

A framework for the assessment of the environmental risk posed by pharmaceuticals originating from hospital effluents

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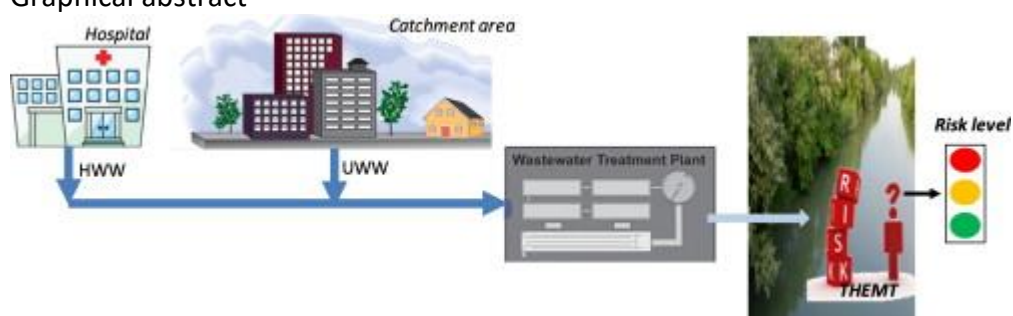
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Abstract

The consumption of pharmaceuticals is increasing in both hospitals and households. After administration, many compounds enter the water cycle as parent compounds or their metabolites via excretion. Conventional municipal wastewater treatment plants are unable to efficiently remove all the different compounds found in sewage and, consequently, treated effluents are one of the main sources of persistent micropollutants in the environment. Hospital patients are administered relatively high quantities of drugs and therefore hospital wastewaters can consistently contribute to treatment plant influent loads, with the magnitude of environmental risk posed by pharmaceuticals originating from hospital effluents largely unknown. This study has therefore developed a framework to enable authorities responsible for hospital management and environmental health to evaluate such risk, considering site-specific information such as the contribution of human population and hospital sizes, wastewater treatment removal efficiency, and potential dilution in the receiving water body. The framework was applied to three case studies, that are representative of frequent situations in many countries, and findings demonstrated that the degree of risk posed by any compound was site-specific and depended on a combination of several factors: compound concentration and toxicity, compound removal efficiency in the wastewater treatment plant and dilution factor. Ofloxacin, 17 α -ethinylestradiol, erythromycin and sulfamethoxazole were identified as compounds of concern and might require management in order to reduce risk.

Graphical abstract



Keywords

Environmental risk; Framework; Hospital effluent; Management; Pharmaceuticals; Treatment

1. Introduction

The consumption of pharmaceutical compounds (PhCs) is increasing in both hospitals and households ([Van der Aa et al., 2011](#), [Ortiz de Garcia et al., 2013](#), [Deo and Halden, 2013](#)). Pharmaceuticals consumed by humans are excreted in urine and feces as parent compounds or metabolites and enter the sewage system. They usually reach the wastewater treatment plant (WWTP) where they are partially removed before being discharged into surface water. Residues of pharmaceuticals in surface water have been correlated with the discharges of WWTPs ([Al Aukidy et al., 2012](#)). As the human body may only metabolize a fraction of the administered PhC, it enters the water cycle as the parent compound and/or its metabolites via excretion, mainly in urine (55–80%) and to a lesser extent the feces (4–30%) ([Jjemba, 2006](#)). The excretion rate is strictly correlated to a specific compound and to individual human characteristics, including age, gender, health status and concurrent assumption of other substances ([Johnson and Williams, 2004](#)).

Conventional municipal WWTPs are unable to efficiently remove all the different compounds found in sewage, and treated effluents are therefore one of the main sources of PhC release into the environment ([Verlicchi et al., 2012b](#)). Over the last ten to fifteen years, increasing attention has been paid to the fate and effects of PhCs in the environment and in particular in surface water bodies. PhC concentrations in the different water environments (raw and treated urban wastewater (WW) and surface water) have been extensively monitored in order to assess the removal ability of conventional treatment plants and their occurrence in the final water bodies. Some compounds were found to cause negative effects to the environment: among them diclofenac ([Oaks et al., 2004](#)) and hormones ([Routledge et al., 1998](#)).

Nevertheless, PhCs are still unregulated (emerging) compounds, and there is an ongoing debate within the scientific community regarding which PhCs to include among the substances demanding priority attention ([Bottoni et al., 2010](#)). Indeed, according to the [European Community Directive, 2013/39 \(2013\)](#), the anti-inflammatory diclofenac and the hormones 17 β -estradiol and 17 α -ethinylestradiol have been included in the European Watch List, while according to the US EPA, erythromycin, nitroglycerin, and 9 hormones need to be considered a priority ([Richardson and Ternes, 2011](#)).

Hospital wastewater (HWW) represents a particular concern. In the last few years it has become the object of several investigations (among them: [Verlicchi et al., 2010b](#), [Ort et al., 2010](#), [Escher et al., 2011](#), [Santos et al., 2013](#)), but up to now studies dealing with it are still fewer than those referring to urban wastewater (UWW). These investigations are made difficult not only by high analysis costs, but also by the difficulties in organizing water-sampling campaigns inside health facilities. Nonetheless, according to some recent literature ([Ort et al., 2010](#), [Riazul Haq et al., 2012](#), [Verlicchi et al., 2010a](#), [Verlicchi et al., 2010b](#), [Verlicchi et al., 2013b](#)), HWW represents the main source for some pharmaceuticals in terms of the PhC load generated, prompting the scientific community to question the acceptability of the general practice of discharging it into public sewers, where it is conveyed to municipal WWTPs and co-treated with UWWs ([Kümmerer and Helmers, 2000](#), [Pauwels and Verstraete, 2006](#), [Verlicchi et al., 2010a](#), [Verlicchi et al., 2010b](#)). Initially, the discussion centered on the concentrations of regulated (e.g. organic substances, N and P compounds, and microorganisms) and unregulated (residual of PhCs) pollutants in both hospital and urban WWs ([Kümmerer and Helmers, 2000](#), [Pauwels and Verstraete, 2006](#)). The focus then shifted to the evaluation of consumption and load of selected PhCs (on the basis of high consumption and negative environmental effects documented by literature) produced by a hospital and its catchment area ([Escher et al., 2011](#), [Heberer and Feldmann, 2005](#), [Ort et al., 2010](#), [Riazul Haq et al., 2012](#), [Schuster et al., 2008](#), [Verlicchi et al., 2012a](#)). In this context, [Escher et al. \(2011\)](#) reported that in a Swiss hospital of 338 beds 1154 kg of PhCs were consumed in 2007 and in the corresponding catchment area 18,700 kg were consumed by the resident population (250,000 inhabitants) in the same year. The cited studies estimated the relative contributions made by the hospital to its catchment area for each compound under investigation, revealing that in some cases the hospital is indeed the main source of certain PhCs in WW, for example the antibiotics ciprofloxacin, spiramycin, clarithromycin, azithromycin and ofloxacin ([Le Corre et al., 2012](#), [Riazul Haq et al., 2012](#), [Santos et al., 2013](#), [Verlicchi et al., 2012a](#)) and the lipid regulator atorvastatin ([Ort et al., 2010](#), [Verlicchi et al., 2012a](#)).

At the same time, several research groups set out to quantify the environmental risk generated by selected PhCs in raw hospital and urban WWs, as well as in municipal WWTP effluents ([Escher et al., 2011](#), [Verlicchi et al., 2012a](#)). Through evaluation of a compound's risk quotient (RQ), i.e. the ratio between its measured or predicted concentration and its predicted no-effect concentration (PNEC), these studies have shown that for some compounds the risk is high ($RQ > 1$) in raw WWs and remains high in the WWTP effluent. However, once the effluent is discharged into the receiving water body, its dilution with surface water may mitigate the effect of residual PhCs and the associated risk quotient may decrease ([Gros et al., 2010](#)), sometimes even to medium or low levels. Traces of PhCs were also detected in groundwater and drinking water, being this the result of a contamination of the aquifer and of water works not able to remove micropollutants such as PhCs.

All cited studies were conducted with the aid of local PhC consumption data and/or field monitoring campaigns. These types of investigations are costly and time-consuming. Therefore, in the case of construction of a new hospital, for example, a simple screening procedure, able to provide a rough estimation of the potential impact of the PhCs in its effluent on the local environment, would be valuable for the authorities and decision-makers responsible for hospital management and environmental protection. To this end, the aim of this study is to provide the authorities responsible for hospital management and environmental health with a simple approach (a framework) to evaluate the potential environmental impact of the hospital effluent, taking in consideration site-specific information such as the number of hospital beds, the quantity of wastewater discharged in the catchment area, the removal efficiency of the local WWTP, and the available dilution of the discharged effluent in surface water body. This study also aims to assess the relative importance of PhC main sources (HWWs, UWWs) for a single compound. The case of the priority candidate diclofenac, considered a target compound for individual WWTPs, will be presented. Such information will then be discussed to demonstrate its potential to assist with options for reducing PhC risk in discharges and to highlight the need to adopt management options.

2. Materials and methods

2.1. The proposed framework

This framework is designed to estimate, for a given hospital, the potential environmental impact posed by selected PhCs in the hospital effluent in terms of their RQ ranges. It takes into consideration the characteristics of: (i) the hospital in question (number of beds, wards, water consumption), (ii) its catchment area (number of inhabitants, water demand), (iii) the treatment process used for the hospital effluent and the corresponding removal efficiencies

for the selected compounds, and (iv) the characteristics of the receiving water body (dilution and hydrodynamic features).

The PhCs discussed in this study focused on the minimum number of compounds that should be considered in any study on PhC in water management. These compounds have been defined as high priority or priority substances by different research groups worldwide (Besse and Garric, 2008, De Voogt et al., 2009, European Community Directive 2013/39, 2013, Ginebreda et al., 2012, NRMMC, 2008, Perazzolo et al., 2010, Richardson and Ternes, 2011, Roos et al., 2012, Ruel et al., 2012, Santos et al., 2013, Sui et al., 2012, Verlicchi et al., 2012b). An in-depth analysis is reported in Table SI-1 in the Supplementary information section. A total of thirty two PhCs were selected, among them six analgesics and anti-inflammatories, twelve antibiotics, one antihypertensive, three beta-blockers, one contrast medium, four hormones, two lipid regulators, two psychiatric drugs and one antagonist drug (Table SI-1). Many of these pollutants are as yet unregulated; some of them have been included in the European “Watch List” (diclofenac, 17 β -estradiol, 17 α -ethinylestradiol) (European Community Directive, 2013/39, 2013) and in the US contaminant candidate list (erythromycin, 17 α -ethinylestradiol, 17 α -estradiol, 17 β -estradiol, equilenin, equilin, estriol, estrone, mestranol and norethindrone) (Richardson and Ternes, 2011).

For each of the selected PhCs, the framework draws on four databases compiled from an extensive review of literature (Table 1), detailing (i) their concentration ranges measured in HWW (Database 1, DB1), (ii) their concentration ranges observed in raw UWWs (Database 2, DB2), (iii) their removal efficiencies observed in biological treatments, namely conventional activated sludge (CAS) and membrane biological reactor (MBR) processes (Database 3, DB3), and (iv) their PNEC values (Database 4, DB4). In addition, the framework requires site-specific information such as the number of hospital beds, the number of inhabitants in the catchment area, the volume of wastewater per day per bed, the volume of wastewater per day per inhabitant and, finally, the flow of the receiving water body.

Table 1. Contents and main references of the four databases of the framework.

Database	Contents	References and notes
Database (DB1)	1 Measured concentrations of selected PhCs in HWWs.	Data collected from literature (see Table SI-2); min and max in Table 2
Database (DB2)	2 Measured concentration of PhCs in UWWs	From the review by Verlicchi et al. (2012b) ; min and max in Table 2
Database (DB3)	3 Removal efficiency of PhCs at the WWTP (CAS, MBR,...)	See footnotes in Table 2
Database (DB4)	4 PNEC values for selected PhCs	See footnotes in Table 2

2.1.1. Evaluation of the environmental risk posed by PhCs in HWWs

The expected range of environmental risk associated with the presence of PhCs in HWWs is calculated by means of the minimum and maximum risk quotients. For each selected compound, the range of risk is assessed by dividing its minimum and maximum values of concentration in HWW by its corresponding PNEC value ([Table 2](#)), according to (Eq. (1)).

$$(1) \text{HRQ}_{\min}, \text{HRQ}_{\max} = \text{Ch}_{\min} / \text{PNEC}, \text{Ch}_{\max} / \text{PNEC}$$

Table 2. Minimum and maximum concentrations of selected PhCs in HWWs and UWWs (µg/L), percentage removal efficiency in biological WWTPs (%) and PNEC values (µg/L).

Class	Compound	Database 1 ^a		Database 2 ^b		Database 3 ^c		Database 4 ^d
		HWW Concentration		UWW Concentration		WWTP removal		PNEC
		Min	Max	Min	Max	CAS	MBR	
Analgesic/anti-inflammatory	Acetaminophen	2.5	330	0.013	246	80	99 ^e	1
Analgesic/anti-inflammatory	Codeine	0.067	50	0.1	35	29	88 ^e	16
Analgesic/anti-inflammatory	Diclofenac	0.046	15	0.0005	11	5	23	9.7
Analgesic/anti-inflammatory	Ibuprofen	0.069	75	0.0005	373	26	95	1.65
Analgesic/anti-inflammatory	Ketoprofen	0.099	17.4	0.0005	6.47	7	62	15.6
Analgesic/anti-inflammatory	Naproxen	0.01	18	0.038	52.9	35	71	2.62
Antibiotic	Chlortetracycline	0.011	0.08	0.0045	0.0045	82	78 ^e	0.05 ^e
Antibiotic	Ciprofloxacin	0.038	237	0.09	13.6	50	36 ^e	938

Class	Compound	Database 1 ^a		Database 2 ^b		Database 3 ^c		Database 4 ^d
		HWW Concentration		UWW Concentration		WWTP removal		PNEC
		Min	Max	Min	Max	CAS	MBR	
Antibiotic	Clarithromycin	0.0075	11	0.33	4.82	4.5	41	0.07
Antibiotic	Doxycycline	0.0005	7	0.002	0.114	14	–	0.3
Antibiotic	Erythromycin	0.019	83	0.06	10.02	4.3	26	0.02
Antibiotic	Lincomycin	0.119	2	0.06	0.08	17	–	82
Antibiotic	Metronidazole	0.033	6	0.044	0.96	38.7	95 ^e	2.5
Antibiotic	Norfloxacin	0.029	44	0.018	0.52	18.18	–	8 ^f
Antibiotic	Ofloxacin	0.005	73	0.022	31.7	13	91 ⁱ	0.016 ^g
Antibiotic	Sulfamethoxazole	0.004	83	0.003	10	10	37	0.027
Antibiotic	Tetracycline	0.0015	2	0.002	1.3	24	82 ⁱ	0.09
Antibiotic	Trimethoprim	0.013	15	0.005	10.5	5.1	30	2.6
Antihypertensive	Diltiazem	0.05	2	0.005	5.25	41 ⁱ	–	1.9
B-blocker	Atenolol	0.17	7	0.03	25.14	14	70 ^e	30
B-blocker	Metoprolol	0.018	25	0.02	1.2	7	26 ^e	8
B-blocker	Propranolol	0.018	1	0.01	1.9	1	24 ^e	0.244
Contrast medium	Iopromide	0.461	1400	0.01	6.6	50	19 ^e	137 ^e
Hormone	17 α -Ethinylestradiol	0.005	0.4	0.002	0.04	70	25	0.0001 ^h
Hormone	Estradiol	0.004	0.2	0.003	3	22	99	0.002 ^h
Hormone	Estriol	0.017	1	0.05	0.25	85 ⁱ	95 ^{mi}	0.06 ^h
Hormone	Estrone	0.001	0.1	0.002	0.67	94	96	0.006 ^h
Lipid regulator	Bezafibrate	0.01	7	0.048	29.8	9.1	88.2 ⁱ	5.3
Lipid regulator	Gemfibrozil	0.019	3	0.3	17.1	5	32.5 ⁱ	0.9
Psychiatric drug	Carbamazepine	0.037	3	0.0025	21.5	5	4.4	13.8

Class	Compound	Database 1 ^a		Database 2 ^b		Database 3 ^c		Database 4 ^d
		HWW Concentration		UWW Concentration		WWTP removal		PNEC
		Min	Max	Min	Max	CAS	MBR	
Psychiatric drug	Fluoxetine	0.019	0.1	0.011	2.3	33	80 ^e	0.024 ^g
Receptor antagonist	Ranitidine	0.115	4	0.072	11.15	24.5	90 ^e	63

The complete list of references for each compound is reported in Table SI-2.

Data are taken from [Verlicchi et al. \(2012b\)](#) (minimum, 5% quantile, median, 95% quantile and maximum are reported in Fig SI-1).

Where not specified, data are from the review by [Verlicchi et al. \(2012b\)](#).

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- [Halling-Sørensen \(2000\)](#).
- [Tong et al. \(2011\)](#).
- [Santos et al. \(2013\)](#).
- [Caldwell et al. \(2012\)](#).
- [Verlicchi et al. \(2013c\)](#).
- [Radjenovic et al. \(2009\)](#).
- [Nielsen et al. \(2013\)](#).
- [Jia et al. \(2011\)](#).
- [Wijekoon et al. \(2013\)](#).
- [Dolar et al. \(2012\)](#).
- [Reif et al. \(2013\)](#).

where HRQ_{min} and HRQ_{max} are the minimum and maximum hospital risk quotients associated with the presence of a PhC in HWWs, $C_{h,min}$ and $C_{h,max}$ are its minimum and maximum HWW concentrations expressed in $\mu\text{g/L}$ (see Database 1 in [Table 2](#)), and $PNEC$ is its predicted no-effect concentration expressed in $\mu\text{g/L}$ (see Database 4 in [Table 2](#)). Moreover, within each range of HRQ , the 5% quantile, the median (50% quantile) and the 95% quantile are calculated by Eq. (1), using the corresponding values of pharmaceutical concentration (on the basis of all the data reported in Table SI-2 for each compound; see also Fig. SI-1).

2.1.2. Evaluation of the environmental risk in surface water posed by PhCs originating from HWWs

In order to quantify the range of the risk posed by HWWs in the environment (surface water) due to the presence of PhCs, the following reference scenario has been considered: the hospital discharges its effluent into the public sewer system where the pharmaceutical concentration is reduced by a dilution factor that depends on the volume of effluent flowing in the sewer. This, in turn, depends on the size of the hospital and catchment area. Subsequently, this effluent is treated by the local WWTP, undergoing various removal mechanisms and finally it is discharged into the receiving water body where the reduction in

concentration is due to the dilution factor of the surface water. The dilution in the sewer system, removal in WWTP and dilution in the surface water should be taken into account and evaluated case by case. The variability range of RQ in the environment (surface water) is calculated by Eq. (2).

$$(2) ERQ_{min}, ERQ_{max} = Ch_{min} \times Df_u \times 1 - R \times Df_e PNEC, Ch_{max} \times Df_u \times 1 - R \times Df_e PNEC$$

where ERQ_{min} and ERQ_{max} are the minimum and maximum environmental risk quotients in surface water posed by PhCs originating from HWW, R is the removal efficiency of PhCs in WWTP (from the precautionary principle, minimum values reported in literature have been adopted), Df_u is the urban dilution factor due to the discharge of HWWs in the sewer system (from local conditions data), and Df_e is the environmental dilution factor, due to the discharge of WWTP into the receiving water body (from local conditions data). As for HRQ , the 5% quantile, the median and the 95% quantile are also calculated for ERQ . Suggested values of R for a conventional activated sludge process (CAS) and a membrane biological reactor (MBR) are reported in Table 2, based on literature reviews as remarked in the footnote of the aforementioned table.

The dilution factor Df_u (Eq. (3)) is the ratio by which HWW will be diluted in a sewer system, and is dependent on two variables: the size of the hospital and the size of the catchment area. The dilution factor Df_e (Eq. (4)) is the ratio by which a WWTP effluent will be diluted in a receiving water body and is dependent on two variables: the flow of the WWTP and the flow of the receiving water body. It is clear that the flow of the receiving water body varies during different seasons and even within a season, so the lowest flow should be taken when calculating the dilution factor to present the worst case that may occur:

$$(3) Df_u = \frac{Bed \times WW_{bed}}{Bed \times WW_{bed} + Inhabitants \times WW_{inhabitant}}$$

$$(4) Df_e = \frac{Bed \times WW_{bed} + Inhabitants \times WW_{inhabitant}}{\text{volume of receiving water body per day}}$$

where Bed is the number of hospital beds under investigation (local conditions data), WW_{bed} is the volume of WWs per bed per day (local conditions data), $Inhabitants$ is the number of inhabitants in the catchment area under investigation (local conditions data), and $WW_{inhabitant}$ is the volume of WWs per capita per day. Referring to this last parameter, the value of 200 L/inhabitant/day is assumed as a default value (see Table SI-4), as it is often considered

in many developed countries ([Ashton et al., 2004](#), [Bound and Voulvoulis, 2006](#)). However, it can be changed if a different specific water demand characterizes the study area.

This framework is applied to the three cases described in [Table 3](#), in order to estimate the environmental risk in different catchment areas. They refer to a large hospital in a large catchment area (case 1), a medium-small hospital in a small urban settlement (case 2) and a large hospital in a very small urban settlement (case 3). In addition, they differ with regard to the hydraulic characteristics of the receiving water body resulting in different environmental dilution factors. The parameter bed density (defined as the number of hospital beds per 1000 inhabitants of the catchment area) clearly indicates the relative size of the hospital with respect to its catchment area. These three case studies were selected as they represent frequent situations that can be found in the area of the Po Valley, Northern Italy as investigated in previous works ([Verlicchi et al., 2010a](#), [Verlicchi et al., 2012a](#)).

Table 3. Main characteristics of the three case studies.

Table 3: Main characteristics of the three case studies.							
Parameters	Case study 1		Case study 2		Case study 3		
Hospital							
Number of beds	900		300		900		
Specific water consumption (L/bed/day)	670		550		670		
Catchment area							
Number of inhabitants	138,000		5000		1700		
Specific water consumption (L/inh/day)	200		200		200		
Bed density (beds/1000 inh)	6.5		60		529		
Flow rate of the receiving water body (m ³ /s)	30		0.016		0.010		
Comment	Large area	hospital/big catchment	Medium town	hospital/small	Large town	hospital/small	

The risk quotient values were then classified into three risk levels: low (values ≤ 0.1), medium (between 0.1 and 1) and high (values ≥ 1) ([Hernando et al., 2006](#)).

2.1.3. Sensitivity analysis and validation of the proposed framework

A sensitivity analysis was performed for the proposed framework in order to evaluate the influence of the different variables including in the model on the risk quotient assessment (Eqs. (1), (2), (3), (4)). The analyzed variables are: pharmaceutical concentrations in hospital effluent C_h , dilution factor in urban sewage D_{fu} , and removal efficiency for each compound at the WWTP R and dilution factor in the environment D_{fe} . For each of them, a specific variability range was set according to available literature data (C_h and R), specific considerations and expert judgment (D_{fu} and D_{fe}):

-

The intervals assumed for the concentration in HWW (C_h) for each compound were based on literature data that are all reported in Table SI-2 (see also Fig. SI-1);

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The interval set for the dilution factor D_{fu} was based on an in depth analysis of the expected variability of the specific daily water consumption within the hospital and the catchment area and on the expected variability of the number of occupied beds and resident population (Table SI-5);

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The intervals assumed for R of each compound were based on the data reported by Verlicchi et al. (2012b) (Table SI-6);

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The interval set for the dilution factor D_{fe} was set based on expert judgment (Table SI-7).

In the sensitivity analysis, only one parameter could change its value at a time within its defined range, while the others assume a constant value equal to that reported in Table 2, Table 3. The new values of HRQ and ERQ can be evaluated by means of Eqs (1), (2), and the percentage variation of each of them with respect to the corresponding average value is then assessed $[(HRQ_{new} - HRQ_{average}) / HRQ_{average} \times 100]$ and $[(ERQ_{new} - ERQ_{average}) / ERQ_{average} \times 100]$. In the Supplementary information all the details of the sensitivity analysis are provided, and in Section 3.4 the main results are reported and discussed.

The critical analysis of the proposed framework is completed with a validation test, on the basis of a set of real data of PhC concentrations in HWW, removal efficiencies in a conventional activated sludge system, and urban and environmental dilution factors, already

published ([Verlicchi et al., 2012a](#), [Verlicchi et al., 2013b](#), [Verlicchi et al., 2013a](#), [Verlicchi et al., 2013c](#)). The validation test is applied for case study 1.

2.1.4. Evaluation of the relative impact of hospitals and catchment areas on the risk of PhCs in the influent of WWTPs

In order to estimate the importance of the relative risk posed by a single compound to each WWTP influent, the expected range of risk has been evaluated by using Eqs. (5), (6), taking into consideration the pharmaceutical loads originating from both the hospital and its catchment area. This evaluation was carried out here for the analgesic diclofenac, as it was considered a target compound, being recently included among the watch list substances ([European Community Directive, 2013/39, 2013](#)). The same procedure may be applied to any other compound of interest.

$$(5) IRQ = I_c / PNEC$$

$$(6) I_c = C_h \times Bed \times WW_{bed} + C_U \times Inhabitants \times WW_{inhabitants} / Bed \times WW_{bed} + Inhabitants \times WW_{inhabitants}$$

where IRQ is the WWTP influent risk quotient of a specific PhC (in this study diclofenac), I_c is its WWTP influent concentration ($\mu\text{g/L}$), C_h is its concentration in HWW ($\mu\text{g/L}$) (see Database 1), and C_U is its concentration in UWW ($\mu\text{g/L}$) see (Database 2). Assuming that C_h and C_U may vary in their min–max range reported in [Table 2](#), by means of Eq. (6), the range of variability of the influent concentration I_c in a site-specific WWTP was determined. In this way, the WWTP influent risk IRQ generated from the occurrence of the target compound in HWW and UWW was evaluated (Eq. (5)) and depicted in a 3D surface chart ([Fig. 3](#)).

The analysis was performed for the three case studies described in [Table 3](#).

3. Results

3.1. Occurrence of the selected PhCs in HWWs and comparison with UWWs

Table SI-2 reports the concentrations of the selected PhCs in HWWs along with their references. The investigations were mainly conducted in Europe with some others in the USA, India, Korea, Taiwan and Vietnam. The most investigated compounds are ciprofloxacin, sulfamethoxazole, ofloxacin, ibuprofen, acetaminophen and diclofenac. A few data are available for estriol, 17α -ethinylestradiol, chlortetracycline and lincomycin. The range of concentration varies among compounds and from several ng/L (doxycycline) to several mg/L (iopromide). The highest concentration values were observed for iopromide ($1400 \mu\text{g/L}$), acetaminophen ($330 \mu\text{g/L}$) and ciprofloxacin ($237 \mu\text{g/L}$).

In order to compare the occurrence of PhCs in HWWs with the occurrence in UWWs, a descriptive statistical analysis was performed in terms of minimum, 5% quantile, median, 95% quantile and maximum values and is depicted in Fig. SI-1. Data regarding the occurrence of the selected PhCs in UWWs were taken from the review by [Verlicchi et al. \(2012b\)](#). For 22 out of the selected 32 compounds, the median concentrations were higher in HWWs than in UWWs. In addition, the median concentration was found to be three orders of magnitude higher in HWW than UWW for iopromide and one order of magnitude higher for ciprofloxacin, norfloxacin, sulfamethoxazole, trimethoprim, diltiazem and chlortetracycline. The median concentration of bezafibrate was, on the other hand, one order of magnitude higher in UWW than in HWW. For the remaining compounds, the values were quite similar (Fig. SI-1).

These findings confirm that PhC concentrations in HWW are often higher than those detected in UWWs.

3.2. Environmental risk posed by PhCs in HWWs

The results of the expected range of risk posed by PhCs in HWWs are presented in [Fig. 1](#). It emerges that the range width may vary among the investigated compounds. This could be due to the fact that some PhCs were quite often investigated in different countries and periods within the year (among them ciprofloxacin, sulfamethoxazole, acetaminophen, as shown in Fig. SI-1) and a wide range of concentrations were reported in literature (Table SI-2) with respect to other compounds (such as hormones, lincomycin and fluoxetine). The data are ranked with decreasing HRQ_{max} . For sixteen compounds the median HRQ was found to be higher than 1 (the highest values were for ofloxacin and sulfamethoxazole). For 17 α -ethinylestradiol, erythromycin, acetaminophen and estradiol the whole range of risk is always in the high region ($HRQ \geq 1$), which means that based on these investigations, they always pose a high risk in HWWs. Ofloxacin, sulfamethoxazole, clarithromycin, estrone, estriol, fluoxetine and chlortetracycline have a risk laying in the medium–high region ($HRQ \geq 0.1$). Ibuprofen, doxycycline, tetracycline, iopromide, naproxen, trimethoprim, propranolol, norfloxacin, codeine, metoprolol, gemfibrozil, metronidazole, diclofenac, bezafibrate, ketoprofen, diltiazem, ciprofloxacin, carbamazepine and atenolol have a risk ranging between low and high levels. Finally, ranitidine and lincomycin have a risk ranging within the low interval level ($HRQ \leq 0.1$).

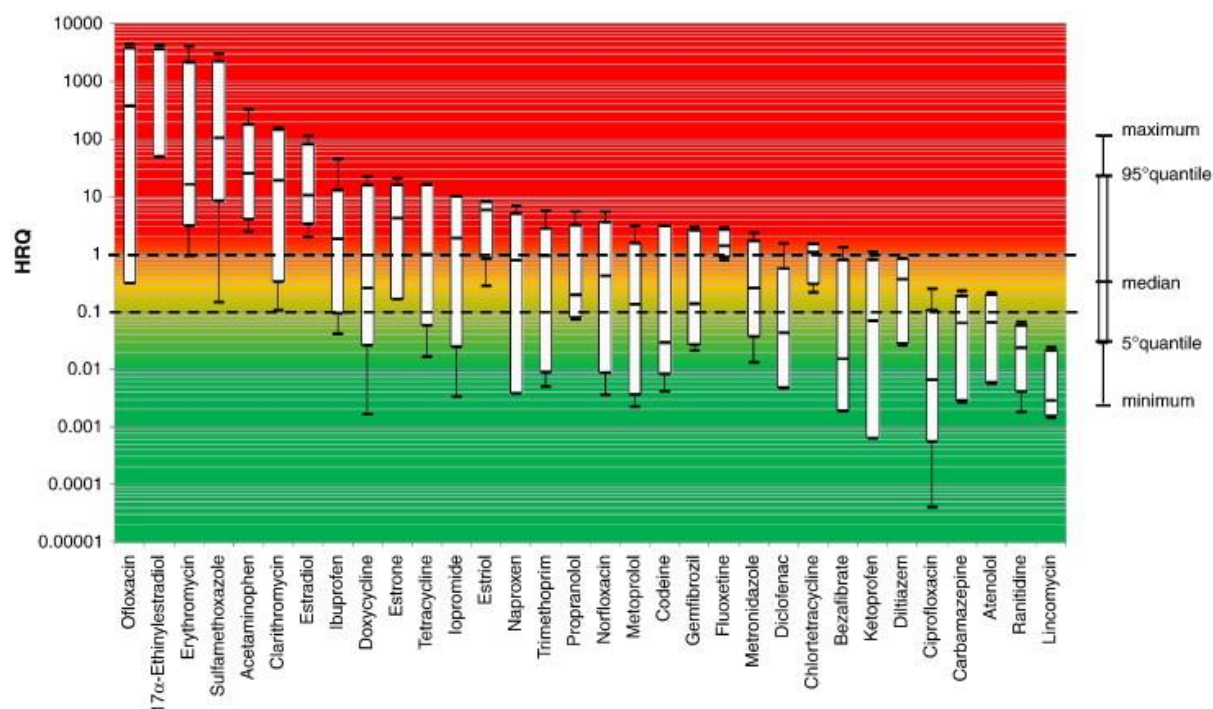


Fig. 1. Expected range of risk posed by PhCs in raw HWWs.

A similar analysis of the risk posed by the selected 32 PhCs in UWW is shown in Fig. SI-2 in the Supplementary information section, where compounds are reported according to the same order as [Fig. 1](#). A rapid glance at these two graphs shows that the variability range of the estimated risk is wider for UWW than HWW. In HWW, for 26 compounds out of the selected 32 HRQ_{max} is higher than 1, while in UWW URQ_{max} is greater than 1 for 21 compounds. In both cases the highest risk values were posed by antibiotics and hormones.

3.3. Environmental risk in surface water posed by PhCs originating from HWWs

[Fig. 2](#) shows the expected range of risk downstream the WWTP discharge in the three cases described in [Table 3](#). For each compound, the range width remained constant in the three catchment areas, with the sole variation being that of risk level. This is due to the fact that input data (hospital effluent concentrations and removal efficiency) used in the current analysis are the same (those reported in [Table 2](#)). As expected ([Verlicchi et al., 2012a](#)), the number of compounds posing a high risk increases with increased bed density, where the hospital contribution becomes more influential. No compound was observed to have an expected range falling within the high risk area ($ERQ \geq 1$) in case study 1; while this occurred for nine compounds in case study 2 (ofloxacin, 17 α -ethinylestradiol, erythromycin, sulfamethoxazole, acetaminophen, clarithromycin, estradiol, ibuprofen and doxycycline) and for fifteen compounds in case study 3 (ofloxacin, 17 α -ethinylestradiol, erythromycin,

sulfamethoxazole, acetaminophen, clarithromycin, estradiol, ibuprofen and doxycycline, tetracycline, iopromide, naproxen, trimethoprim, propranolol and norfloxacin).

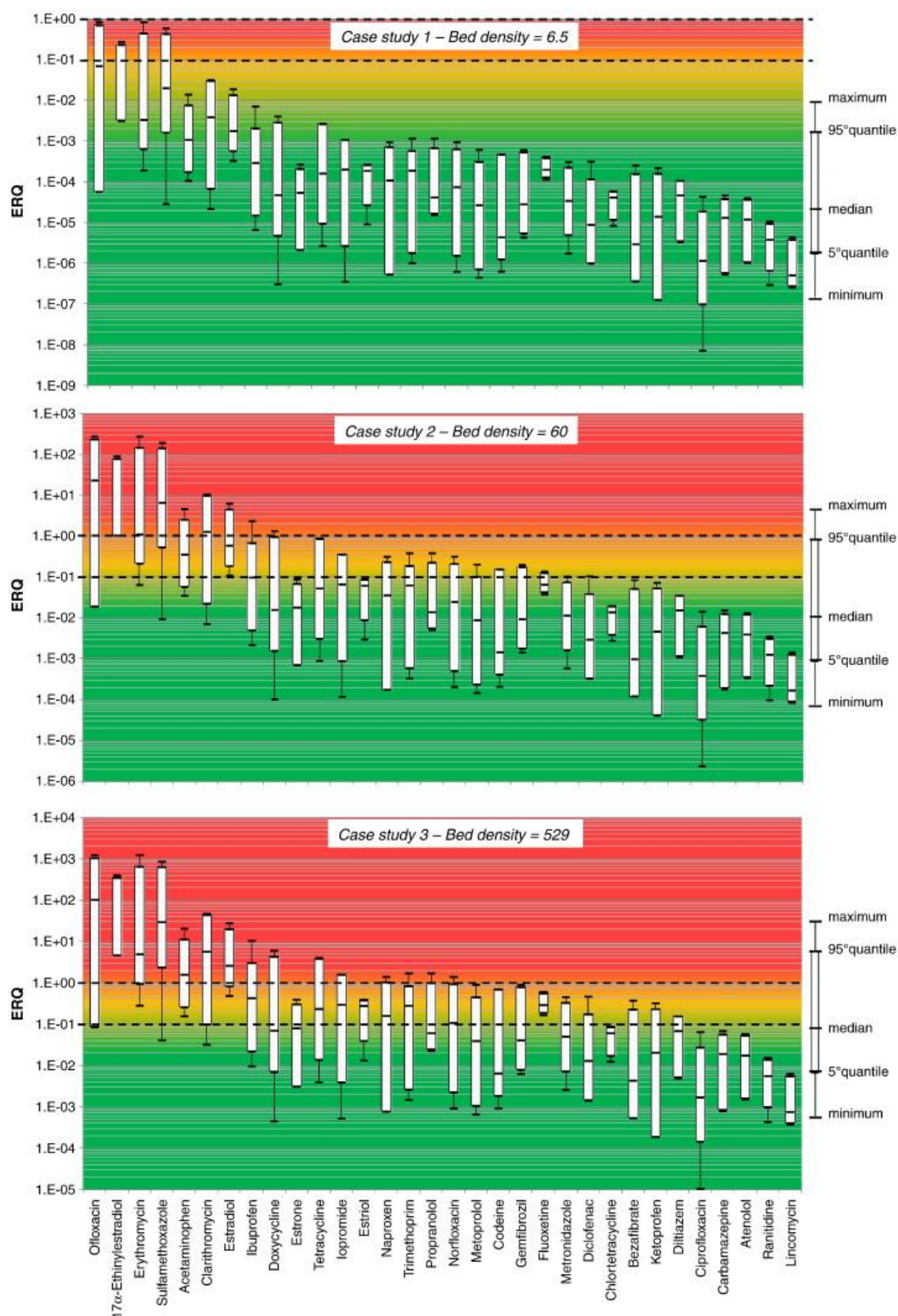


Fig. 2. Expected range of risk in surface water (*ERQ*) posed by PhCs originating from only HWWs in the three different case studies characterized by the same scenario: HWW co-treated with UWW in a CAS.

Ofloxacin, 17 α -ethinylestradiol, erythromycin and sulfamethoxazole were found to pose the highest risk in HWWs and their risk is still high downstream of the WWTP in case studies 2 and 3, while in case study 1 it is medium, despite the dilution in sewer systems, removal in WWTPs and dilution in surface water that have occurred. This is determined by their high toxicity (low PNEC values) and high exposure. The high *ERQ* associated with the contrast agent iopromide is determined by its high initial concentration which was found to be 1400 $\mu\text{g/L}$ in HWWs. Carbamazepine and ranitidine were found to have a low risk level ($ERQ \leq 1$) due to their low toxicity and low initial concentration, while the antibiotic ciprofloxacin has a low *ERQ* due to its low toxicity, although its concentration in HWWs is high and could reach 237 $\mu\text{g/L}$.

Since the removal efficiency for each compound in WWTPs was assumed to be equal in all the case studies, it is evident that dilution in sewer systems and surface water had a larger effect on the decrease of *ERQ* and this is also evidenced in literature (Escher et al., 2011). In general, according to the adopted scenario, in the current management of HWWs (co-treatment with UWWs at the municipal WWTP), the risk posed by HWWs due to the presence of PhCs can be reduced by various orders of magnitude, and it is dependent on the characteristics of each catchment area where the hospital is situated. The range of the risk posed by HWWs (Fig. 1) is reduced by four orders of magnitude in case study 1 (Fig. 2, top), one order of magnitude in case study 2 (Fig. 2, medium) and it is still in the same order of magnitude in case study 3 (Fig. 2 bottom). Acetaminophen, estrone, estriol and chlortetracycline exhibit slightly more reduction with respect to the other compounds and this is achieved by their high observed removal efficiencies in WWTP (80, 94, 85, 82% respectively).

3.4. Sensitivity analysis and validation of the proposed framework

The results of the sensitivity analysis are reported in details in Table SI-3 in the Supplementary information section. On the basis of this analysis it emerges that the highest uncertainties in risk quotient assessment are associated to the assumed values of PhC concentration in HWW and WWTP removal efficiencies. Uncertainty due to urban dilution factor resulted consistent for a few compounds, namely estriol, fluoxetine, and chlortetracycline and the uncertainty due to environmental dilution factor was consistent only in the case of fluoxetine.

Due to the fact that the framework assumes the lowest values of removal efficiency for each compound (Table 2) and the lowest value for D_{fe} of its corresponding variability range, the resulting percentage variations of the risk quotient associated to the sensitivity analysis of these two parameters are always negative. The reason for these assumptions is that the

framework aims to simulate the worst scenario, according to a precautionary principle in the environmental risk assessment.

The influence of the variability in PhC concentrations was already included in the framework concept as *HRQ* and *ERQ* were assessed for all the PhC concentration variability ranges ([Fig. 1](#), [Fig. 2](#)). Moreover as those graphs provide 5 and 95 quantiles and median value of risk quotient for each PhC, it is also possible to know the distribution of the assessed *HRQ* and *ERQ*.

A validation of the model was also carried out on the basis of the set of real data referring to case study 1 (see Table SI-8) and to 22 PhCs out of the 32 included in the framework. All these data were already presented and discussed in other studies ([Verlicchi et al., 2012a](#), [Verlicchi et al., 2014](#)). The results of this analysis were reported in the Supplementary information section in Fig. SI-4 (*HRQ*) and Fig. SI-5 (*ERQ* — case study 1) where they are compared with the expected range of variability of the corresponding *HRQ* and *ERQ*. It was found that the values of risk quotient were always within the expected range for all the compounds with the exception of clarithromycin for *HRT* (a higher value was found on the basis of real data) and acetaminophen for *ERQ* (a lower value found on the basis of the real data).

3.5. The relative impact of hospital and catchment area on the risk of PhCs in the WWTP influent —

The example of diclofenac

The site-specific estimated risk posed by PhCs originating from HWWs and the catchment area UWWs in the WWTP influent (*IRQ*) is assessed for the target compound diclofenac and depicted in [Fig. 3](#). The X- and Y-axes represent the two input parameters, which are the literature concentration ranges of the selected compound in HWWs and UWWs respectively (see [Table 2](#)), while the vertical Z-axis represents the associated *IRQ* value for each of the defined X and Y coordinates.

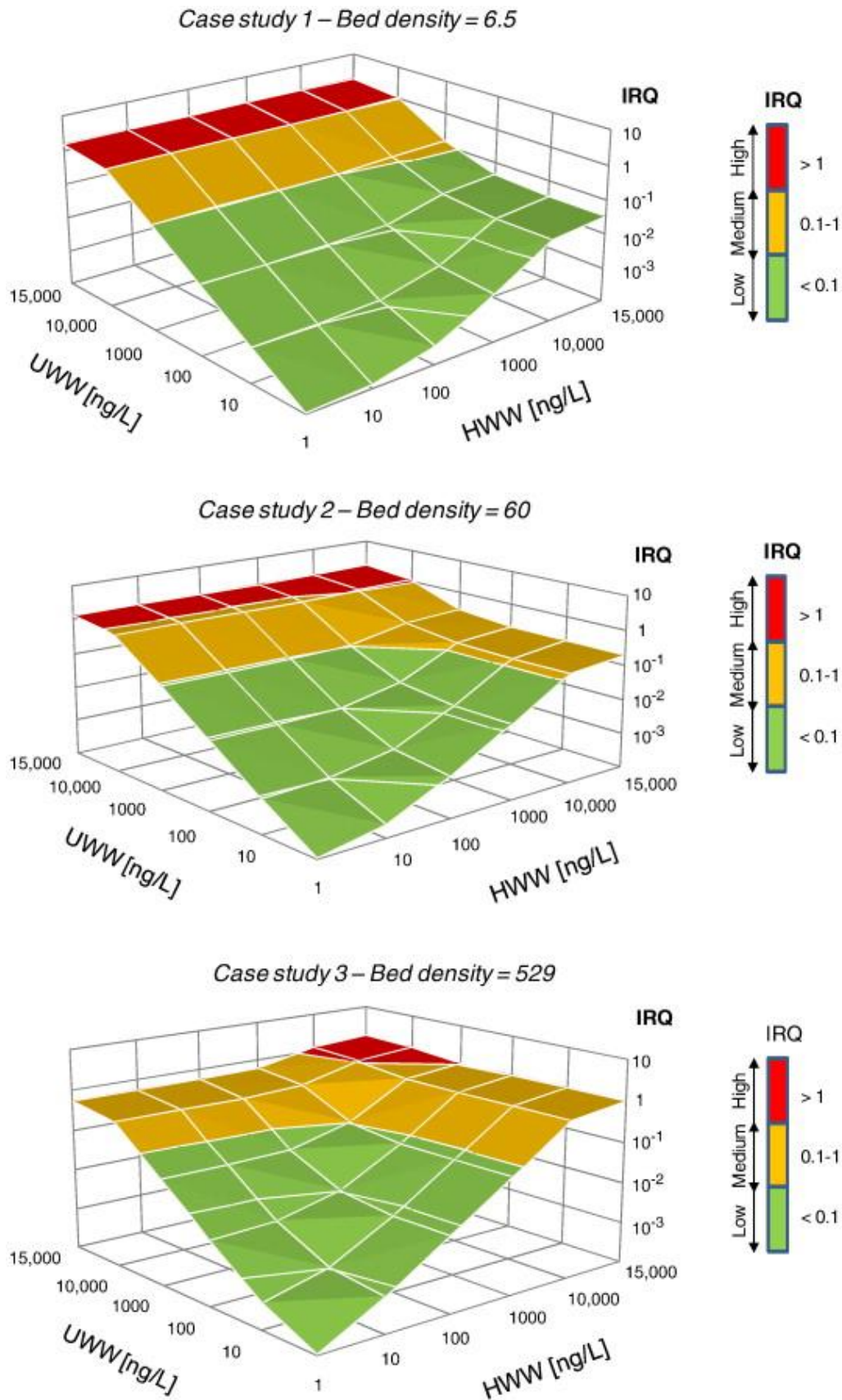


Fig. 3. Risk patterns posed by the target compound diclofenac in the influent of WWTP in the three case studies investigated.

In all three case studies, the results showed that the risk posed by diclofenac in the influent of WWTP varies from low to high with a maximum value of $IRQ = 1.5$. In case study 1 (with low bed density), medium and high risks could occur when there are high concentrations ($> 1 \mu\text{g/L}$) of diclofenac in UWWs, independent of the level of concentration in HWWs. This pattern is different in case studies 2 and 3, where the influence of HWWs on the risk had a greater impact. In these cases the medium risk could occur also when diclofenac was present in high concentrations in HWWs, independent of the concentration in UWWs. The observed high risk in case studies 1 and 2 with respect to study case 3 is due to the high load discharged in sewer systems from the catchment area.

4. Discussion

Evaluating the potential risk of HWWs due to the occurrence of PhCs requires the availability of data regarding the concentration of PhCs in HWWs and the removal efficiency in the WWTP to which HWWs are subjected, as well as PNEC values. The assumptions made when employing these data imply that PhC concentration will be the same for each hospital, and the variation between hospitals will only be a result of variation in flow (resulting from variation in the number of beds and in the assumed specific daily water consumption). This is obviously not the case as within each hospital there will be variations in PhC concentration levels due to the differences in their consumption patterns, their consumption policies, services, and department and research activities. Moreover, the framework assumes that water consumption in the hospital and in the catchment area is constant, while the reality is that the profile of water consumption varies during the day, month and year, as reported in literature ([Coutu et al., 2013](#), [Verlicchi et al., 2013b](#)).

It is also worth noting that in the case of a combined sewage network, during rain events, the overflow could represent a consistent environmental source of pharmaceutical as recently remarked by [Philips et al. \(2012\)](#) and [Chèvre et al. \(2013\)](#). The proposed framework does not take into consideration this flow and in this version it can simulate dry periods in the case of combined sewage and dry and wet periods in the case of separate sewage. The implementation of the effect of rain events on the framework is beyond the current research. Despite the limitations facing the framework, evaluating the potential impact of hospital effluents is very important in order to reduce the PhC loads discharged into the environment. Accordingly, the results generated by the proposed framework suggest that due to the presence of PhCs, HWWs pose a risk to the receiving environment and their risk depends on several factors: compound concentration and toxicity; compound removal efficiency in the

WWTP and dilution factors in sewage systems and in the receiving water body. Ofloxacin, 17 α -ethinylestradiol, erythromycin and sulfamethoxazole are potential compounds of concern in the HWWs and require attention, while other compounds may not due to their low risk. In some cases, HWWs contribute consistently to the site-specific risk in the influent of a WWTP, and their contribution is correlated to bed density. The evaluated contribution of the hospital effluent to the total load of diclofenac in the WWTP influent in case study 1 was observed to be 2% ([Verlicchi et al., 2012a](#)) while the contribution in other catchment areas with different bed densities in other countries was observed to be 10% (Germany, bed density = 12, [Heberer and Feldmann, 2005](#)), 1.6% (Norway, bed density = 4, [Thomas et al., 2007](#)), 1% (Australia, bed density = 4.4 [Ort et al., 2010](#)) and 7–9% (Germany, bed density = 33.5, [Beier et al., 2011](#)).

Different strategies to decrease pharmaceuticals in HWW are discussed in literature (e.g. [Lienert et al., 2011](#)) and they could either be technical (pretreatment of the effluent) or organizational (prior intervention). Based on the results obtained from the proposed framework, the implementation of decentralized WWTP for the HWWs as a technical strategy to reduce pharmaceutical impacts does not seem to be efficient in case studies 1 and 2, where the *IRQ* could be ≥ 1 even when the concentration in HWWs is at low levels. However, for case study 3 it seems to be efficient since $IRQ \geq 1$ is mainly caused by HWWs.

In the case of co-treatment of HWW with UWW, it is important to evaluate the percentage of hospital contributions to the total WWTP influent ([Le Corre et al., 2012](#), [Santos et al., 2013](#), [Verlicchi et al., 2010a](#)). This value depends on relative sizes of the hospital and urban population (bed density).

4.1. Application of the framework and management options

Estimating the risk posed by PhCs originating from HWWs to the receiving environment could provide valuable information regarding the magnitude of the risk posed by HWWs and hence on the type of management options that should be adopted. As there is no specific treatment that is able to achieve a high level of removal of the many kinds of PhCs typically found in HWWs, due to their differing behavior during treatments, and as many PhCs are resistant to conventional treatments, innovative solutions to this problem are required like MBR and AOPs ([Lipp et al., 2012](#)). Different operational configurations should be developed and deeply analyzed in order to provide information for potential practitioners about the financial aspects and overall risks associated with putative treatments of HWWs ([Pauwels and Verstraete, 2006](#), [Verlicchi et al., 2010a](#)). In doing this, further treatment steps could be

adopted, for instance end-of-pipe treatments and, consequently, the resulting overall removal efficiencies (R) for the target compounds would increase according to Eq. (7).

$$(7) R = 1 - (1 - R_{I1} - R_{II} \dots 1 - R_n)$$

where R_i is the removal efficiency referring to the step i ($i = I, II, \dots, n$), provided by literature data or on field investigations.

For each defined hospital effluent treatment train, the risk ERQ may be identified by using this framework, and alternatives in the HWW treatments could be evaluated in order to reduce this risk. For instance, the first option could be assuming an MBR instead of a CAS. This would lead to a replacement of the removal efficiency values referred to CAS applied to this framework with the minimum removal values reported in literature observed with MBR (see Table 2). In doing this, the ERQ posed by all selected PhCs is reduced in the three case studies (as shown in Fig. SI-3) with the exception of 17α -ethinylestradiol, iopromide, chlortetracycline and carbamazepine, whose removal efficiencies reported for MBR were less than those referred to CAS. ERQ is reduced to a low risk level for two compounds in case study 1, and five compounds in case studies 2 and 3 (see Fig. SI-3). In the same manner, by means of the proposed framework, it is possible to evaluate the effect of adoption of further treatments for the HWW.

Dedicated treatment of HWWs is preferred for large hospitals in small urban settlements or rural areas, where their treated effluents may be indirectly reused for irrigation after their discharge into a surface water body (Verlicchi et al., 2010a). In fact, although co-treatment with UWWs at a municipal WWTP is a common practice, it has several fundamental drawbacks. Among them, dilution of HWWs with UWWs is undesirable, as some substances in the hospital effluents may cause inhibition of the treatment plant biomass and thereby reduce the removal efficiency. Moreover, hospitals contain pathogens like viruses and bacteria, whose removal before entering the sewer system could be a matter of importance (Czekalski et al., 2012, Chèvre et al., 2013). At the same time, a dedicated treatment for hospital effluent may also contribute in reducing the risk of dissemination of resistances to specific antibiotics that was found to be higher in hospital effluent rather than in urban wastewater (PILLS Project, 2012).

5. Conclusions

The proposed framework allows to predict the impact of a hospital effluent on the environment taking in account the characteristics of the catchment area in which the hospital is situated. It could help decision-makers and technicians in the phase of discussion of how to

better manage and treat the effluent of a hospital and that of the surrounding area in order to reduce the environmental impact posed by residues of pharmaceuticals in raw wastewaters.

The risk posed by HWWs due to the presence of PhCs might be reduced by various degrees, depending on the characteristics of each catchment area where the hospital is situated. In some cases, the pathways of HWWs contribute significantly to the risk in the influent of a site-specific WWTP, due to the resulting PhC loads and concentrations, and their contribution is correlated to the bed density.

Ofloxacin, 17 α -ethinylestradiol, erythromycin and sulfamethoxazole were found to be compounds of potential concern in the HWWs and they require management, while other compounds may not require any management due to their low risk.

As the number of PhCs included in the Database of the framework could be increased based on data availability and related concerns and further wastewater treatment steps could be included (by adding the expected removal efficiencies achieved), the proposed framework could be amended covering a wider spectrum of compounds and treatment scenarios.

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