment of pharmaceuticals from hospital wastewater. *Water Res.* **2011**, *45*, 75–92. [CrossRef] [PubMed]
18. Gosset, A.; Wiest, L.; Fildier, A.; Libert, C.; Giroud, B.; Hammada, M.; Hervé, M.; Sibeud, E.; Vulliet, E.; Polomé, P.; et al. Ecotoxicological risk assessment of contaminants of emerging concern identified by “suspect screening” from urban wastewater treatment plant effluents at a territorial scale. *Sci. Total Environ.* **2021**, *778*, 146275. [CrossRef] [PubMed]
19. Kondor, A.C.; Molnár, É.; Vancsik, A.; Filep, T.; Szeberényi, J.; Szabó, L.; Maász, G.; Pirger, Z.; Weiperth, A.; Ferincz, Á.; et al. Occurrence and health risk assessment of pharmaceutically active compounds in riverbank filtrated drinking water. *J. Water Process Eng.* **2021**, *41*, 102039. [CrossRef]
20. Verlicchi, P.; Galletti, A.; Masotti, L. Management of hospital wastewaters: The case of the effluent of a large hospital situated in a small town. *Water Sci. Technol.* **2010**, *61*, 2507–2519. [CrossRef] [PubMed]

21. Carraro, E.; Bonetta, S.; Bertino, C.; Lorenzi, E.; Bonetta, S.; Gilli, G. Hospital effluents management: Chemical, physical, microbiological risks and legislation in different countries. *J. Environ. Manag.* **2016**, *168*, 185–199. [[CrossRef](#)] [[PubMed](#)]
22. Emmanuel, E.; Perrodin, Y.; Keck, G.; Blanchard, J.; Vermande, P. Ecotoxicological risk assessment of hospital wastewater: A proposed framework for raw effluents discharging into urban sewer network. *J. Hazard. Mater.* **2005**, *117*, 1–11. [[CrossRef](#)] [[PubMed](#)]
23. Wiest, L.; Chonova, T.; Bergé, A.; Baudot, R.; Bessueille-Barbier, F.; Ayouni-Derouiche, L.; Vulliet, E. Two-year survey of specific hospital wastewater treatment and its impact on pharmaceutical discharges. *Environ. Sci. Pollut. Res.* **2018**, *25*, 9207–9218. [[CrossRef](#)]
24. BCRenal Agency. *Cleaning & Disinfecting Hemodialysis Machines & Stations*; BCRenal Agency: British Columbia, Canada, 2016; Available online: <http://www.bcrenal.ca/resource-gallery/Documents/Cleaning%20and%20Disinfecting%20Hemodialysis%20Machines%20and%20Stations.pdf> (accessed on 20 December 2021).
25. Tarrass, F.; Benjelloun, O.; Benjelloun, M. Towards zero liquid discharge in hemodialysis. Possible issues. *Nefrología* **2021**, *41*, 620–624. [[CrossRef](#)]
26. Santos, L.H.M.L.M.; Gros, M.; Rodriguez-Mozaz, S.; Delerue-Matos, C.; Pena, A.; Barceló, D.; Montenegro, M.C.B.S.M. Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals. *Sci. Total Environ.* **2013**, *461–462*, 302–316. [[CrossRef](#)] [[PubMed](#)]
27. Lau, S.M.; McGuire, T.M.; Van Driel, M.L. Consumer concerns about paracetamol: A retrospective analysis of a medicines call centre. *BMJ Open* **2016**, *6*, e010860. [[CrossRef](#)] [[PubMed](#)]
28. Wirtz, V.J.; Herrera-Patino, J.J.; Santa-Ana-Tellez, Y.; Dreser, A.; Elseviers, M.; Vander Stichele, R.H. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. *Trop. Med. Int. Heal.* **2013**, *18*, 665–673. [[CrossRef](#)] [[PubMed](#)]
29. Peña-Guzmán, C.; Ulloa-Sánchez, S.; Mora, K.; Helena-Bustos, R.; Lopez-Barrera, E.; Alvarez, J.; Rodriguez-Pinzón, M. Emerging pollutants in the urban water cycle in Latin America: A review of the current literature. *J. Environ. Manag.* **2019**, *237*, 408–423. [[CrossRef](#)] [[PubMed](#)]
30. Velásquez, J. Pharmaceutical and Personal Hygiene Products (PPcPs): A Threat Little Studied in Colombian Waters. *Agric. Res. Technol.* **2019**, *22*, 1–8. [[CrossRef](#)]
31. Verlicchi, P.; Al Aukidy, M.; Zambello, E. Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment—A review. *Sci. Total Environ.* **2012**, *429*, 123–155. [[CrossRef](#)] [[PubMed](#)]
32. Keller, V.D.J.; Williams, R.J.; Lofthouse, C.; Johnson, A.C. Worldwide estimation of river concentrations of any chemical originating from sewage-treatment plants using dilution factors. *Environ. Toxicol. Chem.* **2014**, *33*, 447–452. [[CrossRef](#)] [[PubMed](#)]
33. Alfonso-Muniozguen, P.; Serna-Galvis, E.; Bussemaker, M.; Torres-Palma, R.; Lee, J. A review on pharmaceuticals removal from waters by single and combined biological, membrane filtration and ultrasound systems. *Ultrason. Sonochem.* **2021**, *76*, 105656. [[CrossRef](#)]
34. Angeles, L.F.; Mullen, R.A.; Huang, I.J.; Wilson, C.; Khunjar, W.; Sirotkin, H.I.; McElroy, A.E.; Aga, D.S. Assessing pharmaceutical removal and reduction in toxicity provided by advanced wastewater treatment systems. *Environ. Sci. Water Res. Technol.* **2020**, *6*, 62–77. [[CrossRef](#)]
35. Giannakis, S.; Rtimi, S.; Pulgarin, C. Light-assisted advanced oxidation processes for the elimination of chemical and microbiological pollution of wastewaters in developed and developing countries. *Molecules* **2017**, *22*, 1070. [[CrossRef](#)] [[PubMed](#)]
36. Marjanovic, M.; Giannakis, S.; Grandjean, D.; Felipe, L.; Alencastro, D.; Pulgarin, C. Effect of μM Fe addition, mild heat and solar UV on sulfate radical-mediated inactivation of bacteria, viruses, and micropollutant degradation in water. *Water Res.* **2018**, *140*, 220–231. [[CrossRef](#)] [[PubMed](#)]
37. Serna-Galvis, E.A.; Silva-Agredo, J.; Botero-Coy, A.M.; Moncayo-Lasso, A.; Hernández, F.; Torres-Palma, R.A. Effective elimination of fifteen relevant pharmaceuticals in hospital wastewater from Colombia by combination of a biological system with a sonochemical process. *Sci. Total Environ.* **2019**, *670*, 623–632. [[CrossRef](#)] [[PubMed](#)]
38. Serna-Galvis, E.A.; Botero-Coy, A.M.; Martínez-Pachón, D.; Moncayo-Lasso, A.; Ibáñez, M.; Hernández, F.; Torres-Palma, R.A. Degradation of seventeen contaminants of emerging concern in municipal wastewater effluents by sonochemical advanced oxidation processes. *Water Res.* **2019**, *154*, 349–360. [[CrossRef](#)] [[PubMed](#)]
39. Serna-Galvis, E.A.; Porras, J.; Torres-Palma, R.A. A critical review on the sonochemical degradation of organic pollutants in urine, seawater, and mineral water. *Ultrason. Sonochem.* **2022**, *82*, 105861. [[CrossRef](#)] [[PubMed](#)]
40. Moratalla, Á.; Cotillas, S.; Lacasa, E.; Cañizares, P.; Rodrigo, M.A.; Sáez, C. Electrochemical technologies to decrease the chemical risk of hospital wastewater and urine. *Molecules* **2021**, *26*, 6813. [[CrossRef](#)] [[PubMed](#)]
41. Orias, F.; Perrodin, Y. Characterisation of the ecotoxicity of hospital effluents: A review. *Sci. Total Environ.* **2013**, *454–455*, 250–276. [[CrossRef](#)] [[PubMed](#)]
42. Tell, J.; Caldwell, D.J.; Häner, A.; Hellstern, J.; Hoeger, B.; Journal, R.; Mastrocco, F.; Ryan, J.J.; Snape, J.; Straub, J.O.; et al. Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations. *Integr. Environ. Assess. Manag.* **2019**, *15*, 312–319. [[CrossRef](#)]
43. Aa van der, N.G.F.M.; Van Vlaardingen, P.L.A.; Van Leeuwen, L.C.; Post, M. *Assessment of Potential Risks of 11 Pharmaceuticals for the Environment: Using Environmental Information from Public Databases*; RIVM Letter Report 601711003; RIVM of Netherlands, Bilthoven: Catharijnesingel, The Netherlands, 2001.

44. Chen, Y.; Xi, X.; Yu, G.; Cao, Q.; Wang, B.; Vince, F.; Hong, Y. Pharmaceutical compounds in aquatic environment in China: Locally screening and environmental risk assessment. *Front. Environ. Sci. Eng.* **2015**, *9*, 394–401. [[CrossRef](#)]
45. Godoy, A.A.; Kummrow, F.; Pamplin, P.A.Z. Ecotoxicological evaluation of propranolol hydrochloride and losartan potassium to *Lemna minor* L. (1753) individually and in binary mixtures. *Ecotoxicology* **2015**, *24*, 1112–1123. [[CrossRef](#)]
46. FASS. *Environmental Risk Classification for Esomeprazole and Omeprazole*; FASS: Stockholm, Sweden, 2020; Available online: https://webcache.googleusercontent.com/search?q=cache:Ox1g2YcytlQJ:https://www.fass.se/LIF/product%3F-1.ILinkListener-documentTabPage-tabs-panel-article~{}tools~{}bottom-articletools-printbiglink%26userType%3D0%26nplId%3D20130822000064%26docType%3D78%26docTypeDynTab%3D78%26focus%3Dtab_miljoinfo+&cd=1&hl=es&ct=clnk&gl=co (accessed on 13 November 2021).
47. Zhou, S.; Di Paolo, C.; Wu, X.; Shao, Y.; Seiler, T.-B.; Hollert, H. Optimization of screening-level risk assessment and priority selection of emerging pollutants—The case of pharmaceuticals in European surface waters. *Environ. Int.* **2019**, *128*, 1–10. [[CrossRef](#)]
48. EAWAG Biocatalysis/Biodegradation Database. Available online: <http://eawag-bbd.ethz.ch/predict/> (accessed on 1 September 2018).