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Hospital effluent: Investigation of the concentrations and distribution of pharmaceuticals and environmental risk assessment

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ABSTRACT

A study was conducted in an area in north, Italy, on the effluent of two different sized hospitals and the influent and effluent of the receiving municipal treatment plant of one of the examined hospitals. The aim was to investigate 73 selected pharmaceuticals, belonging to twelve different classes, comparing their occurrence in the effluent directly exiting the hospital with that, mixed with the local urban effluent, at the point of its entry and exit from the treatment plant.

Consistent differences were found in the concentrations of some antibiotics, analgesics and lipid regulators in the two wastewaters, confirming that hospital effluents should not be considered as possessing the same pollutant nature as urban wastewater. Furthermore, analysis of percentage contributions of the hospital to the treatment plant influent evidences that hospitals represent one of the main sources of pollutants, in particular antibiotics, receptor antagonists and lipid regulators.

Hence, an environmental risk assessment, performed on the effluent from the hospital and the influent and effluent from the treatment plant, revealed a high risk for 9 pharmaceuticals in hospital effluent and for 4 of the 9 substances in the treatment plant influent and effluent, with antibiotics being the most critical compounds in terms of contribution and potential environmental risk for the hospital.

1. Introduction

During recent years, the issue of pharmaceutical compounds (PhCs) in wastewater has become a major concern in terms of both human health and the environment. This has prompted the launch of several monitoring studies into the most commonly administered compounds in urban wastewater (Lishman et al., 2006; Santos et al., 2007; Terzic et al., 2009) and surface water (Kolpin et al., 2002).

However, a considerably smaller number of studies have been devoted to characterizing PhCs sources, mainly hospital effluents (Boillot et al., 2008; Kosma et al., 2010; Kummerer, 2001; Sim et al., 2011). In fact, in quite all countries worldwide, no distinction is usually made between these wastewaters and urban effluent, and they, along with their potentially hazardous loads, are generally discharged directly into the public sewage network and conveyed for co-treatment at the nearest municipal wastewater treatment plant (WWTP).

Nonetheless, considering the multiple research and laboratory activities carried out in these structures, as well as the treatments performed and pharmaceuticals administered and excreted within them, a wide range of concentrations of hazardous substances may be present in hospital effluent (Verlicchi et al., 2010). Hospital wastewaters are composed of the effluents of different services: kitchen, internal laundry, heating and cooling systems, laboratories, radiology departments, outpatients departments, transfusion centres and wards. Due to the nature and quantity of the micro-pollutants they harbor, such as active substances of medicines and their metabolites, chemicals, heavy metals, disinfectants, sterilizers, and radioactive markers, which are typically present at concentrations of μg/L, they should be earmarked for special consideration. Previous studies investigated the occurrence in hospital effluents of detergents, disinfectants, organic compounds (alcohols, acetone, formaldehyde, acetaldehyde, phenols) and several metals (Emmanuel et al., 2005; Boillot et al., 2008) and the proliferation of drug-resistant microorganisms (Hawkshead, 2008). The issue of PhC occurrence in hospital effluents has already been investigated by different Authors, among them Thomas et al., 2007; Gomez et al., 2006; Mahnik et al., 2007; Suarez et al., 2009; Kummerer, 2001.

It would therefore be of interest to discover the percentage contributions of PhCs from hospitals to those in the total municipal WWTP influent, in order to discover whether specific treatments for hospital effluent are necessary to reduce environmental contamination by persistent and hazardous micropollutants. To date, however, very

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little data on this topic has been reported in the literature (Beier et al., 2011; Heberer and Feldmann, 2005; Langford and Thomas, 2009; Ort et al., 2010; Thomas et al., 2007), and those studies have been conducted to a limited number of compounds.

In order to investigate the differences between hospital and urban wastewaters, an assessment of the (acute and chronic) risk posed to aquatic organisms by the two effluents would be advisable. In fact, although the ecotoxicological effect of PhCs in treated urban wastewaters has been investigated (Ferrari et al., 2003; Kostich and Lazorchak, 2008), once again, very little data is available regarding hospital effluent, and what is available generally relies on predicted, rather than measured, concentrations (Escher et al., 2011).

Therefore, in this study we set out to investigate the occurrence of 73 common PhCs from 12 different therapeutic classes in the effluent of two hospitals (medium-sized and large) in a town in the Po Valley, north Italy, and in the influent and effluent of the local municipal WWTP, which also receives and co-treats the wastewater from the larger hospital. The aims of the study were: (i) to compare the PhC concentrations discharged by the two hospitals over the same period, (ii) to evaluate the PhCs discharged by the large hospital over two different periods, (iii) to compare these concentrations with those found in the influent to the WWTP during the same period, (iv) to evaluate the contribution, in terms of the compounds detected, of the large hospital to the total influent to the WWTP, and finally (v) to assess and compare the potential environmental risk of hospital effluent and WWTP influent by evaluating the ratio between the measured environmental concentration (MEC) and the predicted no-effect concentration (PNEC) for these wastewaters.

In this way, our study attempts to provide an initial assessment of these issues with a view to comparing the chemical and ecotoxicological characteristics of hospital effluent with those of the influent to the WWTP charged with co-treating hospital wastewater.

2. Experimental materials and methods

2.1. The two hospitals and WWTP under investigation

Hospital A: it is a medium-sized hospital with 300 beds, 650 members of staff and twelve main wards. It is situated in a small urban settlement (5000 inhabitants), few km from the sea, in a coastal area that is densely populated in summertime due to tourist influx (in the peak months of July and August, the population is seven times higher than the resident one). Hospital flow rate is regularly monitored by the internal Water and Wastewater Network Managing Body. The resulting average flow rate is equal to 160 $m^3\ d^{-1}$, corresponding to a specific water consumption of about 550 $L\ bed^{-1}\ d^{-1}$.

Hospital B: it is a large hospital with 900 beds, 2000 members of staff and a total of over 50 wards and departments. It is located in the centre of a town (135 000 inhabitants) and its effluent is directly discharged into the combined sewage network, conveyed to the large municipal WWTP and co-treated with the urban WWs. Hospital B flow rate is regularly monitored by the internal Water and Wastewater Network Managing Body. The resulting average flow rate is equal to 603 $m^3\ d^{-1}$, corresponding to a specific water consumption of about 670 $L\ bed^{-1}\ d^{-1}$, and its bed density, that is the number of beds per 1000 inhabitants, is roughly 6.5.

The large municipal WWTP: designed for 120 000 population equivalent (pe), it performs preliminary treatments (screening and grit removal), a biological treatment and a final NaClO disinfection step. The biological treatment consists of a conventional activated sludge system including denitrification ($V = 4000\ m^3$) and nitrification ($V = 6100\ m^3$) steps, followed by secondary sedimentation ($V = 6000\ m^3$). It operates at a low-to-medium load, at an average hydraulic retention time of 6 h, a sludge age of 8 d and a mixed liquor concentration of approximately 3.5 $kg\ m^{-3}$. The WWTP influent flow rate is on average 28 000 $m^3\ d^{-1}$, and Hospital B contributes roughly 2% of the influent hydraulic load.

2.2. Target compounds

The 73 PhCs under investigation are reported in Table 1, grouped according to their therapeutic class. These compounds were selected due to their high prescription rates or volumes, the availability of a reliable analysis methods (Gros et al., 2006), as well as due to their occurrence and ubiquity in the aquatic environment (Bell et al., 2011; Daughton and Ternes, 1999; Fatta-Kassinos et al., 2011; Pal et al., 2010). The selected compounds represent the most consumed within their corresponding therapeutical class. It is quite evident that analgesics and anti-inflammatories are the groups most investigated, followed by beta-blockers and lipid regulators.

2.3. Sampling sites and sample preparation

Four sampling points were monitored: the effluents from Hospitals A and B and the influent and the effluent of the large municipal WWTP. Two experimental campaigns were carried out in August 2009 (summer) and in March 2010 (winter). In the first period, water samples were taken from the raw effluent of Hospital A ($n = 4$) and Hospital B ($n = 4$), while in the second one, from the effluent of Hospital B ($n = 4$) and the influent and the effluent of the large municipal WWTP ($n = 4$).

Manholes located on the property line of each hospital were selected as sampling points, based on their suitability for covering all of the sewage discharges from the facility. Portable auto samplers (Sigma 900) were used to collect samples from each sampling point.

24-hour composite water samples were collected over four days on each sampling point at a rate of one sample per hour (a total of 24 sub-samples, 125 mL each were collected over 24 h). To insure representative sampling and consistency in the estimation of the mass loadings at the differing locations, identical sampling strategies (the same sampling frequencies) were used for both Hospital B effluent and WWTP influent. Water samples were collected only in dry days in order to avoid dilution effects. Wastewater samples were collected in amber glass bottles, pre-rinsed with ultra-pure water, as 24-h composite samples. The samples were immediately transported to the near laboratory under cooled conditions (4 °C). Upon reception, samples were filtered through 0.45 μm Nylon filters (Whatman, Maidstone, UK) to eliminate suspended solid matter and then frozen until analysis (less than a week) at −20 °C. It is important to observe that the fraction of the selected pharmaceutical sorbed onto the suspended solids is removed during preparation phase and, as a consequence, the values of (measured) concentrations found correspond to the dissolved fraction of the investigated compounds.

2.4. Standards

All standard solutions used were of a high purity grade (>90%). Isotopically labelled compounds, used as internal standards, were: ^{13}C-phenacetin, fluoxetine-d_5 and flumequine from Sigma-Aldrich (Steinham, Germany), sulfathiazole-d_4 from Toronto Research Chemicals, diazepam-d_5 and phenobarbital-d_5 from Cerilliant (Texas, USA), atenolol-d_7, carbamazepine-d_{10}, ibuprofen-d_3 from CDN isotopes (Quebec, Canada) and mecoprop-d_3 from Dr. Ehrenstorfer (Augsburg, Germany).

Both individual stock standard and isotopically labelled internal standard solutions were prepared on a weight basis in methanol, except fluoroquinolones, which were dissolved in a water:methanol mixture (1:1) containing 0.2% v/v hydrochloric acid (Golet et al., 2002). After preparation, standards were stored at −20 °C.

Due to their limited stability, fresh stock solutions of antibiotics were prepared monthly, while stock solutions for the other substances were renewed every three months.

Table 1
Investigated pharmaceutical compounds grouped according to therapeutic class.

	Therapeutic class	Compounds
A	Analgesics/anti-inflammatories	Acetaminophen, codeine, diclofenac, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, phenazone, phenylbutazone, propyphenazone, salicylic acid
B	Antibiotics	Azithromycin, chloramphenicol, chlortetracycline, ciprofloxacin, clarithromycin, danofloxacin, doxycycline, enoxacin, enrofloxacin, erythromycin, josamycin, metronidazole, nifuroxazide, norfloxacin, ofloxacin, oxytetracycline, roxythromycin, spiramycin, sulfadiazine, sulfamethazine, sulfamethoxazole, tetracycline, tilmicosin, trimethoprim, tylosin A
C	Anti-diabetics	Glibenclamide
D	Anti-hypertensives	Enalapril, hydrochlorothiazide, lisinopril
E	Barbiturates	Butalbital, pentobarbital, phenobarbital
F	Beta-agonists	Clenbuterol, salbutamol
G	Beta-blockers	Atenolol, betaxolol, carazolol, metoprolol, nadolol, pindolol, propranolol, sotalol, timolol
H	Diuretics	Furosemide
I	Lipid regulators	Atorvastatin, bezafibrate, clofibric acid, fenofibrate, gemfibrozil, mevastatin, pravastatin
J	Psychiatric drugs	Carbamazepine, diazepam, fluoxetine, lorazepam, paroxetine
K	Receptor antagonists	Cimetidine, famotidine, loratadine, ranitidine
L	Antineoplastics	Tamoxifen

A mixture of all pharmaceuticals was prepared by appropriate dilution of individual stock solutions in methanol–water (25:75, v/v). Working standard solutions, also prepared in a methanol–water (25:75, v/v) mixture, were renewed before each analytical run. A separate mixture of isotopically labelled internal standards, used for internal standard calibration, was prepared in methanol, and further dilutions in methanol–water (25:75, v/v) mixture.

2.5. Analytical methods

The multiresidue analytical method developed by Gros et al. (2009) was used to measure the selected pharmaceuticals in wastewaters. Briefly, after filtration, an appropriate volume of aqueous solution of 5% Na2EDTA were added to 200 mL of WWTP effluent and 100 mL of influent (hospital and urban) wastewaters, respectively, to achieve a final Na2EDTA concentration of 0.1% in the samples. The measured volumes were afterwards preconcentrated onto a lipophilic–hidrophilic balanced Oasis HLB (60 mg and 3 mL) cartridge, using a Baker vacuum system (J.T. Baker, Deventer, The Netherlands) at a flow rate of 5 mL/min. After sample preconcentration, cartridges were rinsed with 5 mL of HPLC grade water and were dried under vacuum for 15–20 min, to remove excess of water. Elution of target compounds was performed with 2×4 mL pure methanol. Extracts were evaporated to dryness under a gentle nitrogen stream and reconstituted with 1 mL of methanol–water (25:75, v/ v). Finally, 10 μL of a 1 ng/μL standard mixture containing the internal standards were added in the extract for internal standard calibration. Instrumental analysis was performed by liquid chromatography, using an Agilent HP 1100 HPLC (Palo Alto, CA, USA) system, equipped with an auto sampler and connected in series with a 4000 QTRAP hybrid triple quadrupole-linear ion trap mass spectrometer operating with a Turbo Ion Spray source (Applied Biosystems-Sciex, Foster City, CA, USA). Chromatographic separation was achieved with a Purospher Star RP-18 endcapped column (125 mm × 2.0 mm, particle size 5 μm) preceded by a C18 guard column (4×4.5 μm), both supplied by Merck (Darmstadt, Germany). For the analysis in NI mode , eluent A was a mixture of acetonitrile–methanol (1:1, v /v) and eluent B was HPLC grade water at a flow rate of 0.2 mL/min, where as the analysis in PI mode was performed using acetonitrile as eluent A and HPLC grade water with 0.1% formic acid as eluent B.

Supplementary Data provides details of the optimized QqLIT-MS parameters (two SRMs, collision energies) for each investigated compound in negative and positive ionization modes (Table SD-1).

Limits of detection (LOD) for the investigated compounds were in the range 1–16 ng/L for the WWTP influent and the effluent form the two hospitals and in the range 1–18 ng/L for the WWTP effluent. Table 2 reports the values for each selected substance.

Recoveries of the methods were determined by analyzing fortified samples of each type of wastewater spiked in triplicate to 1 μg/L. They were in the range 22–145%. The single values with relative standard deviation (RSD) are reported in Table 2.

2.6. Risk quotients (RQ) and ecotoxicological risk assessment

The potential risk of PhCs was assessed by means of their risk quotient values (RQ), calculated as the ratio between their MEC and PNEC. PNEC values were estimated on the basis of toxicity data reported for several aquatic organisms: bacteria, algae, invertebrates and fish (Table SD-2 in the Supplementary Data). According to (EC, 2003; Tauxe-Wuersch et al., 2005), PNEC values were estimated as 1000 times lower than the most sensitive species assayed (marked in bold in Table SD-2), so as to take into account the effect on other, potentially more sensitive, aquatic species to those used in toxicity studies. A commonly used risk ranking criterion was applied: $RQ<0.1$, minimal risk to aquatic organisms, $0.1\leq RQ<1$, median risk; $RQ\geq1$, high risk (De Souza et al., 2009; Hernando et al., 2006; Zhao et al., 2010).

3. Results and discussion

Table 3 shows the ranges of concentrations and the corresponding average values (in brackets) of the investigated compounds in the effluents from Hospital A (in summer), Hospital B (in summer and in winter) and in the influent and effluent of the large WWTP (in winter). The final row reports the number of compounds detected during the investigation periods (occurrence).

In descending order, the highest occurrence of PhCs was detected in the WWTP influent (63), in Hospital B effluent in winter (62), Hospital A effluent in summer (61) and in the WWTP effluent (58). The lowest number of detected substances was found in the Hospital B effluent in summer (49).

Among the analgesics/anti-inflammatories, also in descending order, the highest average concentrations were found for ketoprofen (5 μg/L), acetaminophen (4.5 μg/L) in Hospital A effluent, acetaminophen (4.1 μg/L) and indomethacin (2.2 μg/L) in Hospital B effluent in summer, naproxen (4.9 μg/L) and ibuprofen (2.6) in Hospital B effluent in winter, ibuprofen (1.0 μg/L) and naproxen (0.83 μg/L) in the WWTP influent, followed by mefenamic acid (0.66 μg/L) and diclofenac (0.28 μg/L) in the WWTP effluent.

Among the antibiotics, the most prevalent compounds were: ofloxacin (19 μg/L) and ciprofloxacin (12 μg/L) in Hospital A effluent, ofloxacin (3.7 μg/L) and sulfamethoxazole (1.8 μg/L) in Hospital B effluent in summer, ofloxacin (31 μg/L) and sulfamethoxazole (21 μg/L) in Hospital B effluent in winter, ciprofloxacin (2.2 μg/L) and ofloxacin

Table 2
Recovery and limits of detection (LOD) of the selected compounds.

Therapeutic class	Compound	% Recovery (±RSD)					LOD (ng/L)				
		Hospital A (summer)	Hospital B (summer)	Hospital B (winter)	WWTP infl (winter)	WWTP effl (winter)	Hospital A (summer)	Hospital B (summer)	Hospital B (winter)	WWTP infl. (winter)	WWTP effl. (winter)
Analgesic/anti-inflammatories A	Acetaminophen	92 (±3)	121 (±1)	96 (±4)	131 (±9)	80 (±15)	2	3	7	11	8
	Codeine	86 (±8)	78 (±5)	113 (±3)	75 (±6)	94 (±2)	3	3	2	6	7
	Diclofenac	127 (±12)	89 (±3)	78 (±11)	100 (±9)	102 (±5)	4	5	5	2	2
	Ibuprofen	83 (±13)	91 (±7)	105 (±5)	111 (±14)	133 (±8)	8	6	11	9	9
	Indomethacin	80 (±13)	94 (±6)	116 (±1)	103 (±3)	81 (±5)	2	3	3	6	7
	Ketoprofen	55 (±3)	112 (±6)	89 (±8)	62 (±4)	73 (±13)	3	4	7	7	8
	Mefenemic acid	128 (±1)	124 (±5)	95 (±2)	86 (±7)	63 (±15)	6	7	4	5	3
	Naproxen	98 (±4)	118 (±2)	116 (±1)	104 (±1)	95 (±3)	11	5	5	6	3
	Phenazone	100 (±3)	103 (±1)	96 (±15)	85 (±13)	78 (±11)	2	3	8	5	6
	Phenylbutazone	120 (±9)	111 (±4)	81 (±4)	67 (±3)	92 (±16)	3	5	4	6	3
	Propyphenazone	119 (±9)	130 (±3)	104 (±15)	123 (±12)	98 (±21)	2	6	3	2	5
	Salicylic acid	91 (±4)	88 (±8)	78 (±25)	56 (±6)	91 (±7)	12	9	8	11	6
Antibiotics B	Azithromycin	45 (±3)	58 (±1)	85 (±9)	78 (±7)	76 (±13)	3	4	2	2	4
	Chloramphenicol	87 (±13)	95 (±2)	96 (±25)	86 (±1)	78 (±6)	9	8	4	9	7
	Chlortetracycline	56 (±4)	90 (±7)	100 (±8)	56 (±1)	74 (±9)	12	11	8	14	9
	Ciprofloxacin	103 (±3)	62 (±5)	105 (±5)	107 (±7)	123 (±13)	3	4	3	3	2
	Clarithromycin	89 (±23)	95 (±2)	91 (±1)	78 (±6)	121 (±9)	4	3	6	6	2
	Danofloxacin	101 (±9)	109 (±6)	104 (±3)	103 (±4)	95 (±2)	7	8	5	9	3
	Doxycycline	94 (±7)	56 (±3)	67 (±10)	41 (±26)	103 (±3)	11	8	15	16	18
	Enoxacin	120 (±6)	98 (±7)	121 (±4)	133 (±9)	89 (±17)	3	6	5	7	2
	Enrofloxacin	89 (±1)	107 (±3)	88 (±1)	79 (±4)	93 (±3)	4	5	5	2	3
	Erithromycin	99 (±3)	96 (±9)	112 (±16)	103 (±3)	95 (±5)	7	5	8	7	8
	Josamycin	112 (±9)	91 (±4)	87 (±7)	46 (±4)	23 (±8)	3	2	3	2	1
	Metronidazole	37 (±5)	22 (±1)	47 (±9)	56 (±3)	45 (±7)	6	5	3	4	1
	Nifuroxazide	111 (±2)	56 (±4)	79 (±5)	96 (±1)	87 (±1)	11	14	12	9	7
	Norfloxacin	56 (±3)	43 (±9)	112 (±2)	118 (±7)	109 (±1)	8	5	6	6	3
	Ofloxacin	135 (±1)	94 (±7)	79 (±25)	98 (±23)	79 (±1)	1	2	1	1	1
	Oxytetracycline	100 (±23)	105 (±18)	95 (±12)	78 (±8)	45 (±9)	6	8	7	12	15
	Roxithromycin	120 (±1)	94 (±5)	56 (±3)	99 (±9)	78 (±8)	4	5	6	3	2
	Spiramycin	145 (±5)	80 (±4)	98 (±7)	93 (±6)	109 (±11)	2	3	2	3	2
	Sulfadiazine	131 (±6)	45 (±3)	105 (±3)	103 (±4)	56 (±24)	2	4	4	5	7
	Sulfamethazine	56 (±5)	97 (±8)	96 (±9)	124 (±3)	65 (±5)	2	4	5	2	6
	Sulfamethoxazole	73 (±1)	56 (±1)	98 (±3)	87 (±5)	120 (±3)	1	3	2	3	1
	Tetracycline	81 (±7)	85 (±28)	123 (±18)	99 (±5)	95 (±2)	7	9	12	14	13
	Tilmicosin	145 (±3)	103 (±3)	78 (±1)	94 (±1)	82 (±16)	1	2	1	3	6
	Trimethoprim	57 (±7)	51 (±7)	86 (±6)	119 (±11)	88 (±18)	1	1	2	1	1
	Tylosin A	103 (±3)	86 (±8)	107 (±19)	102 (±7)	145 (±1)	2	1	2	3	1
Anti-diabetic C	Glibenclamide	56 (±3)	76 (±1)	98 (±7)	112 (±21)	97 (±15)	3	5	2	4	2
Anti-hypertensives D	Enalapril	92 (±11)	106 (±17)	65 (±8)	93 (±3)	69 (±7)	2	1	3	2	4
	Hydrochlorothiazide	83 (±15)	86 (±19)	100 (±1)	103 (±3)	87 (±9)	6	9	8	12	13
	Lisinopril	91 (±4)	98 (±7)	134 (±8)	111 (±6)	95 (±3)	2	3	12	15	9
Barbiturates E	Butalbital	103 (±3)	56 (±12)	45 (±2)	47 (±1)	69 (±1)	2	1	5	6	3
	Pentobarbital	45 (±7)	51 (±23)	119 (±4)	99 (±19)	103 (±6)	5	2	3	4	3
	Phenobarbital	35 (±1)	48 (±4)	75 (±3)	44 (±8)	26 (±2)	1	1	2	3	2
Beta-agonists F	Clenbuterol	105 (±23)	91 (±7)	95 (±2)	115 (±8)	117 (±7)	2	2	1	1	1
	Salbutamol	80 (±20)	89 (±11)	135 (±1)	97 (±1)	78 (±9)	1	1	1	2	1
Beta-blockers G	Atenolol	34 (±5)	83 (±13)	145 (±8)	58 (±4)	118 (±6)	4	5	11	13	9
	Betaxolol	118 (±3)	56 (±3)	95 (±2)	101 (±1)	120 (±5)	2	3	2	2	1
	Cerazolol	99 (±1)	98 (±7)	92 (±16)	79 (±9)	91 (±6)	1	1	1	2	1
	Metoprolol	113 (±5)	107 (±3)	129 (±1)	136 (±6)	95 (±2)	1	2	1	3	1
	Nadolol	106 (±12)	96 (±9)	90 (±1)	87 (±8)	97 (±3)	2	2	1	1	2
	Pindolol	45 (±3)	75 (±23)	103 (±3)	108 (±9)	49 (±16)	3	1	3	2	4
	Propranolol	69 (±8)	61 (±5)	104 (±1)	70 (±8)	57 (±9)	2	2	1	1	1
	Sotalol	73 (±9)	117 (±19)	110 (±4)	56 (±7)	91 (±7)	3	5	9	8	10
	Timolol	45 (±12)	79 (±3)	62 (±15)	56 (±6)	101 (±14)	2	1	5	3	2
Diuretics H	Furosemide	78 (±19)	59 (±9)	100 (±1)	96 (±7)	92 (±3)	3	5	6	8	9
Lipid regulators I	Atorvastatin	89 (±19)	131 (±12)	111 (±1)	118 (±3)	85 (±3)	1	3	5	3	4
	Bezafibrate	134 (±1)	95 (±1)	97 (±5)	95 (±7)	56 (±3)	1	1	2	2	2
	Clofibric acid	135 (±1)	120 (±7)	108 (±15)	71 (±3)	98 (±7)	1	2	1	1	1
	Fenofibrate	110 (±9)	117 (±18)	92 (±1)	79 (±9)	107 (±3)	2	1	3	1	1
	Gemfibrozil	145 (±1)	64 (±23)	67 (±1)	87 (±5)	96 (±9)	2	3	2	1	1
	Mevastatin	126 (±9)	113 (±2)	110 (±7)	72 (±9)	87 (±9)	5	6	8	9	7
	Pravastatin	114 (±23)	69 (±3)	98 (±1)	90 (±7)	71 (±14)	12	11	9	13	15
Psychiatricdrugs J	Carbamazepine	92 (±19)	68 (±9)	92 (±1)	145 (±8)	111 (±7)	3	4	2	4	5
	Diazepam	101 (±15)	45 (±26)	76 (±12)	103 (±3)	59 (±16)	1	1	2	1	2
	Fluoxetine	139 (±1)	96 (±5)	92 (±6)	109 (±9)	107 (±6)	3	2	2	1	2
	Lorazepam	100 (±3)	123 (±7)	103 (±3)	91 (±1)	98 (±12)	8	7	8	9	11
	Paroxetine	103 (±8)	135 (±15)	87 (±9)	45 (±18)	103 (±3)	2	3	2	2	3
Receptor antagonists K	Cimetidine	103 (±3)	56 (±25)	67 (±3)	78 (±1)	89 (±9)	1	3	3	5	2
	Famotidine	119 (±9)	109 (±13)	92 (±8)	95 (±2)	104 (±6)	2	3	2	4	3
	Loratadine	132 (±3)	79 (±1)	75 (±7)	103 (±3)	98 (±7)	3	1	2	3	2
	Ranitidine	138 (±4)	127 (±15)	94 (±9)	97 (±6)	135 (±1)	8	7	8	11	10
Cytostatic L	Tamoxifen	138 (±1)	65 (±3)	103 (±3)	145 (±2)	92 (±3)	1	1	2	1	1

Table 3
Ranges of concentrations and corresponding average value in brackets of pharmaceuticals in effluents from the two hospitals and in the influent and effluent of the municipal WWTP.

Therapeutic class	Compound, μg/L	Hospital A (summer)	Hospital B (summer)	Hospital B (winter)	WWTP influent (winter)	WWTP effluent (winter)
Analgesics/ anti-inflammatories A	Acetaminophen	3.3–5.9 (4.5)	3.5–4.7 (4.1)	1.4–3.4 (2.5)	0.50–1.2 (0.81)	0.012–0.058 (0.030)
	Codeine	0.26–0.43 (0.36)	0.42–0.64 (0.53)	0.41–3.2 (1.9)	0.09–0.15 (0.11)	0.052–0.082 (0.066))
	Diclofenac	0.17–0.46 (0.30)	0.18–0.27 (0.22)	0.48–0.53 (0.51)	0.36–0.48 (0.44)	0.22–0.33 (0.28)
	Ibuprofen	1.0–2.5 (1.7)	0.38–0.81 (0.60)	2.2–3.2 (2.6)	0.93–1.2 (1.0)	0.010–0.12 (0.081)
	Indomethacin	0.31–4.1 (2.5)	0.90–3.4 (2.2)	0.40–0.61 (0.53)	0.061–0.20 (0.16)	0.06–0.13 (0.10)
	Ketoprofen	2.2–9.8 (5.0)	0.83–1.4 (1.1)	1.1–1.8(1.4)	0.13–0.19 (0.17)	0.056–0.11 (0.085))
	Mefenamic acid	0.18–0.50 (0.33)	0.10–0.13 (0.12)	0.33–0.75 (0.55)	0.56–1.2 (0.90)	0.41–0.91 (0.66)
	Naproxen	1.2–3.2 (2.3)	0.34–0.48 (0.41)	1.1–11 (4.9)	0.78–0.91 (0.83)	0.10–0.21 (0.18)
	Phenazone	<LOD	<LOD	<LOD	<LOD	<LOD
	Phenylbutaz.	0.01–0.05 (0.04)	0.048–0.080 (0.063)	0.12–0.17 (0.14)	0.067–0.13 (0.11)	0.037–0.060 (0.052)
	Propyphen.	<LOD-0.020 (0.011)	<LOD	0.011–0.10 (0.038)	0.038–0.074 (0.053)	0.024–0.068 (0.042)
	Salicylic acid	0.90–1.9 (1.3)	0.99–1.1 (1.0)	1.9–2.4 (2.22)	0.21–1.1 (0.50)	0.11–0.13 (0.12)
Antibiotics B	Azithromycin	<LOD-0.11 (0.030)	0.045–0.050 (0.047)	0.58–1.04 (0.80)	0.01–0.33 (0.13)	0.07–0.18 (0.13)
	Chloramphenicol	<LOD-0.036 (0.012)	<LOD	<LOD-0.01 (0.078)	0.013–0.024 (0.019)	<LOD
	Chlortetracycline	0.02–0.06 (0.04)	0.063–0.094 (0.077)	<LOD	<LOD	<LOD
	Ciprofloxacin	10–15 (12)	1.4–1.9 (1.6)	15–26 (21)	1.1–3.7 (2.2)	0.29–1.1 (0.64)
	Clarithromycin	0.02–0.14 (0.06)	0.050–0.064 (0.058)	9.3–14 (11)	0.11–0.78 (0.31)	0.26–0.31 (0.28)
	Danofloxacin	<LOD	<LOD	<LOD	<LOD	<LOD
	Doxycycline	0.10–0.27 (0.17)	0.056–0.97 (0.078)	<LOD	<LOD	<LOD
	Enoxacin	0.33–0.48 (0.41)	0.058–0.10 (0.080)	0.18–0.45 (0.27)	0.081–0.13 (0.10)	0.03–0.10 (0.061)
	Enrofloxacin	<LOD	<LOD	<LOD	<LOD	<LOD
	Erythromycin	0.06–0.32 (0.16)	0.080–0.086 (0.082)	0.091–0.23 (0.16)	0.010–0.072 (0.045)	0.010–0.033 (0.016)
	Josamycin	<LOD-0.012 (0.003)	0.011–0.015 (0.012)	<LOD-0.01 (0.01)	<LOD −0.007 (0.0020)	<LOD
	Metronidazole	0.33–1.64 (0.72)	0.26–0.39 (0.033)	0.85–1.1 (0.96)	0.028–0.056 (0.042)	0.013–0.041 (0.028)
	Nifuroxazide	0.10–2.56 (1.4)	0.10–0.16 (0.14)	0.22–0.33 (0.29)	0.019–0.076 (0.052)	0.010–0.022 (0.013)
	Norfloxacin	0.04–0.10 (0.07)	0.023–0.044 (0.034)	0.22–0.51 (0.35)	0.15–0.31 (0.020)	0.14–0.17 (0.15)
	Ofloxacin	13–22 (19)	3.3–4.1 (3.7)	25–37 (31)	0.45–2.2 (1.0)	0.22–0.52 (0.39)
	Oxytetracycline	0.30–1.3 (0.78)	0.074–0.10 (0.089)	<LOD	<LOD	<LOD
	Roxithromycin	<LOD	<LOD	0.02–0.14 (0.079)	<LOD-0.14 (0.063)	0.013–0.053 (0.029))
	Spiramycin	<LOD-0.040 (0.010)	<LOD	0.034–0.11 (0.068)	<LOD-0.15 (0.061)	0.019–0.053 (0.029)
	Sulfadiazine	0.029–0.033 (0.032)	0.077–0.12 (0.10)	0.27–0.38 (0.33)	0.013–0.026 (0.022)	0.010–0.021 (0.017)
	Sulfamethazine	<LOD-0.014 (0.0070)	<LOD	0.013–0.03 (0.023)	0.010–0.033 (0.018)	0.010–0.015 (0.011)
	Sulfamethoxazole	3.0–6.5 (4.2)	0.90–2.7 (1.8)	0.94–3.4 (2.0)	0.28–0.74 (0.44)	0.17–0.24 (0.21)
	Tetracycline	<LOD-0.026 (0.014)	<LOD-0.033 (0.017)	<LOD	<LOD	<LOD
	Tilmicosin	0.05–0.07 (0.06)	0.014–0.020 (0.015)	0.12–0.35 (0.26)	0.021–0.46 (0.25)	<LOD-0.081 (0.036)
	Trimeth.	0.80–1.8 (1.2)	0.45–0.86 (0.65)	0.068–0.36 (0.18)	0.039–0.072 (0.058)	0.036–0.051 (0.040)
	Tylosin A	<LOD	<LOD	<LOD	<LOD	<LOD
Anti-diabetics C	Glibenclamide	0.05–0.10 (0.07)	0.066–0.071 (0.068)	0.072–0.11 (0.10)	0.081–0.96 (0.087)	0.01–0.08 (0.055)
Anti-hypertensives D	Enalapril	0.15–0.27 (0.20)	0.091–0.18 (0.13)	0.24–0.40 (0.31)	0.071–0.10 (0.082)	<LOD
	Hydrochlorotiazide	1.3–2.1 (1.8)	0.54–0.82 (0.68)	1.8–2.4 (2.2)	1.4–5.5 (2.7)	0.97–1.4 (1.2)
	Lisinopril	0.08–0.61 (0.25)	0.089–0.34 (0.21)	<LOD	<LOD	<LOD
Barbiturates E	Butalbital	0.014–0.038 (0.022)	0.011–0.052 (0.032)	0.25–0.48 (0.36)	0.072–0.25 (0.13)	0.090–0.13 (0.10)
	Pentobarbital	0.011–0.074 (0.035)	0.014–0.025 (0.019)	0.11–0.15 (0.13)	0.021–0.043 (0.021)	0.01–0.028 (0.018))
	Phenobarbital	<lod-0.029 (0.0014)	0.013–0.030 (0.021)	0.13–0.36 (0.25)	0.11–0.27 (0.21)	0.11–0.17 (0.14)
Beta-agonists F	Clenbuterol	<LOD	<LOD	0.86–1.19 (1.1)	0.22–0.29 (0.26)	0.13–0.21 (0.18)
	Salbutamol	0.04–0.10 (0.062)	0.026–0.030 (0.028)	0.10–0.14 (0.12)	0.011–0.020 (0.013)	0.010–0.017 (0.012)
Beta-blockers G	Atenolol	3.5–6.2 (5.1)	2.2–2.6 (2.4)	5.1–6.6 (5.8)	1.8–2.4 (2.1)	0.55–0.98 (0.073)
	Betaxolol	<LOD-0.020 (0.011)	<LOD	<LOD-0.01 (0.01)	<LOD-0.007 (0.002)	<LOD
	Cerazolol	<LOD	<LOD	<0.0018–0.0023 (0.002)	<LOD-0.01	<LOD
	Metoprolol	0.58–0.99 (0.83)	0.51–0.97 (0.74)	0.86–1.2 (1.1)	0.22–0.29 (0.26)	0.13–0.21 (0.18)
	Nadolol	<LOD	<LOD	<LOD-0.0034 (0.0012)	<LOD-0.016 (0.011)	<LOD
	Pindolol	0.032–0.26 (0.12)	<LOD	0.034–0.048 (0.038)	<LOD-0.011 (0.0030)	<LOD
	Propranolol	<LOD-0.051 (0.023)	0.076–0.094 (0.085)	0.030–0.061 (0.043)	0.014–0.045 (0.026)	0.013–0.026 (0.018)
	Sotalol	3.8–5.9 (4.8)	0.35–0.61 (0.048)	3.3–6.7 (5.1)	0.37–0.64 (0.53)	0.21–0.47 (0.32)
	Timolol	<LOD	<LOD	0.022–0.039 (0.033)	0.010–0.016 (0.014)	<LOD-0.013 (0.010)
Diuretics H	Furosemide	11–18 (14)	6.4–7.7 (7.1)	5.3–6.3 (5.8)	0.39–0.47 (0.42)	0.08–0.35 (0.27)
Lipid regulators I	Atorvastatin	0.062–0.10 (0.083)	0.080–0.17 (0.13)	0.24–0.31 (0.27)	<lod −0.018 (0.011)	<LOD-0.010 (0.0060)
	Bezafibrate	0.057–2.9 (0.95)	<LOD	0.042–0.51 (0.20)	0.063–0.12 (0.090)	0.011–0.048 (0.036)
	Clofibric acid	<LOD-0.043 (0.017)	<LOD	0.010–0.014 (0.013)	<LOD-0.012 (0.010)	<LOD-0.0060 (0.0020)
	Fenofibrate	<LOD-0.026 (0.010)	<LOD	<LOD	<LOD-0.020 (0.0060)	<LOD-0.013 (0.0030)
	Gemfibrozil	0.018–0.020 (0.019)	<LOD	0.014–0.064 (0.033)	0.16–0.28 (0.20)	0.04–0.17 (0.11)
	Mevastatin	0.38–2.0 (1.1)	0.45–0.53 (0.49)	0.068–0.20 (0.015)	0.12–0.28 (0.17)	0.03–0.14 (0.083)
	Pravastatin	0.19–1.1 (0.62)	0.064–0.080 (0.077)	0.081–0.27 (0.17)	0.080–0.14 (0.11)	0.04–0.07 (0.54)
Psychiatric drugs J	Carbamazepine	0.64–0.87 (0.73)	0.76–1.2 (0.97)	0.75–1.1 (0.95)	0.30–1.17 (0.58)	0.28–0.44 (0.37)
	Diazepam	<LOD	<LOD	0.021–0.038 (0.031)	0.002–0.010 (0.076)	<LOD
	Fluoxetine	<LOD-0.018 (0.005)	0.024–0.033 (0.027)	0.035–0.069 (0.056)	0.055–0.19 (0.11)	0.010–0.063 (0.044)
	Lorazepam	0.62–0.79 (0.67)	0.17–0.20 (0.18)	0.46–0.70 (0.060)	0.17–0.25 (0.22)	0.08–0.14 (0.12)
	Paroxetine	<LOD	<LOD	0.056–0.076 (0.067)	0.020–0.080 (0.041)	0.010–0.018 (0.013)
Receptor antagonists K	Cimetidine	0.019–0.032 (0.026)	<LOD	0.033–0.26 (0.11)	0.029–0.061 (0.047)	0.012–0.049 (0.031)
	Famotidine	0.087–0.29 (0.16)	0.035–0.048 (0.042)	0.075–0.13 (0.10)	0.010–0.022 (0.014)	<LOD-0.0040 (0.0020)
	Loratadine	<LOD-0.014 (0.003)	<LOD	0.015–0.026 (0.020)	<LOD-0.020 (0.013)	<LOD-0.0050 (0.003)
	Ranitidine	0.24–2.2 (1.5)	1.1–1.5 (1.3)	1.4–4.1 (3.0)	0.093–0.13 (0.11)	0.04–0.10 0.078)
Cytostatic agents L	Tamoxifen	<LOD	<LOD	<LOD	<LOD	<LOD
	Occurrence, no.	*61*	*49*	*62*	*63*	*58*

(1.0 μg/L) in the WWTP influent, followed by ciprofloxacin (0.64 μg/L) and clarithromycin (0.28 μg/L) in the WWTP effluent.

Hydrochlorothiazide was the most present anti-hypertensive at the four sampling points, being detected at concentrations of 1.8 μg/L in Hospital A effluent, 0.68 μg/L in Hospital B effluent (summer), 2.2 μg/L in Hospital B effluent (winter), 2.7 μg/L in the WWTP influent, and 1.2 μg/L in the WWTP effluent.

Among the barbiturates, pentobarbital had the highest concentrations in Hospital A effluent (0.035 μg/L), and butalbital the highest concentrations in Hospital B effluent in summer (0.032 μg/L) and winter (0.36 μg/L), while phenobarbital was most prevalent in the WWTP influent (0.21 μg/L) and effluent (0.14 μg/L).

Salbutamol was the beta-agonist with the highest concentration in the effluent of Hospital A (0.062 μg/L) and Hospital B in summer (0.028 μg/L), whereas clenbuterol had the highest concentrations in Hospital B effluent in winter (0.18 μg/L).

The most represented beta blockers were: atenolol at 5.1 μg/L and sotalol at 4.8 μg/L in Hospital A effluent, and atenolol 2.4 μg/L in Hospital B effluent in summer; in winter atenolol was detected at 5.8 μg/L and sotalol at 5.1 μg/L in Hospital B effluent, while in the WWTP influent, atenolol was found at 2.1 μg/L and sotalol at 0.53 μg/L, in contrast with the 0.32 μg/L sotalol and 0.073 μg/L atenolol detected in the WWTP effluent.

Among the lipid regulators, those with the highest concentrations were mevastatin in Hospital A effluent (1.1 μg/L) and in Hospital B effluent in summer (0.49 μg/L), atorvastatin in Hospital B effluent in winter (0.27 μg/L), and gemfibrozil in the WWTP influent (0.20 μg/L) and effluent (0.11 μg/L).

The psychiatric drug carbamazepine and the receptor antagonist ranitidine displayed the highest concentrations of their type at all the sampling points.

There are limited data that allow for a comparison referring to PhC occurrence in hospital effluents, however Verlicchi et al. (2010) reviewed the variability ranges for some compounds of different therapeutic classes in raw hospital wastewater. Based on these findings, measured concentrations for PhCs in Hospital A and B effluents are in agreement with those reported in Verlicchi et al. (2010), except for erythromycin (measured concentrations are 2 order of magnitude lower than those of the review), propranolol and gemfibrozil (1 order of magnitude lower).

More literature data are available regarding the presence of PhCs in urban wastewaters. A comparison with the variability intervals found in different countries by Jelicic and Ahel (2003), Kasprzyk-Hordern et al. (2009), Radjenovic et al. (2009), Roberts and Thomas (2006), Rosal et al. (2010), Sipma et al. (2010), Sui et al. (2010) and Verlicchi et al. (2010) shows that measured concentrations in the influent of the municipal WWTP is in good agreement with them except for codeine, erythromycin, propranolol and cimetidine that were at a concentrations of 1 order of magnitude lower than those reported by literature.

On the basis of the concentration data reported above, the following comparisons were made between: the two hospital effluents in summer, the effluent of Hospital B in summer and winter, and Hospital B effluent and WWTP influent (which, in addition to urban wastewater, receives that of Hospital B) in winter.

3.1. Comparison of PhC concentrations in the effluent from Hospitals A and B in summer

Data reported in Table 3 show that, for the majority of the compounds considered, concentrations were higher in the effluent of Hospital A than those in that of Hospital B. Only 12 out of the 73 investigated PhCs, codeine, phenylbutazone, azithromycin, chlortetracycline, josamycin, sulfadiazine, butalbital, phenobarbital, propranolol, atorvastatin, carbamazepine and fluoxetine, were detected in lower concentrations in Hospital A effluent than those found in Hospital B.

The relatively large dose/population ratios detected in Hospital A could be due to the fact that: (*i*) Hospital A is situated in a coastal area, densely populated by tourists in the summertime, the period in which the water samples were taken; thus, analyses may reflect that a higher consumption of PhCs than average occurred; and/or (*ii*) Hospital A has a lower daily water demand, resulting in lesser dilution of the micropollutants present.

3.2. Comparison between summer and winter concentrations of PhCs in Hospital B effluent

Data of Table 3 show that 49 compounds were detected in summer and 62 in winter. Five compounds were found only in summer and 18 only in winter. Only 6 compounds (phenazone, danofloxacin, enrofloxacin, tylosin A, fenofibrate and tamoxifen) were not detected at either sampling point at any time. Of the 44 compounds found at least in one sampling point, the winter concentrations were, on average, greater than those detected in the summer, with their ratio ranging between 1.1 (sulfamethoxazole) and 190 (clarithromycin), with an average value of 10.4, a standard deviation of 31.3, and a 95th-percentile equal to 16.9. Only 2 anti-inflammatories (acetaminophen and indomethacin), 5 antibiotics (chlortetracycline, doxycycline, josamycin, oxytetracycline, tetracycline and trimethoprim), the anti-hypertensive lisinopril, the beta-blocker propanolol, the diuretic furosemide, the lipid regulator mevastatin and the psychiatric drug carbamazepine were found at 1.3–4 times higher summer concentrations than those detected in the winter (on average 2.3 times).

3.3. Comparison between winter concentrations of PhCs in Hospital B effluent and WWTP influent

The data reported in Table 3 show that average concentrations of PhCs in Hospital B effluent were higher than those found in the influent of the municipal WWTP, with the exception of two analgesics/anti-inflammatories (mefenamic acid and propyphenazone), two antibiotics (chloramphenicol and roxythromycin), the anti-hypertensive hydrochlorothiazide, three beta-blockers (betaxolol, cerazolol and nadolol), two lipid regulators (gemfibrozil and mevastatin) and one psychiatric drug (fluoxetine).

As regards the other compounds, the ratio between Hospital B effluent and WWTP influent concentrations ranged between 1.03 and 35.5, with an average value of 7, standard deviation of 8.5 and 95th-percentile of 27.

3.4. Contribution of Hospital B loads to WWTP influent

Table 4 reports the percentage average contribution of Hospital B to the load of the investigated compounds in WWTP influent.

Compounds were classified according to the average percentage contributions ($\leq$5%, 5–15%, $>$15%). Hospital contributions were $\leq$5% for 32 substances, between 5 and 15% for 18 compounds and $>$15 for 12 PhCs (7 antibiotics, 2 receptor antagonists, 1 analgesic, 1 diuretic and 1 lipid regulator). The highest contributions were found for ofloxacin (67%), azithromycin (67%), clarithromycin (53%), ranitidine (52%) and metronidazole (45%). This confirms that antibiotics represent a critical class of compound, as reported in Verlicchi et al. (in press), due to their high consumptions inside the hospital and their stability once excreted.

Unfortunately, little data is available in the literature for comparison with our findings. Nevertheless, what little data is available is reported here below (Table 4). For instance, (Thomas et al., 2007; Langford and Thomas, 2009), evaluated the PhC contributions originating from the two main hospitals (in total 1800 beds) in the area of Oslo (440 000 inhabitants), Norway, with a bed density of 4 and (Ort et al., 2010), evaluated the contributions for a 200-bed Australian hospital with a catchment area of 45 000 people (bed density = 4.4). In Germany, (Heberer and Feldmann, 2005), analyzed contributions from the Berlin hospitals (12 000 beds) and their catchment area

Table 4
Hospital B average percentage contributions for the detected compounds with respect to the WWTP influent loads and comparison with other studies.

Classification	Compound	PhC Class	This study	Heberer and Feldmann (2005)	Thomas et al. (2007)	Langford and Thomas (2009)	Ort et al. (2010)	Beier et al. (2011)
Bed density			6.5	12	4	4	4.4	33.5
Contribution ≤ 5%	Betaxolol	G	0.99					
	Chloramphenicol	B	1.1					
	Gemfibrozil	I	1.2				4.1	
	Propyphenazone	A	1.4					
	Hydrochlorothiazide	D	1.7					
	Nadolol	G	1.7					
	Mefenamic acid	A	1.8					
	Roxythromycin	B	2.1				26	
	Diclofenac	A	2.1	10	1.6		1	7–9
	Fluoxetine	J	2.3					
	Sulfamethazine	B	2.3					
	Pravastatin	I	2.4					
	Glibenclamide	C	2.4					
	Cerazolol	G	2.4					
	Carbamazepine	J	2.5	15		1.7	0.4	3–8
	Mevastatin	I	2.5					
	Phenobarbital	E	2.6					
	Clofibric acid	I	2.6					
	Josamycin	B	3.0					
	Loratadine	K	3.2					
	Phenylbutazone	A	3.2					
	Trimethoprim	B	3.2		14		10	
	Naproxen	A	3.9				2.3	
	Ibuprofen	A	4.0		0.7		4.6	3–7
	Acetaminophen	A	4.2		12		5.1	
	Butalbital	E	4.3					
	Timolol	G	4.3					
	Enoxacin	B	4.3					
	Norfloxacin	B	4.6					
	Lorazepam	J	4.6					
	Propranolol	G	4.7			11.4		
	Atenolol	G	4.7			2.52	1.8	
5% < Contribution ≤ 15%	Cimetidine	K	5.6					
	Clenbuterol	F	5.7					
	Metoprolol	G	5.7		1.5		4.1	
	Paroxetine	J	5.9			0.5		
	Sulfamethoxazole	B	6.1		1.2		0.8	
	Indomethacin	A	6.2					
	Diazepam	J	6.8					
	Pentobarbital	E	6.8					
	Bezafibrate	I	7.0					27
	Enalapril	D	7.1					
	Erythromycin	B	7.7				2.6	
	Pindolol	G	8.2					
	Nifuroxazide	B	8.5					
	Tilmicosin	B	8.7					
	Salicylic acid	A	11				4.9	
	Sotalol	G	11					
	Ketoprofen	A	14			0.53		
	Salbutamol	F	14.7					
Contribution > 15%	Ciprofloxacin	B	15.5		311			19–36
	Famotidine	K	16					
	Sulfadiazine	B	19					
	Furosemide	H	21				5.8	
	Atorvastatin	I	25			2.3	3	
	Codeine	A	28				1.5	
	Spiramycin	B	28					
	Metronidazole	B	45					84
	Ranitidine	K	52				4.9	
	Clarithromycin	B	53					61–94
	Azithromycin	B	67					
	Ofloxacin	B	67					

(1 million people, bed density = 12) and (Beier et al., 2011), the contributions from Waldbrol hospital (342 beds) and its catchment area (10 200 inhabitants, bed density = 33.5). Their findings are reported in the last four columns of Table 3, which shows that percentage hospital contributions for the detected compounds vary greatly, depending on bed density and the compound in question. Furthermore, differences are evident in the usage patterns of the various PhCs in the different countries, another influential factor. In fact, the highest levels of almost all compounds were found by (Beier et al., 2011); the hospital they studied had the highest bed density (33.5), of all those reported in the literature, thereby indicating the importance of this parameter.

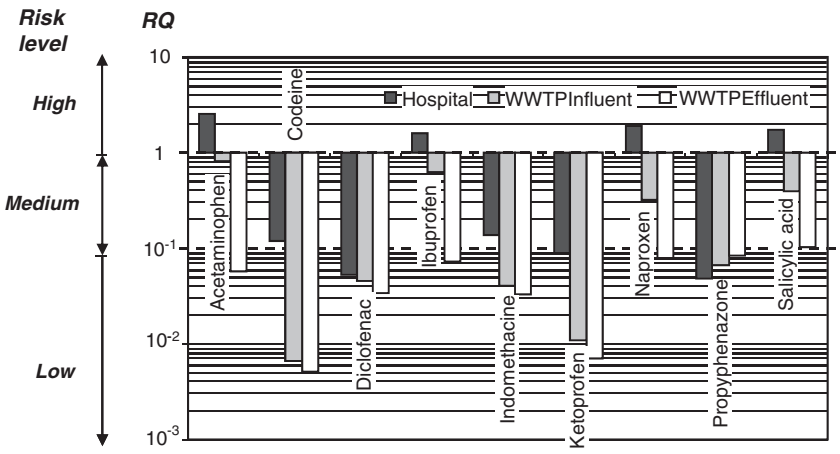

Fig. 1. Risk quotients for analgesic/anti-inflammatories in Hospital B effluent and investigated WWTP influent and effluent.

Another interesting study was conducted by Escher et al., 2011 on a Swiss general hospital (338 beds, average flow rate 115690 m^3/year) whose effluent is conveyed to the near WWTP with conventional biological treatment which serves 54 000 inhabitants. Based on consumption data of the top 40 pharmaceuticals sold in pharmacies, drug stores and doctor's practices, they found that the amount of pharmaceuticals discharged into the WWTP from households totals to 62% of the total pharmaceutical load in the WWTP. Thus the remaining 38% stems from the hospital.

3.5. Environmental risk analysis

A risk analysis was conducted on the effluent of Hospital B and the WWTP influent and effluent (all monitored in winter), using the quotient between the maximum MEC and the PNEC as a marker of risk. Each compound detected was subjected to evaluation, and values refer to acute toxicity. Neither chronic nor mixture toxicity was considered. Results for analgesic/anti-inflammatories, antibiotics and all the other classes are reported in Figs. 1–3, respectively.

These analyses reveal that 9 substances in Hospital B effluent (the four analgesics/anti-inflammatories acetaminophen, ibuprofen, naproxen and salicylic acid, the four antibiotics clarithromycin, erythromycin, ofloxacin and sulfamethoxazole and the psychiatric drug fluoxetine) pose a potential ecotoxicological risk. A high risk was found only for 5 compounds (the same antibiotics and the psychiatric drug) in the influent and the effluent of the municipal WWTP.

RQ classification proposed by (Hernando et al., 2006), showed that the levels of codeine, indomethacin, clenbuterol, atenolol, metoprolol and propranolol detected in the Hospital effluent pose a medium risk, as do the concentrations of acetaminophen, ibuprofen, naproxen, salicylic acid, clenbuterol, metoprolol, propranolol and gemfibrozil in the WWTP influent and, more importantly, salicylic acid, clenbuterol, propranolol, fenofibrate and gemfibrozil in the WWTP effluent.

These findings are closely correlated to the fact that the hospital effluent contained higher concentrations for analgesics/anti-inflammatories and antibiotics than the influent to the WWTP. In addition, they confirm that antibiotics are one of the most critical therapeutic classes used in hospitals, being highly resistant to degradation and removal; indeed, the same 4 antibiotics whose concentrations were found to pose a high risk in hospital effluent were also those found at high levels of potential toxicity in the influent and the effluent of the WWTP.

This confirms that the conventional treatments exploited by this WWTP are unable to effectively remove these micropollutants, being constructed, and later upgraded, with the aim of removing carbon, nitrogen and phosphorus compounds, pollutants which regularly arrive at the WWTP in concentrations to the order of mg L^{-1}.

This study evidences the fact that correct and specific management of hospital effluent on a *local scale* is necessary, and that further research is required to identify the best strategies for managing this type of effluent and evaluating the most suitable technologies for removing the most persistent contaminants, thereby reducing the risk posed to the environment and human health by these substances.

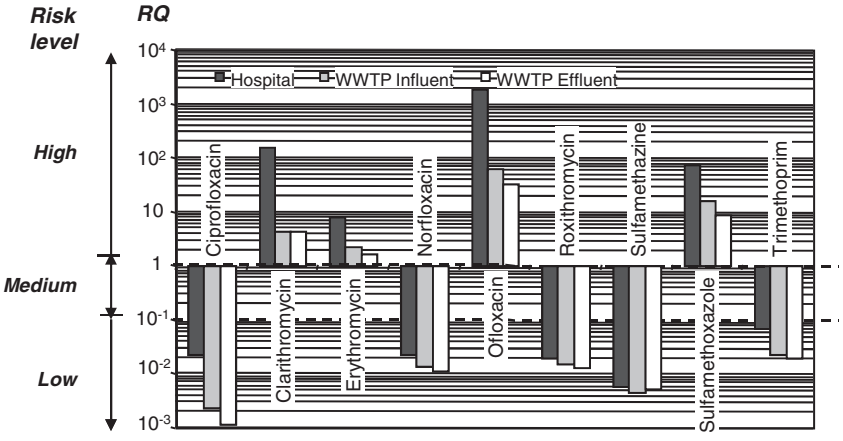

Fig. 2. Risk quotients for antibiotics in Hospital B effluent and investigated WWTP influent and effluent.

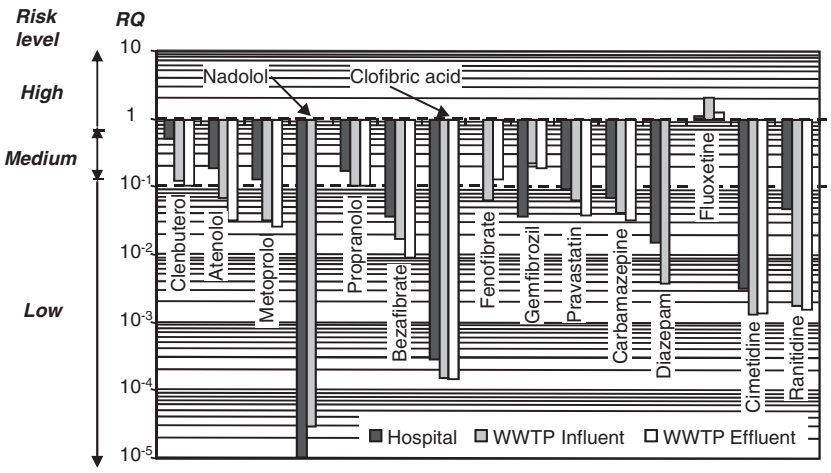

Fig. 3. Risk quotients for other PhCs investigated in Hospital B effluent and municipal WWTP influent and effluent.

4. Conclusions

Hospital effluents are generally considered to possess the same pollutant nature as urban wastewaters and are therefore co-treated at the same WWTP, without any special consideration being given to the potentially harmful nature of the substances they may contain. This study, however, by means of an investigation into 73 PhCs from 12 different therapeutic classes, reveals that these compounds are found in consistently higher concentrations in hospital WW than in urban WW, particularly commonly used drugs such as analgesics and antibiotics.

The characteristics of the hospital effluent seem to be influenced by the size of the structure (the smaller hospital discharged higher mean concentrations than the larger one), and season (concentrations tended to be higher in winter than in summer). The ratio between PhC concentration in hospital effluent and WWTP influent was, on average, 7. The highest values were found for ofloxacin (31) and clarithromycin (36), ranitidine (27), atorvastatin (25), metronidazole (23). Antibiotics, analgesics/anti-inflammatories and lipid regulator were the pharmaceutical compounds found at the highest concentrations.

The percentage load contribution of the hospital varied among the investigated compounds; in particular 12 compounds yielded values between 16 and 67% (some antibiotics, receptor antagonists and lipid regulators).

Environmental risk analysis showed that 9 compounds posed a high risk at the concentrations detected in hospital effluent, while in the WWTP influent and effluent, only 5 of these PhCs were found to exhibit high ecotoxicity. As four out of these five PhCs were antibiotics, we can state that this class of compound should cause the most concern.

These results confirm that, due to their micropollutant content, HWWs require more specific management and treatment in order to protect and safeguard the environment, in particular the surface water body which will receive the final (treated) effluent from the WWTP.

As co-treatment is common practice, and the usual (conventional) treatments are unable to efficiently remove PhCs, this issue needs urgent attention. Indeed, administrators and technicians will need to perform case-by-case analyses on a *local scale*, in particular during WWTP planning and design phases, in order to determine the best means of tackling the problem.

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Appendix A. Supplementary data

Supporting information relating to this article are available online and refer to optimized 9 QqLIT-MS/MS parameters in SRM-negative and -positive ionization modes for the 10 selected compounds as well as their literature ecotoxicological data.Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.scitotenv.2012.04.055.

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