Article

Assessing environmental and human health risks of pharmaceutical contamination in surface water

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Abstract

Pharmaceuticals, also known as medicines, are a mixture of substances used to prevent and treat human or animal diseases or infections. These products are used in many areas, such as medicine, aquaculture, animal husbandry, and, not least, in people's everyday lives. According to the literature, they are classified into several therapeutic classes, the ones of interest for this paper being non-steroidal anti-inflammatory drugs; antidiabetic drugs, and antacid drugs. The mentioned drugs have raised concerns due to their presence in the environment and the potential health risks they pose. Recently, much research has focused on compounds that have direct harmful effects but are found in the environment at relatively low concentrations. These compounds could seriously threaten aquatic ecosystems, especially in the long term, due to their ability to accumulate in living organisms through bioaccumulation or generate secondary metabolites with harmful side effects. To effectively monitor pharmaceuticals in the environment, it is essential to have a variety of rapid, reliable, and sensitive methods capable of detecting numerous compounds. The most commonly employed techniques include solid phase extraction (SPE) followed by high-performance liquid chromatography coupled with mass spectrometry (HPLC/MS). This study supports ongoing efforts to monitor and regulate drug contamination in water sources, evaluating potential risks to human health and emphasizing the importance of addressing these contaminants to protect environmental and public health.

Keywords: contamination, surface water, LC-MS/MS, pharmaceuticals, environmental risk assessment, human health risk

INTRODUCTION

Chemical reagents

The standard substances studied (analgesic; antidiabetic; antacid) were purchased from Sigma-Aldrich (Steinheim, Germany) with purities >98%. The organic solvents: acetonitrile and methanol used for the LC mobile phase and SPE extraction were purchased from Merck (Darmstadt, Germany). The 99.9 % purity formic acid was supplied by Agilent (Supelco Inc.) and the Strata X (500 mg, 6 mL) and Strata C18 (500 mg, 6 mL) cartridges used for the solid phase extraction were purchased from Phenomenex (USA).

Equipment

Experiments to establish the optimal conditions for chromatographic separation and compound detection were conducted using an Agilent 1260 HPLC system. This system was equipped with a binary pump capable of gradient or isocratic elution, supplying a two-component mobile phase with

a variable flow rate. The setup also included a reagent vial holder and a membrane degasser, an autosampler with a 100-position capacity and variable injection volume, and a thermostat for maintaining a constant temperature in both the chromatographic column and the autosampler. The chromatographic separation was coupled with an Agilent 6410 triple quadrupole mass spectrometer detector, featuring an electrospray ionization (ESI) source (Agilent, Palo Alto, CA, USA). Data acquisition and analytical quantification were performed using Mass Hunter software from Agilent Technologies.

The SPE-LC-MS/MS methods were used for identification and quantification of different classes of pharmaceuticals in surface water [13, 15]. For analgesics including ibuprofen, naproxen, piroxicam, ketoprofen, and diclofenac, optimal chromatographic conditions were achieved using a Zorbax Eclipse XDB C18 column at 20°C, with a mobile phase of 10% acetonitrile and water containing 0.1% formic acid, at a flow rate of 0.3 mL/min. The gradient elution allowed for all target analytes to be separated within 9 minutes, resulting in high sensitivity. The mass spectrometry was conducted in full scan mode with an m/z range of 100 to 1000 Daltons and a source temperature of 300°C, employing nitrogen gas for nebulization. For the analysis of anti-diabetic agents, including glimepiride, glibenclamide, and metformin alongside its biodegradation product guanyl urea, an Eclipse C18 column was used at 30°C with a mobile phase consisting of 0.1% formic acid and acetonitrile at a flow rate of 0.2 mL/min, achieving a total run time of 8 minutes. In analyzing gastric antacids like famotidine and omeprazole, a Luna Omega Polar C18 column at 40°C with a mobile phase of 10 mM ammonium acetate and acetonitrile (70/30) at the same flow rate was employed, achieving a run time of 8.5 minutes. Both sets of analyses utilized triple quadrupole mass spectrometry in positive ESI+ mode, with optimized parameters for enhanced detection, including specific collision energies and MRM transitions, ensuring accurate quantification of the compounds present in surface water samples.

Sample preparation

To assess the presence and quantify anti-inflammatory, antidiabetic, and antacid compounds in surface waters intended for drinking purposes, samples were collected from a depth of 30 cm in 1 L glass vials and stored in a refrigerated crate until laboratory analysis was conducted within 48 hours of sampling. To ensure clarity and prevent blockage of solid-phase extraction (SPE) cartridges, visible particulates were filtered using 0.45 μm glass fiber filters. The extraction of all compounds was performed using the SPE AutoTrace 280 system with appropriate cartridges. Analgesic compounds were isolated using Strata X cartridges conditioned with methanol and ultrapure water (pH=2), while hypoglycemic agents were extracted using Strata C18-E cartridges conditioned at pH 10, with the extracts subsequently reconstituted in an initial mobile phase mixture suitable for LC-MS/MS analysis. For the extraction of antacid compounds, both Strata X and Strata C18-E cartridges were used, tailored to the sample pH. An internal standard, 13C3-famotidine, was added to the wastewater samples for accurate quantification. Following analyte retention, matrix interferences were removed through washing, and the compounds were eluted and concentrated near dryness. The residues were then reconstituted in a mobile phase mixture of ammonium acetate and acetonitrile, ensuring the internal standard concentration was adjusted to 50 ng/mL. Any cloudy extracts were filtered using a 0.2 μm PTFE Millipore filter before transferring to LC vials for analysis. This streamlined approach ensured accurate detection and quantification of pharmaceuticals present in the surface water samples, minimizing redundancy in the extraction and analysis processes.

Ecological risk assessment

Ecological risk was evaluated based on Risk Quotient (RQ), using the following equations:

$$PNEC = [NOEC \text{ or } LC (EC_{50})]/AF \qquad (1)$$

$$RQ = NEC/MEC \qquad (2)$$

where MEC represents the maximum concentration detected for each compound in surface waters, while PNEC denotes the predicted no-effect concentration for aquatic species. LC50 is the concentration at which 50% of the test organisms experience lethality, EC50 is the concentration at

which 50% of the organisms show an effect, and NOEC is the highest concentration at which no observable effect is noted on the species in question. The application factor (AF) values were determined based on the European Commission's Technical Guidance Document (TGD) for risk assessment: an AF of 1000 is used for LC50 and EC50 values; an AF of 100 is applied to a single long-term NOEC; and AFs of 50 and 10 are used for two and three long-term NOECs, respectively, across species representing different trophic levels.

The risk levels were categorized as follows: RQ < 0.01: Very low risk; 0.01 < RQ < 0.1: Low risk; 0.1 < RQ < 1: Intermediate risk; RQ > 1: High risk.

Human health risk assessment
The human health risk was assessed based on the acceptable daily intake and water drinking equivalent level for various ages, see equation (3) and (4).

$$HQ = C_S / DWEL \tag{3}$$
$$DWEL = (ADI \times BW \times HQ) / (DWI \times AB \times FOE) \tag{4}$$

where Cs is the concentration of the pharmaceutical compound found in the sample, ADI is the Acceptable Daily Intake (µg/kg day), BW is the 50% percentile values of body weight for the different selected life stages (kg), HQ is the Hazard Quotient assumed to be 1, DWI is the Drinking Water Intake (L/day) where age-specific values were used according to the U.S. EPA (EPA, 2011), AB is the gastrointestinal absorption rate assumed to be 1, and FOE is related to Frequency of Exposure (350 days/365 days = 0.96). Body weight and DWI values are listed in table 3.

RESULTS AND DISCUSSION
Pharmaceutical residues in surface water
Twelve surface water samples (noted in the figures with S1÷S12) were collected and examined for various pharmaceutical indicators. These indicators included ibuprofen, naproxen, piroxicam, ketoprofen, diclofenac, glibenclamide (glyburide), metformin, glipizide, guanyl urea, gliclazide, famotidine, ranitidine, omeprazole, and pantoprazole. The concentrations of these substances were measured, with the minimum, maximum, median, and mean values detailed in table 1.

Table 1. Concentrations (ng/L) of compounds of interest in surface waters (n=3)

Pharmaceutical residues	Min	Max	Median	Average
Ibuprofen	5.3±0.5	1750±178	36±3.67	443±45.2
Naproxen	<2.9	805±82.1	16.5±1.68	260±26.5
Piroxicam	<0.1	96±9.79	36.4±3.71	48±4.92
Ketoprofen	<1.1	823±83.9	385.5±39.3	356±36.3
Diclofenac	<0.8	2270±232	48.2±4.92	640±65.3
Glibenclamide	<0.4	1.10±0.11	0.79±0.08	1.22±0.08
Metformin	<0.3	68.3±6.97	3.61±0.37	12.3±1.19
Glipizide	<0.3	28.3±2.89	2.65±0.27	7.45±0.74
Guanyl urea	<0.2	48.2±4.90	6.42±0.65	10.2±1.01
Gliclazide	<0.2	17.5±1.79	10.7±1.09	10.4±0.98
Famotidine	<0.3	6615±675	2670±272	3236±330
Ranitidine	<1.4	870±88.7	473±48.2	513±52.3
Omeprazole	<0.1	8350±852	443±45.2	2071±211
Pantoprazole	<0.2	5850±597	2004±204	2405±245
Σ Compounds	70.0±0.7	20524±2094	90.9±9.27	4437±453

Of all the compounds analysed, the one that stood out the most was omeprazole, closely followed by famotidine and pantoprazole. As can be seen in figure 1, these indicators showed the highest concentrations for the class of antacids.
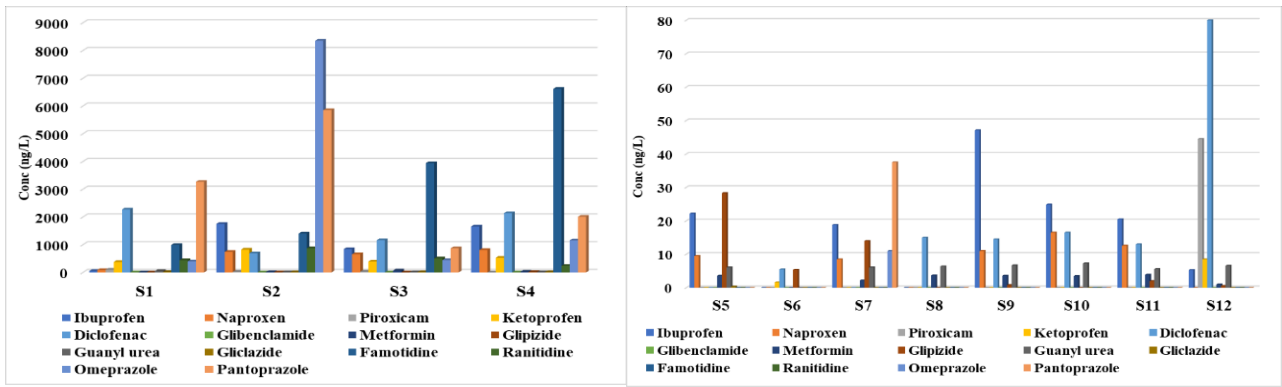
Fig. 1. Presence of tested compounds in surface water samples

For the class of anti-inflammatory drugs, attention was drawn to ibuprofen, which was found in concentrations ranging between 50 and 1750 ng/L. In the same class is also ketoprofen, which was found in surface waters in amounts between 350 and 830 ng/L (Fig.2.).

For the class of antidiabetic compounds, lower values were determined in surface waters, but which may pose a risk to aquatic animals and even human life. Metformin and its metabolite guanyl urea were found in the highest amounts in surface water, with values between 1.5÷70 ng/L and 5.0÷48 ng/L respectively (see Fig. 2).
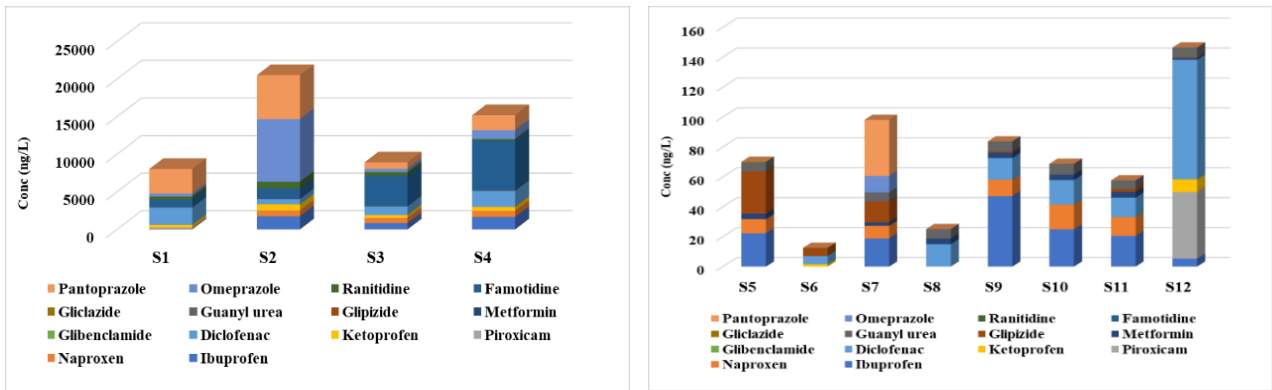

Fig. 2. Concentration of pharmaceutical residues determined in each sample

Figure 3 shows that the distribution of the different drugs varies. S3 and S4 seem to have a more balanced distribution, while S2 is dominated by a single drug.
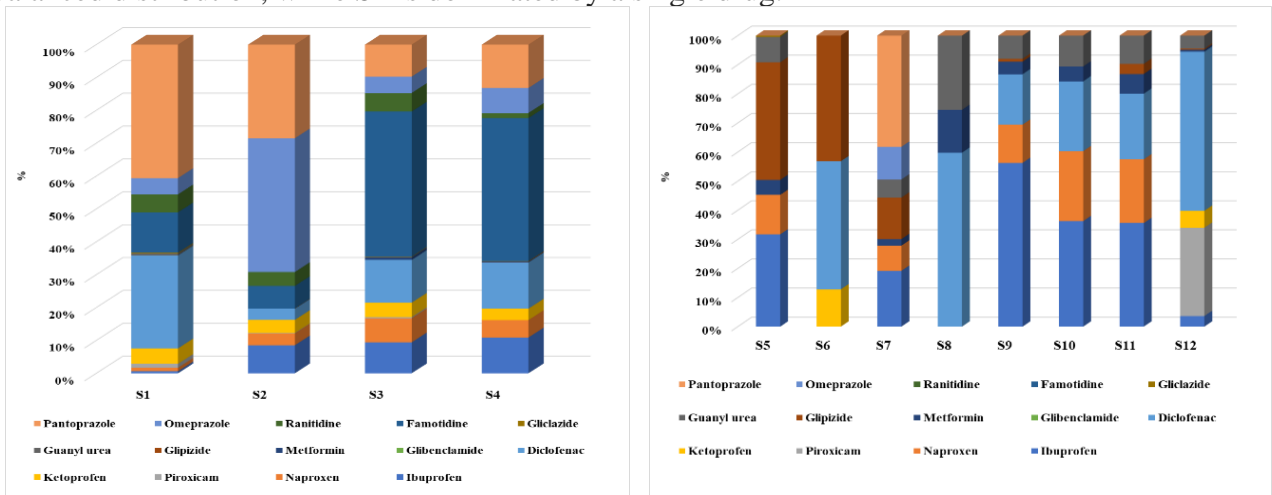

Fig. 3. Percentage distribution of pharmaceutical residues

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Thus, the graph highlights the notable presence in all sets of omeprazole and pantoprazole. This may reflect their frequent use and thus the need for further research. At the same time, a significant variation in drug ratios can be observed between S5 and S12, which may suggest differences in the way drugs are eliminated.

Ecological risk assessment
To assess the risks that pharmaceutical residues pose to aquatic organisms, both the maximum and median concentrations of each analyte in surface water were considered. While these pharmaceuticals are employed in treating various medical conditions, their residues in surface waters may exert toxic effects on aquatic life. Consequently, evaluating risk factors (RQs) is essential for understanding the actual risk to aquatic organisms throughout the food chain. The assessment of environmental risk associated with pharmaceutical residues was based on toxicological studies documented in the literature (refer to Table 2). These parameters were computed in a manner consistent with methodologies employed in prior research [18÷22], utilizing equations (1) and (2).

In evaluating the risks associated with pharmaceutical compounds in surface waters, the table displays the variation in ecological risks (ORs) based on maximum (MEC Max) and median (MEC Median) concentrations for various aquatic species (refer to table 2). Conducting an ecological risk assessment is crucial for understanding the potential impacts of chemical contamination from pharmaceuticals on aquatic ecosystems, as well as its implications for human health and the broader environment.

The first compound analysed is famotidine, which has a maximum RQ of 0.017 for *Daphnia magna* as well as for the other types of aquatic organisms studied, thus indicating a very low risk under maximum exposure conditions. Both the concentrations at which lethal effect was determined (LC50) and those below which no adverse effects are observed (NOEC) suggest that, in general, famotidine does not pose a significant threat to aquatic biodiversity. This is an optimistic observation, given the importance of this substance in the therapy of ulcers and other gastrointestinal disorders.

Ranitidine, another pharmacological agent, shows a worrying maximum RQ of 355 for *Danio rerio*, suggesting an increased vulnerability of this species to ranitidine contamination. This raises questions about the long-term impact on fish populations and the health of aquatic ecosystems, especially given the effects of chemicals on the food chain. In contrast, for other species such as *B. calyciflorus* and *Ceriodaphnia dubia*, the RQ is significantly lower (0.28), suggesting a diversity of ecological responses depending on the species and ecological context. For omeprazole, the calculated maximum risk quotient (RQ) of 1285 for *Alivibrio fischeri* indicates a substantial threat to aquatic microorganisms, which are vital for maintaining aquatic ecosystem functions. Although the RQ at average concentrations presents a lower level of concern, suggesting variability in exposure and impact, additional research could elucidate how different species adapt to omeprazole exposure.

Regarding diclofenac, while the maximum RQ for algae is 0.02 and for *Daphnia* is 2.27, it reaches 45.40 for fish, indicating an intermediate level of risk. This suggests that diclofenac can have a notable effect on aquatic ecosystems. Given its environmental persistence and potential sublethal effects, such as impacts on fertility and behaviour, the management of diclofenac usage is crucial to prevent disruption of ecological balance.

Ketoprofen, another analyte examined, shows a median risk quotient (RQ) of 1.608 for *Pseudokirchneriella subcapitata*, indicating an intermediate level of risk. This finding is concerning as algae serve as the foundation of the aquatic food web, and any disruption to their health can potentially affect the entire ecosystem. Therefore, a comprehensive geological and toxicological evaluation is essential to implement appropriate mitigation measures.

Conversely, ibuprofen and naproxen present a very low risk profile, with RQ values not exceeding 0.03, suggesting minimal impact on the aquatic organisms studied. Nonetheless, due to their widespread use in anti-inflammatory and analgesic treatments, ongoing monitoring of their long-term effects on aquatic environments is warranted.

Table 2. Data on chronic (NOEC) and acute (LC$_{50}$/EC$_{50}$) toxicity of pharmaceutical residues in aquatic organisms

Analyte	Species	Species Type	Stop point	Toxicity	Conc. effect (µg/L)	Ref.	AF	PNEC (ng/L)	MEC Max (ng/L)	RQ Max	MEC Median (ng/L)	RQ Median
	Daphnia magna	Crustacea	LC$_{50}$	acute	398000	[23]	1000	398000		0.017	2670	0.007
Famotidine	*Fathead minnow*	Fish	LC$_{50}$	acute	680000		1000	680000	6615	0.010	2670	0.004
	Oryzias latipes	Fish	LC$_{50}$	acute	100000	[24]	1000	100000		0.066	2670	0.027
	Danio rerio	Fish	NOEC	chronic	0.25	[25]	100	2.4500		355	473	193
Ranitidine	*B. calyciflorus*	rotifer	NOEC	chronic	310	[26]	100	3100	870	0.28	473	0.153
	C. dubia	Water flea	NOEC	chronic	310		100	3100		0.28	473	0.153
	Ceriodaphnia dubia	Crustacea	NOEC	chronic	310	[27]	100	3100		0.28	473	0.153
	Alivibrio fischeri	bacterie	EC$_{50}$	acute	6.50	[28]	1000	6.50		1285	443	68.2
	Pimephales promelas	Fish	NOEC	chronic	10000		100	100000		0.08	443	0.004
Omeprazole	*Green algae*	Algae	NOEC	chronic	18.0	[29]	100	18	8350	464	443	24.6
	Daphnia magna	Crustacea	EC$_{50}$	acute	100000		1000	100000		0.08	443	0.004
	D. rerio	Fish	NOEC	chronic	50.0	[30]	100	50		167	443	8.860
	Pimephales promelas	Fish	LC$_{50}$	acute	95000		1000	95000		0.06	2004	0.021
Pantoprazole	*Daphnia magna*	Crustacea	EC$_{50}$	acute	95000	[31]	1000	95000	5850	0.06	2004	0.021
	Pseudokirchneriella subcapitata	Algae	EC$_{50}$	acute	48000		1000	48000		0.12	2004	0.042
	Algae	Algae	NOEC	chronic	10000		100	100000		0.02	48.2	0.0005
Diclofenac	*Daphnia*	Crustacea	NOEC	chronic	100	[32]	100	1000	2270	2.27	48.2	0.048
	Fish	Fish	NOEC	chronic	5		100	50		45.40	48.2	0.964
	Pseudokirchneriella subcapitata	Alge	EC$_{50}$	acute	240		1000	240		3.43	386	1.608
Ketoprofen	*Ceriodaphnia silvestrii*	Daphnia	EC$_{50}$	Acute	24840		1000	24840	823	0.03	386	0.016
	Danio rerio	Fish	LC$_{50}$	Acute	6110		1000	6110		0.13	386	0.063
	Desmodesmus subspicatus	Algae	EC$_{50}$	Acute	342000		1000	342000		0.01	36	0.0001
Ibuprofen	*Daphnia magna*	Daphnia	LC$_{50}$	Acute	128,500	[33]	1000	128500	1750	0.01	36	0.0003
	Oncorhynchus mykis	Fish	LC$_{50}$	Acute	52000		1000	52000		0.03	36	0.0007
	Pseudokirchinella subcapitata	Algae	EC50	Acute	39000		1000	39000		0.02	16.5	0.0004
Naproxen	*Daphnia magna*	Daphnia	EC50	acute	174000		1000	174000	805	0.005	16.5	0.0001
	Oncorhynchus mykiss	Fish	LC50	acute	52000		1000	52000		0.02	16.5	0.0003
	Algae	Algae	EC50	acute	509000		1000	509000		0.000002	0.79	0.00000
Glibenclamide	*Daphnia magna*	Crustacea	EC50	acute	100000	[34]	1000	100000	1.1	0.000011	0.79	0.00001
	Fish	Fish	EC50	acute	100000		1000	100000		0.000011	0.79	0.00001
	Algae	Algae	EC50	acute	4330	[35]	1000	4330		0.02	3.61	0.0008
Metformin	*Daphnia magna*	Crustacea	NOEC	chronic	67000	[36]	100	670000	68.3	0.0001	3.61	0.0000
	Fish	Fish	EC50	acute	2390	[37]	1000	2390		0.03	3.61	0.0015
Guanyl urea	*Daphnia magna*	Crustacea	EC50	acute	40000	[38]	1000	40000	48.2	0.0012	6.42	0.0002

Addressing the risk factors associated with pharmaceutical compounds in surface waters reveals a range of risks that vary by substance and species. Ecological Risk Assessment (ERA) is essential for informing decisions related to the management of aquatic resources and the safeguarding of biodiversity. As pharmacological contaminants persist in aquatic environments and their usage remains significant, ongoing research and stricter regulatory measures are crucial for the protection of aquatic ecosystems.

A comparative assessment of risk factors among three classes of pharmaceutical compounds such as antihistamines (famotidine, ranitidine), proton pump inhibitors (omeprazole, pantoprazole), and analgesics/anti-inflammatories (diclofenac, ketoprofen, ibuprofen, naproxen) - yields significant insights into their potential impacts on aquatic ecosystems. Antihistamines, such as famotidine and ranitidine, generally exhibit a low-risk profile, with maximum Risk Quotients (RQs) for famotidine below 0.1 and higher for ranitidine, particularly highlighting a critical point (RQ=355) for *Danio rerio*. This suggests that while these substances typically have minimal impact on most aquatic organisms, certain species may be more susceptible, necessitating careful evaluation of ecological management strategies, especially concerning cumulative effects within ecosystems.

In contrast, proton pump inhibitors, including omeprazole and pantoprazole, present a more varied risk profile, indicating the need for further investigation into their ecological consequences. The Risk Quotient (RQ) for omeprazole reveals a substantial environmental concern, with a maximum RQ of 1285 for Alivibrio fischeri, a critical microorganism in aquatic systems. This high RQ indicates a significant risk, underscoring the need for strategies to monitor and mitigate its impact on aquatic microorganisms. In comparison, pantoprazole, while showing a lower maximum RQ of 0.06, still poses a potential threat, highlighting the importance of assessing its effects on aquatic biodiversity.

In comparison, analgesics and anti-inflammatories demonstrate greater potential for harm to aquatic ecosystems than antihistamines and proton pump inhibitors, as indicated by the intermediate to high risk levels observed. This underscores the need for careful management and research into the widespread and uncontrolled use of these substances in medical treatments, as they may significantly disrupt ecological balances.

For analgesics and anti-inflammatories such as diclofenac, ketoprofen, ibuprofen, and naproxen, the risk profile is notably more alarming. Diclofenac, with a maximum RQ of 45.40 for fish, suggests serious risks to these organisms. Ketoprofen, with a median RQ of 1.608, indicates an intermediate risk. These findings emphasize that pharmaceuticals in this category have a higher potential for adverse ecological impacts compared to those in the antihistamine and proton pump inhibitor classes. While antihistamines and proton pump inhibitors generally present lower risk profiles, it remains crucial to continue monitoring and investigating their long-term environmental impacts. In summary, each pharmaceutical class presents a complex risk landscape: antihistamines and proton pump inhibitors are associated with lower risks, whereas analgesics and anti-inflammatories pose notably higher risks to aquatic organisms. This variation in risk levels highlights the necessity for robust chemical management and regulatory measures to safeguard aquatic ecosystems and preserve biodiversity.

Human health risk assessment

Assessing human health risks associated with pharmaceutical residues in surface waters used as drinking water sources is crucial for several reasons. Pharmaceuticals and their byproducts can enter aquatic environments through various pathways, including industrial effluents, domestic waste, and agricultural runoff. The presence of these residues in drinking water can expose the general population, particularly vulnerable groups such as children and individuals with pre-existing health conditions, to potential health risks.

Moreover, the long-term health effects of pharmaceutical exposure are often not well understood or may be underestimated. Interactions among these compounds can produce additive or synergistic effects, further complicating risk assessments. Therefore, comprehensive studies on the impact of these substances are vital to identify both acute and chronic health risks associated with consuming contaminated water. Such assessments are also essential for formulating more effective policies and

regulations for managing water resources and ensuring public health safety. This process involves establishing stringent standards for monitoring and regulating pharmaceutical concentrations in drinking water. By identifying both risks and sources of contamination, proactive strategies can be implemented to prevent pharmaceutical residues from exceeding acceptable levels and thereby safeguard public health. Furthermore, enhancing public awareness and education regarding the effects of pharmaceutical residues in drinking water is crucial. Potential impacts include endocrine disruption, antibiotic resistance, and other health issues arising from exposure to contaminated water. Consequently, risk assessment not only identifies current problems but also fosters an informed public, equipping society to address both health and environmental challenges effectively. In this study, the characterization of human health risk was conducted using risk quotient (RQ) assessments tailored to various life stages, aiming to enhance the precision of the risk evaluation. The selected life stages were chosen according to the recommendations outlined in the U.S. EPA's "Guidance for Selecting Age Groups for Monitoring and Assessing Children's Exposures to Environmental Contaminants" (EPA, 2005), as detailed in table 3.

Table 3. Details of the different age groups selected for human health risk assessment in this study (CDC, 2002; EPA, 2011)

Age group (years)	Average body weight (BW) (kg)	Drinking water consumption (DWI) (L/day)
0÷1	7.20	0.35
1 to <2	11.4	0.84
2 to <3	13.8	0.88
3 to <6	18.6	1.08
6 to <11	31.8	1.24
11 to <16	56.8	1.73
16 to <21	71.6	1.98
≥ 21	79.1	2.81

Risk quotients (RQs) were calculated for pharmaceuticals detected in both drinking water and source water samples by dividing the maximum concentration of each drug by its DWEL (see equation 3). The concentrations observed in raw water were considered as a worst-case scenario to account for potential operational issues in the water treatment plant (WTP). An RQ value exceeding 1 indicates a possible risk associated with unintentional exposure through drinking water. To estimate the DWELs, equation 4 was utilized.

ADI values denote the quantity of a specific substance that is not anticipated to produce adverse effects in the general population, including sensitive groups [39]. In this study, ADIs were derived from existing literature, with the starting point based on the lowest observed therapeutic dose or toxicological effect. These values were then adjusted by applying various uncertainty factors. Table 4 provides values essential for estimating the DWEL for various pharmaceutical compounds, based on ADI values expressed in µg/kg/day. The ADI represents the amount of a chemical that can be ingested daily over a lifetime without posing significant health risks. The analysis of ADI values reveals that substances such as ibuprofen and metformin have relatively high ADI values, resulting in substantial DWELs. For instance, ibuprofen, with an ADI of 110 µg/kg/day, corresponds to a DWEL of up to 4144 µg/L, depending on the concentration range. This indicates that, in aquatic environments, ibuprofen can be present at levels that are unlikely to impact human or ecological health, provided concentrations remain below these thresholds.

Conversely, drugs with very low ADI values, such as glibenclamide (0.021 µg/kg/day), correspond to substantially lower DWELs, ranging from 0.46 to 0.81 µg/L. This underscores the importance of stringent monitoring for such drugs, as elevated concentrations could pose risks to vulnerable populations, such as diabetic patients. Additionally, the absence of ADI values for certain compounds (such as piroxicam, glipizide, guanyl urea, gliclazide, famotidine, omeprazole, and pantoprazole), indicates either a lack of established safe dosing limits or insufficient investigation into these drugs. This gap in toxicological data introduces uncertainties in human health and environmental risk

assessments, underscoring the necessity for further research. Understanding the relationship between ADIs and DWELs is crucial for effectively managing the risks associated with pharmaceutical consumption and water pollution. Rigorous environmental drug monitoring is essential to prevent contamination of water resources and safeguard public health. Consequently, the table underscores the significance of both dosing parameters and the need for stringent regulations to control pharmaceutical pollution.

Table 4. ADI values used in the estimation of the respective DWEL

Pharmaceutical compound	ADI µg/kg/day	DWEL (µg/L)							
		0÷1	1 ÷ < 2	2 ÷<3	3 ÷ <6	6 ÷ <11	11 ÷ <16	16÷<21	≥ 21
Ibuprofen	110[a]	2357	1555	1797	1973	2939	3762	4144	3225
Naproxen	46[b]	986	650	751	825	1229	1573	1733	1349
Piroxicam	-	-	-	-	-	-	-	-	-
Ketoprofen	5[c]	107	71	82	90	134	171	188	147
Diclofenac	67[d]	1436	947	1094	1202	1790	2291	2524	1965
Glibenclamide	0.021[e]	0.46	0.30	0.35	0.38	0.57	0.73	0.81	0.63
Metformin	357[e]	7650	5047	5832	6405	9537	12210	13448	10468
Glipizide	-	-	-	-	-	-	-	-	-
Guanyl urea	-	-	-	-	-	-	-	-	-
Gliclazide	-	-	-	-	-	-	-	-	-
Famotidine	-	-	-	-	-	-	-	-	-
Ranitidine	11[a]	236	156	180	197	294	376	414	323
Omeprazole	-	-	-	-	-	-	-	-	-
Pantoprazole	-	-	-	-	-	-	-	-	-

[a] [39] [b] [40]; [c] [41]; [d] [42] [e] [43]

Table 4 provides an assessment of the RQ for different pharmaceutical compounds about their concentration in water, expressed in µg/L. The RQ is a tool used to estimate the potential hazard of chemicals to human health about their exposure level. This table highlights not only the presence of pharmaceutical compounds in water resources but also the severity of the risks associated with them.

Table 5. RQ estimation for pharmaceutical compounds determined in surface water on human health

Pharmaceutical compound	Cs (µg/L)	0÷1	1 ÷ < 2	2 ÷<3	3 ÷ <6	6 ÷ <11	11 ÷ <16	16÷<21	≥ 21
Ibuprofen	0.443	0.00019	0.00028	0.00025	0.00022	0.00015	0.00012	0.00011	0.00014
Naproxen	0.26	0.00026	0.00040	0.00035	0.00032	0.00021	0.00017	0.00015	0.00019
Ketoprofen	0.356	0.00332	0.00504	0.00436	0.00397	0.00267	0.00208	0.00189	0.00243
Diclofenac	0.64	0.00045	0.00068	0.00058	0.00053	0.00036	0.00028	0.00025	0.00033
Glibenclamide	0.00122	0.00266	0.00403	0.00349	0.00318	0.00213	0.00167	0.00151	0.00194
Metformin	0.0123	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
Ranitidine	513	2.17636	3.29891	2.85496	2.59960	1.74578	1.36362	1.23808	1.59047

In general, an RQ value below 1 indicates minimal risk associated with exposure to a compound, while RQs of 1 or higher suggest a potential threat to human health. Analysis of the RQ values for pharmaceutical compounds in table 5 reveals that ibuprofen and naproxen consistently have RQs below 0.01, even at elevated concentrations in water. This indicates a low health risk, suggesting that these drugs can be used in treatments without significant concerns regarding drinking water contamination. Conversely, ranitidine presents RQ values exceeding 2, correlating with its concentration in drinking water (513 µg/L) and indicating potential risks to human health. These elevated values highlight a significant concern, particularly given recent associations of ranitidine with cancer risks. Consequently, it is essential to review and potentially update regulations on permissible levels of these compounds in water to mitigate adverse public health impacts. In contrast, metformin, which has an RQ of 0 at a detected concentration of 0.0123 µg/L, does not pose a significant health risk. This finding suggests that, despite its common use in diabetes treatment,

metformin at such low concentrations does not have substantial adverse effects on human health. This outcome exemplifies effective management of drug disposal, indicating that metformin can be used without posing major risks when properly managed.

Ketoprofen and diclofenac, however, exhibit slightly higher RQs, signalling a need for more rigorous monitoring. Although their RQs remain below the critical threshold of 1, implying they do not present an immediate threat, their presence highlights the necessity for robust pharmaceutical waste management practices. Effective strategies are crucial to mitigate potential long-term cumulative effects on both human health and the environment, particularly in relation to water pollution. The analysis of RQ values presented in table 5 reveals the varying risk levels associated with different pharmaceuticals detected in drinking water. To safeguard public health, it is crucial to establish and enforce environmental policies that effectively regulate the concentrations of these substances. Enhancing monitoring and management practices for pharmaceuticals in water can mitigate adverse effects on both human health and ecosystems. Given the increasing prevalence of pharmaceuticals in society and the escalating risks associated with prolonged environmental exposure, a proactive approach to ensuring the safety and quality of drinking water is imperative.

CONCLUSIONS

This study offers a comprehensive evaluation of pharmaceutical residues in surface waters and their potential risks to both aquatic ecosystems and human health. The findings underscore notable concerns about pharmaceutical contamination, with significant concentrations detected for a range of analytes, including ibuprofen, naproxen, omeprazole, and ranitidine.

A critical aspect of the research involved identifying compounds with the highest concentrations. Notably, omeprazole, famotidine, and pantoprazole were found at elevated levels in the water samples, indicating their prevalent use and subsequent release into the environment. The ecological risks associated with these compounds were assessed using the RQ. The assessment revealed that while most analytes presented a low risk, certain substances, such as ranitidine, posed a significant risk to specific aquatic species. This highlights an ecological vulnerability that necessitates increased scrutiny and the implementation of effective management strategies.

From a human health perspective, the risk assessment revealed a varied risk profile for different pharmaceuticals. While drugs such as ibuprofen and naproxen are associated with a low-risk profile, substances like ranitidine raise significant concerns about their long-term impacts. The high RQ values for ranitidine emphasize the necessity for stringent regulation and ongoing monitoring of these substances in water, particularly given recent concerns about their potential carcinogenic effects. Regulatory authorities need to implement proactive measures to prevent the contamination of drinking water sources, thereby safeguarding public health, especially for vulnerable groups such as children and individuals with chronic conditions.

The analysis also highlighted the biological risks associated with metformin, the most commonly used pharmaceutical in the study. Although metformin is present in very low concentrations in water, it does not currently pose an immediate risk. This suggests that the management of pharmaceutical residue discharge into the environment is generally effective. However, it underscores the need for further investigation into potential drug-drug interactions and their long-term effects.

The significance of continued research in this domain cannot be overstated. With the rising use of pharmaceuticals and the potential cumulative effects of exposure to these substances, a greater emphasis on toxicological studies and robust environmental regulations is critical. Enhanced monitoring procedures for chemical contaminants in water and the formulation of more stringent legislation for pharmaceutical management are essential steps. Such proactive measures will not only safeguard aquatic ecosystems but also ensure the safety of drinking water, thereby protecting public health. In conclusion, this study underscores the complex interactions between pharmaceutical use and environmental impact, highlighting the need for comprehensive future research and regulatory strategies.

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