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1 **Two year survey of specific hospital wastewater treatment and its impact on**  
2 **pharmaceutical discharges**

3  
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13

14 **Highlights**

- 15 - Hospital and urban effluents are compared  
16 - Impact of hospital wastewater on activated sludge treatment is studied  
17 - Seasonal variations of pharmaceuticals removal efficiency are demonstrated

18 **Keywords**

19 Pharmaceuticals, antibiotics, wastewater treatment, hospital wastewater, removal

20

21 **Abstract**

22 It is well known that pharmaceuticals are not completely removed by conventional activated  
23 sludge wastewater treatment plants. Hospital effluents are of major concern as they present  
24 high concentrations of pharmaceutically active compounds. Despite this, these specific  
25 effluents are usually co-treated with domestic wastewaters. Separate treatment has been  
26 recommended. However, there is a lack of information concerning the efficiency of separate  
27 hospital wastewater treatment by activated sludge, especially on the removal of  
28 pharmaceuticals.

29 In this context, this article presents the results of a two years monitoring of conventional  
30 parameters, surfactants, gadolinium and thirteen pharmaceuticals on the specific study site  
31 SIPIBEL. This site allows the characterization of urban and hospital wastewaters and their  
32 separate treatment using the same process. Flow proportional sampling, solid phase extraction  
33 and liquid chromatography coupled with tandem mass spectrometry were used in order to  
34 obtain accurate data and limits of quantification consistent with ultra-traces detection. Thanks  
35 to these consolidated data, an in-depth characterization of urban and hospital wastewaters was  
36 realized, as well as a comparison of treatment efficiency between both effluents.

37 Higher concentrations of organic carbon, AOX, phosphates, gadolinium, paracetamol,  
38 ketoprofen and antibiotics were observed in hospital wastewaters compared to urban  
39 wastewaters. Globally higher removals were observed in the hospital wastewater treatment  
40 plant and some parameters were shown to be of high importance regarding removal  
41 efficiencies: hydraulic retention time, redox conditions and ambient temperature. Eleven  
42 pharmaceuticals were still quantified at relevant concentrations in hospital and urban  
43 wastewaters after treatment (e.g. up to 1 µg/L for sulfamethoxazole). However, as the urban  
44 flow was about 37 times higher than the hospital flow, the hospital contribution appeared  
45 relatively low compared to domestic discharges. Thanks to the SIPIBEL site, data obtained  
46 from this two years program are useful to evaluate the relevance of separate hospital  
47 wastewater treatment.

## 48 **Introduction**

49

50 Pharmaceutically active compounds (PhAC) are specific micropollutants. They can be  
51 biologically active at very low concentrations, which imply the use of advanced analytical  
52 techniques to study their occurrence. Furthermore, beside the parent molecule, they are often  
53 excreted as metabolites that can be even more toxic than the native molecule (Pico & Barcelo  
54 2015). The main sources of contamination are well-known: domestic discharges, the  
55 pharmaceutical industry, healthcare facilities, releases associated with veterinary activities  
56 and fish farming, and disposal of unused medicines (Boxall et al. 2012). Nevertheless,  
57 uncertainty about their relative contributions still remains. Furthermore, it is well-documented  
58 that PhAC are not completely removed by Conventional Activated Sludge (CAS) treatment  
59 process, which is the most used technique around the world (Noguera-Oviedo & Aga 2016).

60

61 In the last two decades, hospital effluents have gained interest because of their high potential  
62 risk for the environment, due to their specific composition including high concentrations of  
63 PhAC, X-ray contrast media, AOX and the presence of pathogens (Carraro et al. 2016). Due  
64 to these characteristics, the assumption is often made that hospital effluents reduce the  
65 removal efficiency of wastewater treatment plants (WWTP) (Oliveira et al. 2015). Different  
66 treatment processes were studied to improve removal efficiencies of specific pollutants from  
67 hospital WW (HWW). Such additional treatments are for example Membrane Bio Reactor  
68 (MBR), the use of activated carbon and advanced oxidation processes (Verlicchi et al. 2015).  
69 However, very few investigations were performed about PhAC removal from HWWs with  
70 CAS treatment, and to the best of our knowledge, only two at full scale (Al Qarni et al. 2016,  
71 Kosma et al. 2010).

72

73 In this context, the SIPIBEL project, based on a specific WWTP whose configuration allows  
74 the study of HWW, urban WW (UWW) and their treatment separately, in the same  
75 environmental conditions, aims at an in-depth characterization of UWW and HWW and their  
76 treated effluents and the evaluation of the efficiency of a separate treatment (more details  
77 available in Chonova et al. article in this special issue). This article focuses on  
78 physicochemical characterization of WW, with the monitoring of conventional parameters,  
79 surfactants, gadolinium (Gd) and thirteen PhAC: analgesic (paracetamol, salicylic acid), anti-  
80 inflammatory (ibuprofen, ketoprofen, and diclofenac), beta-blockers (atenolol, propranolol),  
81 hormonal contraceptive (ethinylestradiol), antibiotic (ciprofloxacin, sulfamethoxazole, and  
82 vancomycin), anti-fungal (econazole) and anti-convulsant (carbamazepine) products. Targeted  
83 PhAC were first selected according to their consumption (domestic and/or hospital) and their  
84 Persistence, Bioaccumulation and Toxicity (PBT) index, leading to a list of 62 compounds  
85 which was further reduced due to analytical and economic constraints. In order to obtain  
86 accurate data, an analytical method based on advanced techniques was developed and  
87 validated. Limits of quantification in the ng/L range were achieved and the method was  
88 applied to the monitoring of PhAC in raw and treated WW of the SIPIBEL site, during two  
89 years.

90

## 91 **Materials and methods**

92

### 93 **Sampling sites**

94 All sampling sites were located in the area of Scientrier (Haute-Savoie, France) with an  
95 average altitude between 423 and 490 m. The weather is continental with temperatures  
96 between -8°C in winter and 33°C in summer.

97 The main characteristics of the plant during the sampling period are shown in Table 1 and  
98 described in Chonova et al. (2017), in this issue. The WWTP is a low-loaded plant, designed  
99 for carbon removal and nitrification. It is equipped with pre-treatment systems including  
100 aerated grit chambers, combined with grease removers and 3 conventional activated sludge  
101 (CAS) systems: two basins of 2720 and 4000 m<sup>3</sup>, collecting UWW and one dedicated to the  
102 treatment of hospital effluents of 1280 m<sup>3</sup> (Chonova et al. 2016). The same process,  
103 sequential aerobic and anoxic/anaerobic treatment, was applied to UWW and HWW basins.  
104 Every basin was equipped with an aeration system, proportional to the basin capacity, in order  
105 to supply the same amount of oxygen per m<sup>3</sup>-basin-capacity. Due to the low flow rate of  
106 HWW, the release of oxygen per m<sup>3</sup> of discharge was about two times higher than in the  
107 urban basins, even if aeration times of the hospital basin were decreased to 4.4 h/day instead  
108 of 18h. The food to microorganism (F/M) ratio was between 0.1 and 0.2  
109 kgBOD<sub>5</sub>/kgMLVSS.d in the UWW basins and about ten times lower in the HWW basin.

110 The hospital effluent is separately conveyed to the WWTP and comes from a medium-sized  
111 hospital with 450 beds (1300 patients/day) and 1450 staff members. It is composed of 25  
112 wards, including geriatrics, oncology, maternity, emergency, medical imaging, biologic  
113 analysis and kitchen (Lecomte 2016). Sterilization and laundry are outsourced. The collecting  
114 system of the hospital is separated; therefore, there should be no contribution of rain events to  
115 HWW.

116

**Table 1** Characteristics of the WWTP

	WWTP capacity (population equivalent / m <sup>3</sup> )	Hospital bed number	Urban network (inhabitants)	Mean flow rate (m <sup>3</sup> .day <sup>-1</sup> )	Mean HRT (days)
Urban basins	26600 PE / 6720 m <sup>3</sup>	-	20,850	5355	1.6
Hospital basin	5400 PE / 1280 m <sup>3</sup>	450	-	146	8.1

117

### 118 **Sampling**

119 Four sampling sites were selected: urban influent and effluent, hospital influent and effluent  
120 (more details available in Chonova et al. (2017) in this special issue). WW were sampled  
121 before pre-treatment and treated WW after the secondary treatment.

122 Sampling campaigns were performed between June 2013 and December 2015, during dry  
123 days, representing 27 campaigns of the hospital and urban raw WWs. Due to a change of  
124 configuration in October 2014, only 13 campaigns of the hospital and urban treated WW were  
125 achieved. Samples from all sampling sites were collected on the same days and each  
126 campaign started on Tuesday to avoid variability due to the day of sampling. Sampling was  
127 performed following approved French guidelines (Eymery et al. 2011).

128 To ensure representative sampling, identical sampling strategies were used for all locations.  
129 Samples were collected on a 24h-period (from 8 a.m. to 8 a.m.). 24-h composite water

130 samples were collected; the sub-sampling interval was flow-proportional (with basin-specific  
131 flow volume) (Ort et al. 2010). Flows were measured before and after the WWTP. ASP  
132 Station 2000 (Endress hauser) refrigerated automated samplers were used. Both were  
133 constituted of 24 glass bottles with Teflon tubing. The content of the 24 glass bottles was  
134 gathered, mixed and homogenized. Then samples were stored in darkness at 4°C and treated  
135 within 24h.

136

### 137 **Conventional physicochemical parameters**

138 The following physicochemical parameters of influents were analysed: 5-day biochemical  
139 oxygen demand (BOD<sub>5</sub>), chemical oxygen demand (COD), conductivity, dissolved organic  
140 carbon (DOC), total organic carbon (TOC), pH, total suspended solids (TSS), total  
141 phosphorus (TP), phosphates (PO<sub>4</sub><sup>3-</sup>), Kjeldahl nitrogen (TKN), ammonium (NH<sub>4</sub><sup>+</sup>),  
142 adsorbable organic halogen (AOX), Gadolinium (Gd) and cationic, non-ionic and anionic  
143 surfactants. All these parameters were analysed on the whole water except DOC, PO<sub>4</sub><sup>3-</sup>, Gd  
144 and cationic and anionic surfactants which were analyzed on the dissolved fraction. All these  
145 analyses were performed following standard methods (see Table S1) approved by the French  
146 organization of standardization AFNOR, except Gd which was analyzed with a validated  
147 internal method.

148

### 149 **Pharmaceutical analysis**

150 In order to obtain accurate data, an analytical method based on Solid Phase Extraction (SPE),  
151 Liquid Chromatography coupled with Tandem Mass Spectrometry (LC-MS/MS) and the use  
152 of isotope labelled internal standards, was developed for PhAC analysis.

153

#### 154 *Chemicals and reagents*

155 Thirteen pharmaceuticals were analyzed: paracetamol, salicylic acid, ketoprofen, ibuprofen,  
156 diclofenac, atenolol, propranolol, econazole, ethinylestradiol, carbamazepine, and the  
157 antibiotics ciprofloxacin, sulfamethoxazole and vancomycin. All pharmaceuticals and  
158 isotopically labeled internal standards were of high purity grade (see Table S2). Individual  
159 stock standard and isotopically labeled internal standard solutions were prepared at a  
160 concentration of 200 mg/L, by dissolving 2 mg of solid reference standard in 10 mL of  
161 methanol. After preparation, standards were stored in the dark at -18°C. A mixture of these  
162 standards at 10 mg/L, prepared in methanol, stored at -18°C was stable for at least three  
163 months. Diluted working standard solutions were prepared regularly in water and stored at  
164 4°C.

165 LC-MS acetonitrile, methanol and acetic acid were obtained from Sigma-Aldrich (Saint-  
166 Quentin Fallavier, France). Ultra-pure water was obtained with a Milli-Q water system from  
167 Millipore (Molsheim, France). SPE cartridges were Oasis HLB (60 mg, 3 mL) from Waters  
168 (Milford, USA). Glass fiber filters (0.7 µm) were obtained from Millipore (Molsheim,  
169 France).

170

#### 171 *Sample preparation and extraction*

172 Samples were first filtered on glass fiber filters 0.7 µm with a filtration System IT30 142 HW  
173 from Millipore (Molsheim, France). SPE was then conducted with an AutoTrace automated

174 SPE system from ThermoFisher (Roissy, France). Solid phase extraction procedure was  
175 adapted from (Gros et al. 2006). Briefly, according to the nature of water, raw WW/treated  
176 WW, 150/300 mL of filtered water samples were spiked with 150/120  $\mu$ L of a 250  $\mu$ g/L  
177 solution of internal standards. 100/250 mL samples were then loaded at a flow rate of 10  
178 mL/min onto Oasis HLB cartridges previously conditioned with 5 mL methanol then 5 mL  
179 MilliQ water at 1 mL/min. Cartridges were then rinsed with 5 mL MilliQ water at 1 mL/min,  
180 dried 10 min with nitrogen and eluted with 2 x 4 mL methanol at 2 mL/min. The eluates were  
181 dried with a gentle stream of nitrogen at 40 °C and reconstituted in 1 mL of ultra-pure water.  
182 Final extracts were transferred into 2 mL vials and stored at -18°C prior to analysis by HPLC-  
183 MS/MS. Besides, in order to analyze paracetamol and salicylic acid in raw WW, a 10 mL  
184 aliquot of WW filtered at 0.7  $\mu$ m was sampled, further filtered at 0.45  $\mu$ m, diluted 10 times  
185 with ultra-pure water, and spiked with the internal standards solution.

186

#### 187 *Liquid chromatography-tandem mass spectrometry*

188 Chromatographic separations were carried out with an Agilent 1290 series liquid  
189 chromatograph system (Agilent Technologies, Avondale, USA), using a Zorbax Eclipse C18  
190 column (50 mm $\times$ 2.1 mm i.d., 1.8  $\mu$ m) also from Agilent, protected with a KrudKatcher Ultra  
191 In-Line Filter guard column from Phenomenex (Torrence, CA, USA) were used for  
192 chromatographic separation. The column oven temperature was set at 60 °C for the positive  
193 mode and 50°C for the negative mode. Solvent A was Milli-Q quality water with 0.01 %  
194 acetic acid and solvent B was either methanol for the positive ionization mode or  
195 acetonitrile/methanol for the negative mode. Flow rates were 0.6 mL/min and the sample  
196 volume injected was 50  $\mu$ L for positive and negative modes respectively.

197 The LC instrument was coupled to 3200 QTrap (ABSciex, CA, USA) triple quadrupole mass  
198 spectrometer equipped with an electrospray ion source (ESI Turbo V) operated in both  
199 negative and positive modes. The quantitative analysis of the target compounds was achieved  
200 in Multiple Reaction Monitoring (MRM) mode. For quantitative purposes, two MRM  
201 transitions were monitored for each target compound. Nitrogen was used as the drying and  
202 nebulizing gas. All data were acquired and processed using Analyst 1.5.2 software. Gradient  
203 elution programs and MS/MS parameters are given in Tables S3 and S4.

204

#### 205 *Quantification and quality control*

206 In the aim of ensuring a constant performance of the method, analytical blanks and quality  
207 controls were injected at each batch. Field blanks were also regularly performed with MilliQ  
208 water, mineral water and real water samples. In order to evaluate possible adsorption or  
209 desorption in the sampling system, undrawn and withdrawn samples were analyzed.

210 In order to correct for recoveries and matrix effects, internal standard calibration was  
211 performed using the stable isotope labelled analogue of each compound of interest. Indeed,  
212 internal standard calibration is one of the most accurate solutions to correct for matrix effects,  
213 as long as the internal standard co-elutes with the analyte of interest (Hewavitharana 2011).  
214 However, stronger matrix effects were observed in hospital wastewater extracts, leading to  
215 signal suppression of paracetamol and salicylic acid analogue internal standard. It is well-  
216 known that smallest and most polar molecules are more prone to matrix effects (Taylor 2005),  
217 which is the case of paracetamol and salicylic acid. As concentrations of these two

218 compounds in hospital raw wastewater were very high (superior to 100 ng/L), wastewater,  
219 diluted by ten in MilliQ water and spiked with internal standard analogue, was injected  
220 directly in order to quantify them accurately.

221 Besides, in order to fully validate our analytical method, an inter-laboratory assay was  
222 conducted on surface waters (to the author's knowledge, no inter-laboratory assay was  
223 available on WW), thanks to the AGLAE association ([www.association-aglae.fr](http://www.association-aglae.fr)). Z-scores  
224 obtained were between -0.99 for diclofenac and +1.64 for carbamazepine.

225

### 226 **Calculation methods and statistical analyses**

227 Mean removal efficiencies were calculated for each of the measured parameters to compare  
228 the treatment of the two lines (UWW and HWW) and the effect of the temperature on the  
229 treatment efficiency.

230 Furthermore, mass loadings were calculated for each sampling period by multiplying the  
231 concentrations of each compound by the mean daily flow of the respective location (hospital  
232 or urban) and sampling period. To calculate the contribution of the HWW to the total load of  
233 pollutants, first total load was calculated as a sum of hospital and urban loads. The load of  
234 each chemical in the HWW was divided by the total load of the same chemical, and  
235 multiplied by 100. The loads of each chemical used to calculate the hospital contribution  
236 refers to the mean value of all campaigns performed. The same calculation was done for the  
237 hospital treated WW contribution to the total treated effluent in order to comprehend the  
238 effect of the treatment on the mass loadings.

239 Principal component analysis (PCA) was performed to present the main tendencies in the  
240 loads distribution of pharmaceuticals in urban and hospital wastewaters. Data for PCA were  
241 centered and standardized. PCA was done with R software (3.3.0, R development core team)  
242 using the ade4 package (Dray & Dufour 2007).

243

## 244 **Results and discussion**

245

### 246 **Characterization of raw wastewaters**

247

#### 248 *Conventional physico-chemical parameters, surfactants and Gd*

249 Various parameters of hospital and domestic WW were followed every month during two  
250 years. Medians, minimums, maximums and coefficients of variation are reported in Table 2.

251



252 **Table 2** Conventional physico-chemical parameters, surfactants and Gd measured in hospital and urban raw  
 253 wastewaters

Parameter	Hospital raw WW				Median ratio	Urban raw WW			
	Median	Min	Max	CV %		Median	Min	Max	CV %
Flow (m <sup>3</sup> /day)	174	98	277	23	0.04	3892	2598	6549	25
BOD <sub>5</sub> (mg/L O <sub>2</sub> )	400.0	216	700	31	1.4	294.0	139	478	32
COD (mg/L)	918.0	480	1340	26	1.4	659.0	49	1698	52
Conductivity (µS/cm 25°C)	2660.0	2304	3682	13	<u>1.8</u>	1520.0	1079	1830	12
DOC (mg/L)	116.0	5.9	178	47	<u>2.3</u>	50.1	23	103	37
TOC (mg/L)	220.0	79	332	30	<u>1.8</u>	120.0	63	264	40
pH	7.7	7.1	8.5	4.4	1.0	7.6	7.2	7.7	1.4
TSS (mg/L)	310.0	104	690	41	0.8	370.0	96	608	42
TP (mg/L)	12.0	7.3	22	25	1.4	8.5	4.9	18	33
PO <sub>4</sub> <sup>3-</sup> (mg/L)	7.4	2.3	9.7	28	<u>1.9</u>	3.8	2	7.7	37
TKN (mg/L)	67.0	48.0	94	15	1.0	64.0	38	102	27
NH <sub>4</sub> <sup>+</sup> (mg/L)	46.0	16	70	23	1.0	47.0	23	86	26
AOX (mg/L)	0.69	0.2	1.7	44	<u>14</u>	0.05	LOQ	0.1	36
Gadolinium (µg/L)	6.7	1.7	33	96	<u>13</u>	0.5	<LOQ	2.0	74
Cationic surfactant (mg/L)	1.1	<LOQ	2.6	90	<u>11</u>	0.1	<LOQ	3.2	30
Non-ionic surfactant (mg/L)	4.9	0.1	22	70	<u>4.4</u>	1.1	0.1	8.8	109
Anionic surfactant (mg/L)	0.37	0.1	9.6	230	0.2	1.9	0.1	6.6	67

254 Hospital and domestic WW presented similar values of BOD<sub>5</sub>, COD, pH, TSS, TP, TKN and  
 255 NH<sub>4</sub><sup>+</sup>. Besides, the COD/ BOD<sub>5</sub> ratio of hospital and UWW were in the same range, which  
 256 means that they have similar biodegradability. Similar values of pH, TKN and NH<sub>4</sub><sup>+</sup> between  
 257 hospital and urban WW were also reported in the study of (Verlicchi et al. 2010). However,  
 258 such similarities of TSS were in contradiction with what is usually reported (Verlicchi et al.  
 259 2010). Furthermore, TSS concentrations (median of 310 and 370 mg/L for hospital and urban  
 260 WW, respectively) were in the highest range of those reported in other studies (Verlicchi et al.  
 261 2015).

262 The other parameters were significantly different between UWW and HWW. Conductivity,  
 263 PO<sub>4</sub><sup>3-</sup>, TOC and DOC were approximately two times higher in HWW than in UWW. Even  
 264 more important differences were observed in concentrations of AOX and gadolinium, which  
 265 were more than 10 times higher in hospital WW, compared to domestic WW. As one of the  
 266 main ion contributing to conductivity is chloride (Le Bonté et al. 2008), it is not surprising  
 267 that the conductivity of hospital WW is higher than the one of UWW (Verlicchi et al. 2010).  
 268 Concentrations of AOX are consistent with the study of Kümmerer et al. 1998. According to  
 269 Kümmerer 2001, the major mass carriers for AOX in hospital wastewaters are most likely  
 270 iodised X-ray contrast media, solvents, disinfectants, cleaners and drugs containing chlorine.  
 271 The higher concentrations of phosphate in the hospital WW could also be explained by the  
 272 release of detergents with high content of phosphorus and pharmaceuticals containing  
 273 phosphoric antineoplastics from the hospital (Chonova et al. 2016). Higher DOC in hospital  
 274 WW was also reported by Kovalova et al. (Kovalova et al. 2012). Gadolinium is used as a  
 275 contrast agent for Magnetic Resonance Imaging (MRI), which explains its high  
 276 concentrations in HWW. Values reported by Gouille et al. 2012 are consistent with our study.  
 277 Finally, global analysis of anionic and ionic surfactants revealed higher concentrations of  
 278 cationic and non-ionic surfactants in HWW and higher concentrations of anionic surfactants  
 279 in UWW (median concentration of 2 mg/L). More details about the presence of surfactants are  
 280 available in another article of this special issue (Bergé et al. in this issue).

281

282 *Pharmaceutical concentrations*

283 Concentrations of 13 pharmaceuticals in hospital and urban WW were followed every month  
 284 during two years. In order to avoid too high uncertainties on the results, only values superior  
 285 to the limit of quantification are analysed and discussed. Medians, minimums, maximums and  
 286 coefficients of variation are reported in Table 3.

287  
 288 **Table 3** Pharmaceuticals in raw hospital and urban wastewaters: limit of quantification, quantification  
 289 frequency, median, minimum and maximum concentration, coefficient of variation and hospital on urban median  
 290 concentrations ratio (Median ratio)

	Compound	LOQ µg/L	Hospital raw WW					Medi an ratio	Urban raw WW				
			Nb of samples > LOQ	Median µg/L	Min µg/L	Max µg/L	CV %		Nb of samples > LOQ	Median µg/L	Min µg/L	Max µg/L	CV %
Analgesic	Paracetamol	0.012	27/27	813.5	178	1510	34	5	27/27	161.0	31.5	1160	109
Antibiotic	Sulfamethoxazole	0.006	27/27	3.9	0.9	26	99	8	27/27	0.5	0.04	1.5	66
Antibiotic (fluoroquinolone)	Ciprofloxacin	0.035	27/27	21.6	4.6	179	114	172	3/27	0.12	LOQ	0.15	27
Antibiotic	Vancomycin	0.050	27/27	0.77	0.06	7.4	139		0/27	<LOQ	<LOQ	<LOQ	N/A
Antifungal	Econazole	0.001	2/27	0.016	<LOQ	0.018	13		1/27	0.002	<LOQ	0.002	N/A
Anti-inflammatories	Ketoprofen	0.009	27/27	10.0	3.6	20	37	8	27/27	1.3	0.63	2.9	37
Anti-inflammatories	Diclofenac	0.005	27/27	0.31	0.07	1.1	70	0.4	27/27	0.72	0.22	1.5	39
Anti-inflammatories	Ibuprofen	0.0005	27/27	7.1	3.7	17	38	0.8	27/27	8.3	3.6	16	36
Anti-inflammatories (metabolite)	Salicylic acid	0.013	27/27	22.7	0.29	62	55	0.8	26/27	27.4	LOQ	70	66
Beta-blockers	Atenolol	0.004	27/27	3.2	1.0	39	166	1.3	27/27	2.4	1.0	4.6	34
Beta-blockers	Propranolol	0.001	27/27	0.6	0.11	3.8	97	1.7	27/27	0.35	0.20	3.3	117
Hormone	Ethinylestradiol	0.014	0/27	<LOQ	<LOQ	<LOQ	N/A	N/A	0/27	<LOQ	<LOQ	<LOQ	N/A
Psychiatric drug	Carbamazepine	0.001	27/27	0.3	0.01	12	226	0.6	27/27	0.53	0.31	1.5	45

291 Ethinylestradiol was the only compound that could never be quantified during this study.  
 292 Econazole was only quantified once in urban raw WW and twice in hospital raw WW.  
 293 According to Nagarnaik et al. 2010, ethinylestradiol was also not quantified in hospital  
 294 effluents. This hormone is usually quantified at concentrations lower than the ng/L range,  
 295 which is not detectable with our analytical method (Backe 2015). Econazole is often mainly  
 296 detected in the particulate phase (Lachassagne et al. 2015), which was not analyzed in this  
 297 work. Consequently, these two compounds are not included in the statistical analysis.

298  
 299 All other PhAC were quantified in 100% of the samples of HWW. Paracetamol  
 300 concentrations were more than ten times higher than the other PhAC, with median  
 301 concentrations of 813 and 161 µg/L, in HWW and UWW respectively. Concerning HWW, all  
 302 other pharmaceuticals were always quantified with median concentrations varying from 0.3  
 303 µg/L for diclofenac and carbamazepine, to 22.7 µg/L for salicylic acid. In UWW, the same  
 304 pharmaceuticals, except ciprofloxacin and vancomycin, were always quantified with median  
 305 concentrations varying from 0.35 µg/L for propranolol, to 27.4 µg/L for salicylic acid.  
 306 Ciprofloxacin was only quantified three times, in the order of 0.1 µg/L, and vancomycin was  
 307 never quantified.

308  
 309 Concentrations of ibuprofen, salicylic acid, atenolol, propranolol and carbamazepine were in  
 310 the same order in hospital and urban raw wastewaters. Median concentrations of diclofenac  
 311 were two times lower in HWW than in UWW, but minimum and maximum concentrations  
 312 were very close. All these compounds are extremely used, both in hospital and domestic  
 313 sectors. Ibuprofen, salicylic acid and diclofenac belong to the 30 most sold substances in  
 314 urban areas of France (Cavalié 2014). Atenolol and propranolol use is more restricted but  
 315 these high concentrations can be explained by the increase in the average age of the

316 population and the presence of retirement homes in the catchment area. Conversely,  
317 concentrations of two painkillers (paracetamol, ketoprofen) and three antibiotics  
318 (sulfamethoxazole, ciprofloxacin, vancomycin) were significantly higher in HWW than in  
319 UWW. Higher concentrations in hospital WW of these compounds were also reported by Al  
320 Aukidy et al. 2014 which reviewed pharmaceutical concentrations in hospital and urban WW.  
321 Paracetamol is the most prescribed analgesic: its higher concentration in hospital WW can be  
322 explained by the higher proportion of injured people at the hospital. Contrary to the other anti-  
323 inflammatories (ibuprofen, salicylic acid and diclofenac), ketoprofen is only accessible by  
324 prescription, and so more used in the hospital sector. Finally, high concentrations of  
325 antibiotics in hospital WW, compare to domestic WW, have already been reported (Tuc et al.  
326 2017). Vancomycin, which is restricted to hospital use, was only detected in hospital WW,  
327 whereas sulfamethoxazole and ciprofloxacin were quantified in both WW, but in  
328 concentrations respectively 10 and 100 times higher in hospital WW.

329

### 330 **Removal efficiencies**

331

332 Regarding the conventional parameters, removals were very high in both WW lines, hospital  
333 and urban. Median removal of TSS, COD, BOD<sub>5</sub> and NH<sub>4</sub><sup>+</sup> were respectively 99%, 98%,  
334 100% and 99-100%. These values show effective carbon removal and nitrification in UWW  
335 and HWW lines, which meet the standard guidelines given by the Water Framework Directive  
336 (WFD) (European commission, 1991). The WWTP is not designed for denitrification, which  
337 leads to remaining median concentrations of NO<sub>3</sub><sup>-</sup> of 1.3 and 10.4 mg/L and NO<sub>2</sub><sup>-</sup> of 0.1 and  
338 0.03 mg/L in urban and hospital treated WW, respectively.

339

340 Numerous parameters can affect removal efficiency: solid retention time (SRT), HRT,  
341 temperature, pH, nitrification and redox conditions (Falas et al. 2016). In this study, pH and  
342 temperature of urban and hospital WW were similar for both basins, but this was not the case  
343 for HRT and redox conditions. The HRT in the HWW line was around five times higher than  
344 in the UWW line. Furthermore, due to the low hospital discharge, the release of oxygen per  
345 m<sup>3</sup> of discharge was about two times higher than in the urban basins, which may explain the  
346 higher concentrations of nitrate in the hospital basin. These particular operational conditions  
347 and the presence of antibiotics and biocides (Bergé et al. in this issue) in the HWW may  
348 influence the growth and structure of bacterial communities, as demonstrated by Chonova et  
349 al. 2016.

350

351 Concerning pharmaceuticals, removal efficiencies were between 75 and 100% in the HWW  
352 line and between 30 and 100% in the UWW line, except for carbamazepine (Table 4). These  
353 removals were generally higher compared to studies reporting HRT below 24h (Verlicchi et  
354 al., 2012b). Higher HRT for the WWTP studied here, may explain higher removal, especially  
355 for certain molecules (e.g. ibuprofen) (Kosma et al., 2010).

356 The removal efficiency varied strongly depending on the molecule. Removals of paracetamol,  
357 salicylic acid, ibuprofen, ketoprofen, atenolol and the antibiotics ciprofloxacin and  
358 vancomycin were higher than 90%, whereas the remaining four pharmaceuticals propranolol,  
359 sulfamethoxazole, diclofenac and carbamazepine, presented relatively low removals.

360 Carbamazepine and diclofenac even exhibited higher concentrations in the treated effluents,  
 361 than in the raw wastewaters. These negative removals were not regular regarding diclofenac,  
 362 but very frequent concerning carbamazepine, which explains why its removal rates could not  
 363 be calculated (Table 4). This phenomenon for carbamazepine has already been reported in  
 364 several studies (e.g. Radjenović et al., 2009).

365  
 366 **Table 4** Pharmaceuticals in treated hospital and urban wastewaters: limit of quantification, quantification  
 367 frequency, median, minimum and maximum concentration, coefficient of variation, median removal and  
 368 associated coefficient of variation  
 369

Compound	LOQ ng/L	Hospital treated WW							Urban treated WW							Removal range <sup>a</sup> (%)
		Nb of samples > LOQ	Median ng/L	Min ng/L	Max ng/L	CV %	Median Removal %	CV %	Nb of samples > LOQ	Median ng/L	Min ng/L	Max ng/L	CV %	Median Removal %	CV %	
Paracetamol	12.2	8/13	39.0	<LOQ	3272	180	100.0	0.2	9/13	69.4	<LOQ	714	78	99.9	0.1	80-99
Sulfamethoxazole	5.9	13/13	810.0	79.4	1514	68	75.3	33	12/13	119.5	<LOQ	1004	148	73.1	87	10-99
Ciprofloxacin	35.3	8/13	363.5	<LOQ	3414	138	99.2	2.4	2/13	95.1	<LOQ	144	73	94.3	1.0	18-96
Vancomycin	50.0	4/13	27.6	<LOQ	49	44	98.6	6.3	0/13	<LOQ	<LOQ	<LOQ	<LOQ	N/A	N/A	10 <sup>b</sup>
Ketoprofen	9.3	11/13	36.0	<LOQ	83	55	100.0	0.2	13/13	84.0	22	397	90	91.0	12	7-92
Diclofenac	5.0	13/13	76.0	18	874	170	77.0	23	13/13	488.0	42	790	50	30.3	113	3-80
Ibuprofen	0.5	11/13	30.0	<LOQ	88	79	99.7	0.3	11/13	96.0	<LOQ	356	92	98.9	1.6	26-99
Salicylic acid	13.3	1/13	114.0	<LOQ	114	N/A	100.0	0.2	1/13	138.0	<LOQ	138	N/A	100.0	1.6	97-99
Atenolol	4.1	7/13	18.8	13.6	146	94	99.7	1.8	13/13	193.0	8.16	552	74	91.0	8.9	14-85
Propranolol	0.6	13/13	112.0	22	242	56	87	10	13/13	110.0	23	236	57	70.0	42	1-96
Carbamazepine	0.6	13/13	629.0	133	1334	48	-	-	13/13	498.0	231	788	29	-	-	5-78

370 <sup>a</sup>Verlicchi et al. 2012b

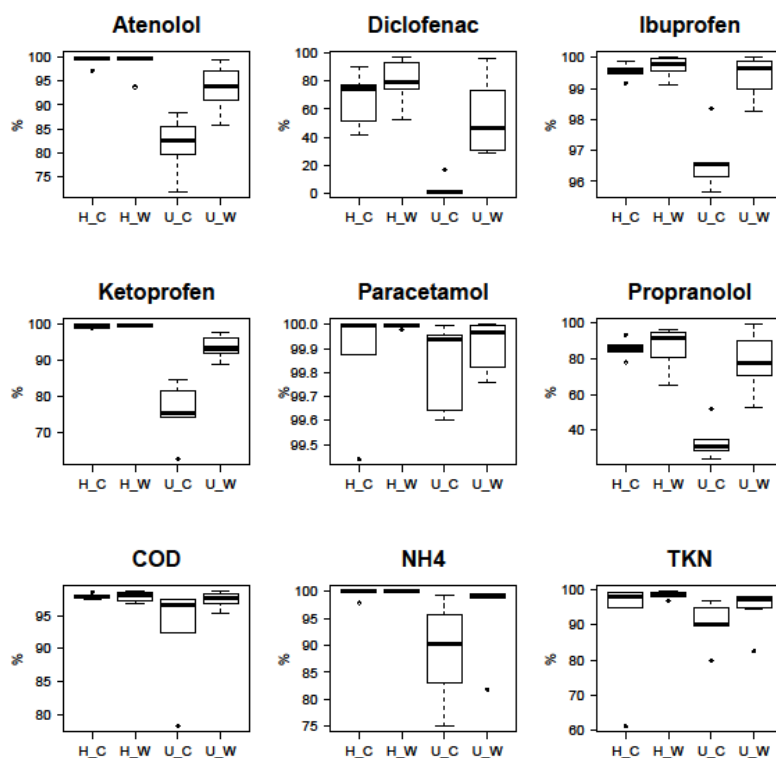
371 <sup>b</sup>Tuc et al. 2017

372  
 373 Main removal mechanisms of micropollutants are biodegradation/biotransformation, sorption  
 374 and volatilization. As pharmaceuticals selected for this study are almost not volatile, the last  
 375 one is expected to be of minor importance. The increase of certain molecules in the treated  
 376 effluents may be due to their excretion as conjugate metabolites in raw WW, which were not  
 377 analyzed and may be transformed into the parent compound after treatment. This has already  
 378 been observed for carbamazepine (Bouju et al. 2016), diclofenac (Bouju et al. 2016) and  
 379 sulfamethoxazole (Guerra et al. 2014, Verlicchi et al. 2015). Other reason may be the  
 380 sampling procedure. Samples from raw WW and treated effluents were taken in the same day;  
 381 hence HRT was not taken into account. This is of particular importance for the hospital WW  
 382 where the mean HRT was 8 days.

383  
 384 Differences in removal efficiency between molecules were already reported (Verlicchi et al.  
 385 2012b). As confirmed in our study, paracetamol, salicylic acid and ibuprofen are highly  
 386 biodegradable molecules. We also observed good removals of ciprofloxacin. However, these  
 387 can also be explained by the high capacity of this molecule to adsorb to sludge - about 60%  
 388 (Zhou et al. 2013). Regarding the other pharmaceuticals, removals were relatively lower,  
 389 especially in the case of the UWW treatment. Differences were observed for example,  
 390 considering ketoprofen and diclofenac removals: in the UWW line, ketoprofen removal was a  
 391 little lower and diclofenac removal decreased dramatically compared to HWW line. Reported  
 392 values of removals of ketoprofen and diclofenac are very variable through the literature and  
 393 may increase with higher HRT, SRT, temperature and with reactors that include nitrification  
 394 and denitrification steps. Consequently, the higher HRT of the HWW line (8 days) is one  
 395 possible explanation of good removals obtained for diclofenac and ketoprofen. This

396 difference can also be explained by the higher concentration of nitrates in the hospital basin.  
397 Indeed, Barbieri et al. 2012 demonstrated the formation of the nitro derivative of diclofenac,  
398 which can be retransformed to the parent compound. Hence, the higher removal in the HWW  
399 basin may reflect a higher transformation of diclofenac into nitro-diclofenac and not its  
400 biodegradation (Chonova et al. 2016). A great variability in the removals of the beta-blockers  
401 atenolol and propranolol was also observed in the literature (Table 4). In our study, removals  
402 of atenolol and propranolol were a bit lower in the UWW line, than in the HWW line. Stadler  
403 et al. 2015 studied the effect of redox conditions on pharmaceutical removals and observed  
404 higher removal of atenolol under fully aerobic conditions. This also highlights the importance  
405 of oxygenation for the removal efficiency of certain molecules and difference in the removal  
406 efficiency between urban and hospital line. Another important parameter that influences the  
407 removal of micropollutants is the F/M ratio. Petrie et al. 2014 observed a good correlation  
408 between the decrease of the F/M ratio from 0.25 to 0.05 kgBOD5/kgMLVSS.d and the  
409 increase of the removal of estrogens. Indeed, a low F/M ratio implies a limitation of the  
410 substrate available for microorganisms, which may lead to the biodegradation of less easily  
411 assimilable carbon substrates.

412  
413 Finally, an important variability of the removal efficiency (Coefficient of Variation > 40%)  
414 was observed in the UWW line, compared to the HWW line. This may be explained by the  
415 lower volume of WW discharged in the hospital basin (Kosma et al. 2010) and by larger  
416 variation of contamination sources and stronger seasonal fluctuations in UWW. Seasonal  
417 differences in removal efficiency, linked to changes in the ambient temperature, were also  
418 observed. However, this trend was only visible in the urban basin. Removal efficiency of the  
419 following molecules showed significant decrease during colder months: atenolol, diclofenac,  
420 ibuprofen, ketoprofen and propranolol (Figure 1). For example, diclofenac removal was very  
421 variable throughout seasons, with a mean removal of 55% in warmer months, and only 1% in  
422 colder months. The same effect of temperature was observed regarding  $\text{NH}_4^+$  removal.  
423 Indeed, nitrifying bacteria growth is dependent on temperature and temperature sensitivity  
424 decreases with increasing SRT (Willers et al. 1993) which may explain why it was only  
425 observed in the urban line.



426  
 427 **Fig. 1** - Boxplots presenting removal rates of some pharmaceuticals and physico-chemical parameters in hospital  
 428 (H) and Urban (U) lines during colder (\_c) (<14°C) and warmer (\_w) (>14°C) months (in %)

429  
 430 **Concentrations of pharmaceuticals in treated WW**

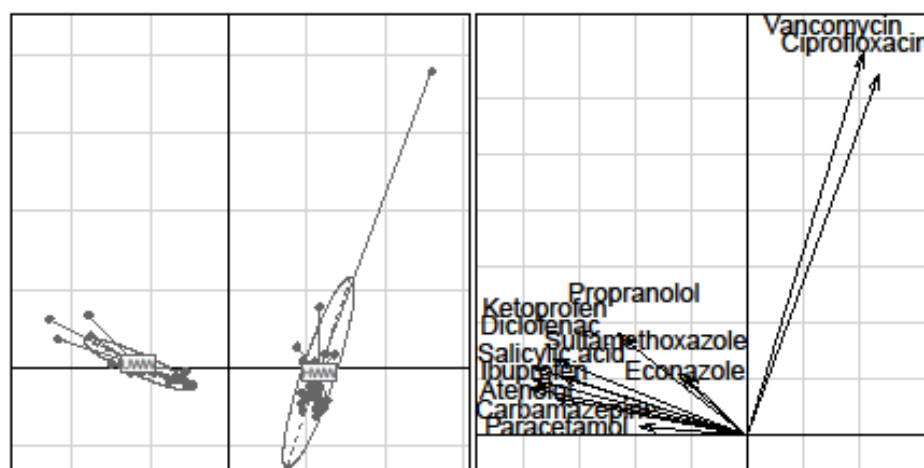
431  
 432 Eleven molecules out of the thirteen monitored pharmaceuticals were quantified in hospital  
 433 and/or urban treated wastewaters: paracetamol, sulfamethoxazole, ciprofloxacin, vancomycin,  
 434 ketoprofen, diclofenac, ibuprofen, salicylic acid, atenolol, propranolol and carbamazepine.  
 435 Median concentrations (Table 4) ranged between 19 ng/L for atenolol and 810 ng/L for  
 436 sulfamethoxazole in HWW. Median concentrations of carbamazepine, which is well-known  
 437 to be resistant to treatments (Chonova et al. 2016, Radjenovic et al. 2009), were also  
 438 significant with 629 and 498 ng/L, in HWW and UWW, respectively. These concentrations  
 439 found in treated WW are consistent with the literature (Al Qarni et al. 2016, Santos et al.  
 440 2013, Verlicchi et al. 2012b)

441 Six pharmaceuticals were quantified in more than 80 % of the samples: sulfamethoxazole,  
 442 ketoprofen, diclofenac, ibuprofen, propranolol and carbamazepine. Regarding differences  
 443 between hospital and urban treated WW, despite a good removal efficiency of the treatment,  
 444 antibiotics concentrations remained higher in hospital effluents than in urban ones.  
 445 Conversely, atenolol and three anti-inflammatories (ketoprofen, diclofenac and ibuprofen)  
 446 were found in higher concentrations in the domestic treated WW.

447  
 448 **Loads and contributions**

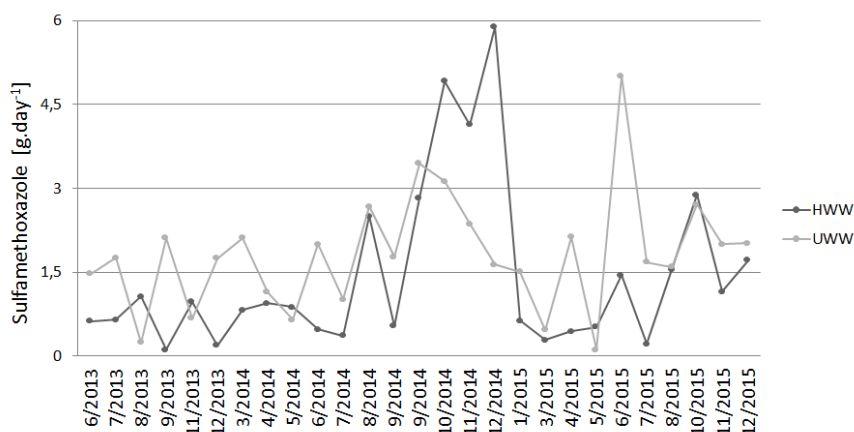
449  
 450 Loads of pharmaceuticals were calculated to reveal the effect of the amount of discharge on  
 451 the quantity of micropollutants released with the urban and the hospital WW. PCA performed

452 to present these loads shows that urban and hospital samples have very different  
 453 characteristics according to the loads of pollutants since they are placed oppositely on the first  
 454 axis (Fig. 2). Exceptions are the pharmaceuticals vancomycin and ciprofloxacin, which are  
 455 more associated to the second axis. Vancomycin and ciprofloxacin are hospital tracers which  
 456 were not regularly detected in UWW (Table 3). This may explain the higher importance of  
 457 their loads in the HWW comparing to other pharmaceuticals. Furthermore, despite higher  
 458 concentrations of certain compounds in the HWW, UWW are characterized by higher loads of  
 459 almost all compounds. This is caused by the different amount of discharge: the urban  
 460 discharge is more than 37 times higher than the hospital discharge. These data confirm that,  
 461 except for antibiotics, UWW are the dominant emission pathway of pharmaceuticals (der  
 462 Beek et al. 2016). Indeed, high concentrations of pharmaceuticals are released by health-care  
 463 facilities. However, their regular quantification in UWW is an evidence for their constant  
 464 consumption at home as well.  
 465



466  
 467 **Fig. 2** - PCA based on loads of pharmaceuticals parameters in the locations UWW and HWW (the first two axes  
 468 represent respectively 50% and 12% of the variability)  
 469

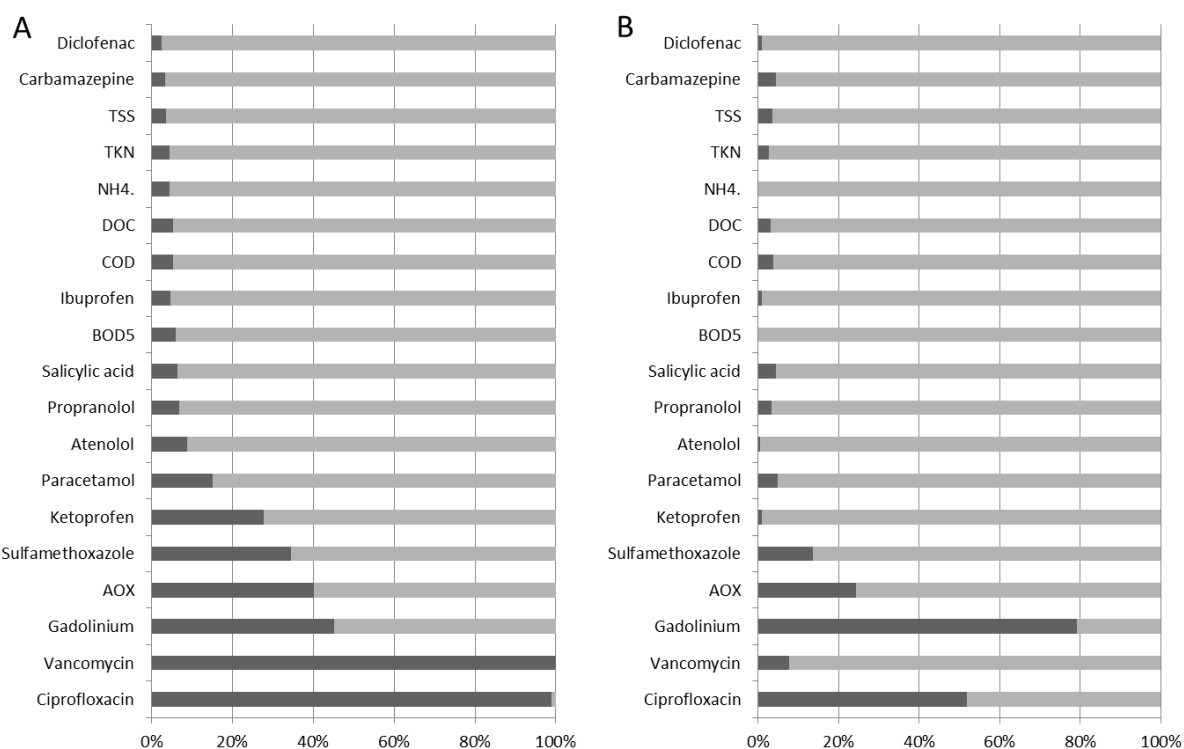
470 Besides, monthly campaigns showed great variability of concentrations and loads, both in  
 471 hospital and urban WW, with coefficients of variation up to 200%. An example is shown in  
 472 Figure 3, for sulfamethoxazole. An increase of sulfamethoxazole load of hospital WW can be  
 473 observed in autumn 2014 and 2015, which can be attributed to an increase in consumption  
 474 during these periods. A higher variation of the HWW load compared to the UWW load is  
 475 observed, which can be explained by the small number of patients compared to the large  
 476 number of people taking pharmaceuticals at home (Ort et al. 2010). Apart from this case, no  
 477 seasonality was observed for the other compounds both in urban and hospital WW, which is  
 478 in accordance with Kosma et al. 2010 (Kosma et al. 2010). This is in contradiction with other  
 479 studies (Fernández et al. 2014, Yu et al. 2013) which reported higher concentrations in winter.  
 480 However they present shorter monitoring period (1 year), lower number of sampling  
 481 campaigns and the WWTP studied were significantly larger. Fernández et al. 2014 also  
 482 studied the seasonality of PhC concentrations in WW and found no tendency.  
 483



484  
 485 **Fig. 3** – Evolution of the load of sulfamethoxazole through SIPIBEL campaigns in hospital and  
 486 wastewaters  
 487

488 Finally, contributions of hospital and urban micropollutants to the total load of  
 489 micropollutants in raw and treated WW were calculated to evaluate the importance of hospital  
 490 WW concerning the input of pollutants (Figure 4). Hospital contribution to the total load of  
 491 raw WW is higher than 10% for Gd (45%), AOX (40%), paracetamol (15%), ketoprofen  
 492 (28%) and the antibiotics sulfamethoxazole (34%), ciprofloxacin (99%) and vancomycin  
 493 (100%). These values are relatively high compared to the literature (Azuma et al. 2016,  
 494 Kleywegt et al. 2016, Ort et al. 2010, Santos et al. 2013). First, the percentage that represents  
 495 the hospital flow to the total flow of the WWTP is quite high (3%), whereas this ratio is lower  
 496 in the other studies: between 0.2% in Kleywegt et al. 2016 study and 2% in Santos et al. 2013.  
 497 Nevertheless, paracetamol, ketoprofen and sulfamethoxazole contributions are consistent with  
 498 Santos et al. 2013. Secondly, the urban network of our study is collecting WW from about  
 499 20,850 inhabitants, which represents a bed density (number of beds per 1,000 inhabitants) of  
 500 21.6. Hospital bed densities in developed countries are usually around 5 beds per 1,000  
 501 inhabitants (Ort et al. 2010). Verlicchi et al. 2012a compared studies with bed density  
 502 between 4 and 33.5: logically, the highest contributions were found in the case of the highest  
 503 bed density. Finally, high contributions of vancomycin and ciprofloxacin are explained by the  
 504 fact that these substances were respectively never quantified and quantified only in 10% of  
 505 the samples in UWW. After treatment, thanks to good overall removal efficiency, hospital  
 506 contribution is higher than 10% only for Gd (79%), AOX (24%), and the antibiotics  
 507 sulfamethoxazole (14%), ciprofloxacin (52%).





508  
 509 **Fig. 4** – Hospital (black) and urban (grey) contributions of conventional parameters and pharmaceuticals to total  
 510 load of pollutants in A: wastewaters and B: treated effluents  
 511

512  
 513 **Conclusion**

514  
 515 This article presents the results of a two years regular monitoring of conventional  
 516 physicochemical parameters and thirteen PhAC of various classes, in urban and hospital raw  
 517 wastewaters and their treated effluents. With the help of accurate sampling strategies and the  
 518 use of advanced analytical techniques, an in-depth characterization of hospital and urban WW  
 519 was performed. Organic carbon, AOX, phosphates, Gadolinium and the pharmaceuticals  
 520 paracetamol, ketoprofen and antibiotics were found in higher concentrations in hospital  
 521 effluents. After activated sludge treatment, only concentrations of antibiotics were still higher  
 522 in hospital effluents. Nevertheless, due to a significantly higher flow from the urban  
 523 catchment, despite higher concentrations for certain compounds in hospital WW, hospital  
 524 contribution of PhAC was lower than domestic contribution. Finally, even if hospital and  
 525 urban WW were treated in the same geographical environment, differences in removal  
 526 efficiencies were observed, which may be due to various factors: the specific composition of  
 527 the hospital WW, hydraulic retention time and redox conditions.  
 528

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534

535

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686 **Figure captions**

687 Figure 1 : Boxplots presenting comparison of removal rates of pharmaceuticals and other  
688 physico-chemical parameters in hospital (H) and Urban (U) during colder (\_c) (<14°C) and  
689 warmer (\_w) (>14°C) months (in %)

690 Figure 2 : PCA based on loads of pharmaceuticals parameters in the locations UWW and  
691 HWW (the first two axes represent respectively 50% and 12% of the variability)

692 Figure 3 : Evolution of the load of sulfamethoxazole through SIPIBEL campaigns in hospital  
693 and urban wastewaters

694 Figure 4 : Hospital (black) and urban (grey) contributions of conventional parameters and  
695 pharmaceuticals to total load of pollutants in A: wastewaters and B: treated effluents

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