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# 1 Occurrence and removal efficiency of pharmaceuticals in an 2 urban wastewater treatment plant: mass balance, fate and 3 consumption assessment

4  
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8  
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## 12 13 **Abstract**

14 The occurrence of 15 pharmaceutically active compounds (PACs) in an urban wastewater  
15 treatment plant (WWTP) was assessed in both influent and effluent samples. PACs were  
16 quantified by gas chromatography coupled to mass spectrometry. The sampling campaign was  
17 carried out during summer (n = 13) to assess the variation in both the influent concentrations and  
18 the removal efficiencies in similar climatic conditions. Among the selected PACs, all were  
19 quantified in influent samples but two of them were not systematically detected mainly due to the  
20 high quantification limit. PACs were detected at  $\mu\text{g.L}^{-1}$  levels with a maximum concentration of  
21  $96.7 \mu\text{g.L}^{-1}$  for Acetaminophen. The mean mass balance of the whole PAC pool during tracking  
22 was  $448.5$  and  $26.3 \text{ g.day}^{-1}$  in influents and effluents respectively. However, the removal  
23 efficiency varied depending on the sample (e.g. between -20 and 50 % for Diclofenac). The fate  
24 of PACs during water treatment therefore depends on the removal quality in general, highlighted  
25 by the removal of nitrogen or  $\text{BOD}_5$ . As a result, effluent concentrations were variable, unlike  
26 influent concentrations which were used to correctly assess the consumption behavior of the

27 population around the sampled WWTP. Although the daily mass loads were comparable with  
28 those found in other studies in Europe for the same type of WWTP, the estimated consumption  
29 sometimes exhibited significant differences with the theoretical one. These differences depend on  
30 the mode of consumption, i.e. whether the therapeutic class treats chronic or episodic diseases,  
31 and on the scale gap between estimated and theoretical concentrations.

32

## 33        **1. Introduction**

34    In recent decades Pharmaceutically Active Compounds (PACs) have been extensively  
35    investigated as they represent a common and persistent form of pollution in numerous  
36    water compartments, from wastewaters to drinking water (Mompelat et al., 2009; Ternes,  
37    1998). Due to their high frequency of detection (Loos et al., 2010; Lopez et al., 2015;  
38    Vulliet and Cren-Olivé, 2011) and their significant concentrations in natural waters (i.e.  
39    from  $\text{ng.L}^{-1}$  to  $\mu\text{g.L}^{-1}$ ), they are now considered as a potential hazard for numerous living  
40    beings, including humans (de Jongh et al., 2012; Grabicova et al., 2014). A study has  
41    recently demonstrated at field-relevant concentration (i.e. tested at  $1.8\mu\text{g.L}^{-1}$ , for a field  
42    concentration of  $0.58 \mu\text{g.L}^{-1}$ ) the impact of a benzodiazepine on the behaviour of the  
43    European Perch (Brodin et al., 2013).

44    The main origin of these contaminants is human and cattle therapies which lead to variable rates  
45    of excretion via urine and faeces, depending on the PACs characteristics (Lienert et al., 2007).  
46    Due to the continuous increase in drug consumption during the XX<sup>th</sup> century, the levels of  
47    contamination raise serious questions about the amounts of PACs prescribed (Daughton, 2014).

48    Activated sludge treatment plants are the most common and therefore the most widely  
49    studied type of Wastewater Treatment Plant (WWTP) around the world (Collado et al.,  
50    2014; Lindberg et al., 2014; Yan et al., 2014). This type of plant allows a significant  
51    removal of classical chemical parameters such as  $\text{BOD}_5$  or TP (Jones et al., 2007).  
52    However, the removal of PACs remains insufficient (Petrie et al., 2013; Verlicchi et al.,  
53    2012). The discrepancy between this insufficient removal and the increase in drug  
54    consumption means that contamination by PACs will remain a problem for the  
55    foreseeable future.

56 Several studies propose innovative tertiary treatments in order to improve the removal of  
57 PACs (Altmann et al., 2015; Gerrity et al., 2016; Lee et al., 2016; Thiebault et al., 2016a).  
58 Their use is nevertheless expensive and it seems important to better understand the origin  
59 of this lack of efficiency in activated sludge treatment.

60 Estimating the link between the consumption of a drug and the contamination level in  
61 effluent is important for field managers in order to assess the level of pollution in real  
62 time. Tracking the concentration of PACs in influents can also provide information on the  
63 consumption behaviour of the population concerned in order to determine some site-  
64 specific features (Baz-Lomba et al., 2016). To address this issue, influents and effluents  
65 were sampled within the same season. Several studies have demonstrated that the removal  
66 efficiency is not constant throughout the year, due to a seasonal effect (Papageorgiou et  
67 al., 2016; Sui et al., 2011). It also appeared important to assess the variability in removal  
68 efficiency within a single season, in our case summer, in order to determine whether  
69 removal remains constant during the same climatic event and what the origin of these  
70 variations is, such as for example variation in the efficiency of treatment step.

71 The analytical method selected in the present work was GC-MS. Previous studies have  
72 demonstrated that, although not widely used, this technique is suitable for the analysis of  
73 pharmaceutical residues at field-relevant concentrations (Jones et al., 2007; Togola and  
74 Budzinski, 2008). While GC-MS presents some disadvantages compared to HPLC-MS<sup>2</sup>  
75 (analytical duration and sample preparation), the equipment is widely available and the  
76 method has certain advantages (weak matrix effect, low analytical cost) that offset its  
77 drawbacks (Hao et al., 2007).

78 The aim of this study was therefore to optimize this technique for the analysis of PACs  
79 generated by human consumption in both influents and effluents in order to assess the fate

80 of PACs during activated sludge treatment within the same season. The results obtained  
81 should suggest new tools for a better prediction of removal assessment and consequently  
82 of environmental contamination.

## 83 **2. Materials and Methods**

### 84 **2.1. Site settings**

85 The WWTP investigated is one of the three main plants that serve the town of Orléans.  
86 The purification capacity of the installation is 93,933 population equivalent (PE). Influent  
87 arrive at the WWTP by two routes: the first collects the industrial effluents of a paper mill  
88 and the second collects domestic waste. Since 1989, the effluents have been discharged  
89 into the Loire river.

90 The treatment chain of domestic effluents consists in a conventional activated sludge  
91 treatment (Figure S1) with a hydraulic retention time of 2 days and a solid retention time  
92 between 10 and 20 days.

### 93 **2.2 Sample Collection**

94 Influent and effluent were collected by an automatic sampler indexed to the flow  
95 between April and August 2015 ( $n = 13$ ). Each sample was a 24h-composite and was  
96 collected in 5-liter glass jars. After collection, samples were filtered with glass fiber filters  
97 (GF/A and GF/F, Whatman) and 0.45 $\mu$ m filters (Millipore) within 2 hours. The filters  
98 were previously heated at 105°C during 24 hours to eliminate any residual water.  
99 Residues were stored in the fridge before solid-phase extraction, carried out within the  
100 following 2 days.

101 The physico-chemical parameters (BOD<sub>5</sub>, COD, etc.) of the collected samples were also  
102 analyzed and are summarized in Table S1.

### 103 **2.3. Chemical Reagents**

104 The 15 PAC standards (purity grade > 98 %; see Table 1 for details) were obtained from  
105 Sigma-Aldrich for Acetaminophen (ACM), Atenolol (ATE), Carbamazepine (CBZ),  
106 Codeine (COD), Diazepam (DIA), Doxepin (DOX), Gemfibrozil (GEM), Ketoprofen  
107 (KET), Metoprolol (MET), Naproxen (NAP), Oxazepam (OXA), Salicylic acid (SCA),  
108 Tramadol (TRA), and from Acros Organics for Diclofenac (DIC) and Ibuprofen (IBU).

109 The PAC standards were selected from various therapeutic classes: analgesics (ACM and  
110 SCA), anti-inflammatory drugs (DIC, IBU, KET and NAP), psychotropic drugs (CBZ,  
111 DIA, DOX and OXA),  $\beta$ -blockers (ATE and MET) and lipid regulators (GEM). The  
112 internal standards Tramadol-d<sub>6</sub> and 5 $\alpha$ -cholestane were purchased from Sigma-Aldrich.

113 Chemical reagents of analytical grade, methanol (MeOH) and pyridine were purchased  
114 from Fisher Scientific. N-tert-Butyldimethylsilyl-N-methyltrifluoroacetamide  
115 (MTBSTFA, 95 %) was supplied by Sigma-Aldrich.

### 116 **2.4. Residues concentration and analysis**

117 Leachate solutions were concentrated by Solid-Phase Extraction (SPE) and analyzed by  
118 Gas Chromatography coupled to Mass Spectrometry (GC-MS). This methodology was  
119 already used in previous studies (Thiebault et al., 2016a, 2016b) but was optimized here  
120 for low concentrations.

121 PAC concentration was carried out on a 6 mL glass cartridge filled with HR-X phase  
122 (Macherey-Nagel). Cartridges were conditioned with 5 mL of MeOH followed by 5 mL of  
123 ultra-pure water. Columns were filled with 100 mL of sample, previously spiked with the

124 appropriate amount of the first internal standard (i.e. Tramadol-d6), and then rinsed with 5  
125 mL of ultra-pure water before drying for 30 minutes under vacuum. Finally, elution was  
126 performed with 3 x 5 mL of MeOH. Thereafter, the second internal standard (i.e. 5 $\alpha$ -  
127 cholestane) was added to organic layers in order to control the conservation and the  
128 injection of the samples. Then, organic layers were evaporated under reduced pressure.  
129 Residues were finally derivatized in a pyridine-MTBSTFA mix (60:40) at 60°C during 60  
130 minutes.

131 Analyses were performed on a Trace GC Ultra gas chromatograph (GC) coupled to a TSQ  
132 Quantum XLS mass spectrometer equipped with an AS 3000 autosampler (both from  
133 Thermo Scientific). The GC was fitted with a Thermo Trace Gold TG-5 MS capillary  
134 column (60 m, 0.25 mm i.d., 0.25  $\mu$ m film thickness).

135 The temperature of the column was held at 50°C for 3 min, increased from 50 to 120°C at  
136 30°C min<sup>-1</sup>, and from 120 to 310°C at 3°C min<sup>-1</sup> with a final isothermal hold at 310°C for  
137 21 min. 2  $\mu$ L of sample was injected in splitless mode at 280°C. Helium was the carrier  
138 gas (1 mL min<sup>-1</sup>). The mass spectrometer was operated in EI mode at 70 eV, from m/z 50  
139 to 500.

140 Calibration curves were realized following the same preparation procedure as for the  
141 samples. The Method Quantification Limit (MQL) was estimated by using a signal to  
142 noise ratio of up to 10 (Jelic et al., 2011).

## 143 **2.5. Processing of Results**

144 The use of raw concentrations is not a consistent way to assess the removal efficiency of  
145 WWTPs and the daily variation in the amount of PACs. The irregularity of the flow of  
146 both influents and effluents impacts the assessment of the removal efficiency based on  
147 concentrations. It is therefore necessary to calculate both influent and effluent load. In the



148 present study, they were two reasons for this irregularity: (i) the flow generated by the  
149 industrial installation is not regular over the week since the factory closes during the  
150 weekend; (ii) influents are contaminated by rainwater despite the splitter network. By  
151 taking into account the flow, it is possible to calculate the load of PACs that passed  
152 through the WWTP for each sampling campaign.

$$\text{load} = C \times F$$

153 with load, the mass load of PACs in  $\text{mg}\cdot\text{day}^{-1}$ ,  $C$ , the concentration in  $\mu\text{g}\cdot\text{L}^{-1}$ , and  $F$ , the  
154 flow in  $\text{m}^3\cdot\text{day}^{-1}$

155 The removal efficiencies were hereafter calculated based on loads.

$$\text{Removal} = 100 - \frac{(\text{load}_{eff} \times 100)}{\text{load}_{inf}}$$

156 with *Removal* the removal efficiency in %

157 Another mandatory back-calculation is to normalize the load by the number of PE.

$$\text{DML} = \frac{\text{load}}{n_{PE}}$$

158 with DML, the daily mass load in  $\text{mg}\cdot\text{day}^{-1}\cdot\text{PE}^{-1}$  and  $n_{PE}$ , the population-equivalent  
159 number around the WWTP.

160 Lastly, to calculate the consumption of each PAC, a correction factor must be applied by  
161 taking into account the sorption on suspended particles and the molar ratio between the  
162 parent and the targeted residue (Baker et al., 2014; Gracia-Lor et al., 2016). In the present  
163 study, two PACs are concerned by this molar ratio variation, SCA and OXA, in order to  
164 calculate the consumption of acetylsalicylic acid and DIA respectively. The use of by-  
165 product derived from the original PAC is justified when the former exhibits a better

166 stability than the latter (Baker et al., 2014). The consumption was back-calculated on  
 167 influent DML only.

$$Consumption = \frac{DML_{inf}}{ExR} \times \frac{Mwp}{Mwr} \times \left( \frac{100}{100 - SSP} \right)$$

168 with *Consumption*, the estimated consumption in  $mg \cdot day^{-1} \cdot PE^{-1}$ , *ExR*, the excretion rate in  
 169 %, *Mwp*, the molecular weight of the parent compound in  $g \cdot mol^{-1}$ , *Mwr*, the molecular  
 170 weight of the targeted residue in  $g \cdot mol^{-1}$  and *SSP* the sorption onto suspended particles in  
 171 %.

172 Correlation matrix and pairwise *p*-values were performed by using the package FactoMineR of  
 173 the R software (Lê et al., 2008). Statistical analyses were performed on removal values calculated  
 174 based on loads. The Pearson correlation was used to assess both the correlation matrix and *p*-  
 175 values.

176 Table 1: Studied compounds with various parameters (CAS-Number, Log Kow the octanol/water  
 177 partition, pKa and MW the molecular weight in  $g \cdot mol^{-1}$ ), and method validation data: m/z ratio  
 178 (quantification and confirmation), RR, the recovery ratio obtained by SPE  $\pm$  the relative standard  
 179 deviation of triplicates in %,  $r^2$  the linearity of calibration curves, MQL the method quantification limit for  
 180 influent and effluent in  $\mu g \cdot L^{-1}$ , and RSD the standard deviation of analytical triplicates in %

Class	PAC	CAS-Number	pKa	Log Kow	TR	MW	m/z ratio	RR	$r^2$	MQL <sub>inf</sub>	MQL <sub>eff</sub>	RSD
<i>Analgesics</i>												
	ACM	103-90-2	9.4	0.46	41.71	151.2	322 248	85.0 $\pm$ 0.49	0.993	0.067	0.008	6
	SCA	69-72-7	3.5	1.19	37.36	138.1	309 195	82.5 $\pm$ 0.96	0.996	0.045	0.006	5
<i><math>\beta</math>-blockers</i>												
	ATE	29122-68-7	9.6	0.16	61.99	266.3	437 72	68 $\pm$ 2.07	0.992	0.243	0.078	8
	MET	56392-17-7	9.6	1.79	47.86	267.4	223 324	70.8 $\pm$ 1.98	0.994	0.155	0.040	11
<i>Psychotropic drugs</i>												
	CBZ	298-46-4	13.9	2.25	53.56	236.3	193 237	73.3 $\pm$ 0.80	0.997	0.032	0.003	10
	DIA	439-14-5	3.4	2.82	53.34	284.7	256 221	62.2 $\pm$ 1.96	0.992	0.282	0.025	19
	DOX	1229-29-4	8.9	3.86	46.98	279.4	58 313	116 $\pm$ 2.51	0.995	0.058	0.018	8
	OXA	604-75-1	1.7- 11.6	2.31	60.16	287.0	457 147	73.2 $\pm$ 0.86	0.999	0.036	0.002	5
<i>Anti-inflammatory drugs</i>												

	DIC	15307-79-6	4.2	4.06	54.61	296.2	352 214	85.0 ± 0.82	0.999	0.022	0.006	7
	IBU	15687-27-1	4.9	3.72	33.78	206.3	263 303	78.7 ± 1.09	0.990	0.025	0.005	6
	KET	22071-15-4	4.5	2.81	51.71	254.3	311 295	65.4 ± 1.02	0.999	0.042	0.005	10
	NAP	22204-53-1	4.2	3.00	48.18	230.3	287 185	85.1 ± 2.09	0.998	0.153	0.032	8
<i>Lipid regulator</i>												
	GEM	25812-30-0	4.8	3.40	44.41	250.3	243 185	70.8 ± 1.96	0.999	0.368	0.080	17
<i>Opioids</i>												
	COD	76-57-3	8.21	1.20	59.33	299.4	313 235	71.5 ± 5.2	0.998	0.030	0.008	6
	TRA	27203-92-5	9.4	2.51	38.06	263.4	58 263	98.7 ± 2.82	0.994	0.064	0.016	8

181

182

### 183 3. Results

#### 184 3.1. Occurrence of PACs

185 Table 2: Minimum, median and maximum concentrations (in  $\mu\text{g.L}^{-1}$ ) and number of detections ( $n = 13 =$   
 186 100 %) of each selected PAC in influent and effluent samples; n.d corresponds to non-detected  
 187 concentration

Class	PAC	Influent				Effluent			
		min	med	max	<i>n</i>	min	med	max	<i>n</i>
<i>Analgesics</i>									
	ACM	22.6	55.8	96.7	13	n.d	0.013	0.172	11
	SCA	2.36	10.6	25.5	13	0.007	0.096	0.423	13
<i><math>\beta</math>-blockers</i>									
	ATE	3.56	16.4	26.5	13	n.d	0.893	9.32	12
	MET	0.277	1.26	2.76	13	n.d	0.121	1.75	8
<i>Psychotropic drugs</i>									
	CBZ	0.051	0.215	0.937	13	0.005	0.163	0.357	13
	DIA	n.d	n.d	0.420	1	n.d	n.d	0.030	1
	DOX	0.092	0.279	1.02	13	n.d	0.028	0.299	11
	OXA	0.154	1.20	2.02	13	0.005	0.499	1.13	13
<i>Anti-inflammatory drugs</i>									
	DIC	0.063	0.245	1.19	13	0.043	0.079	1.38	13
	IBU	1.56	2.27	7.28	13	0.006	0.038	0.284	13
	KET	0.149	1.70	6.56	13	0.015	0.047	0.176	13
	NAP	0.457	1.33	4.74	13	n.d	0.058	0.238	12

<i>Lipid regulator</i>									
GEM	n.d	n.d	0.648	4	n.d	n.d	0.105	2	
<i>Opioids</i>									
COD	0.279	0.933	2.11	13	n.d	0.137	0.518	12	
TRA	1.35	1.63	9.86	13	0.072	0.273	1.19	13	

188

189 The occurrence of the selected PACs in influent and effluent samples is presented in Table 2.

190 In influent samples, three PACs presented a median concentration up to 10  $\mu\text{g.L}^{-1}$ , namely ACM,

191 SCA and ATE. They were also among the most abundant compounds with a frequency of

192 detection of 100 %. Only two PACs, DIA and GEM, exhibited a frequency of detection less than

193 100 % during the tracking in influents. The MQL of these two compounds is significantly high

194 (Table 1), which could explain this weak frequency of detection.

195 In effluent samples, the most abundant PACs were OXA, ATE and TRA (Table 2), with median

196 concentrations up to 0.2  $\mu\text{g.L}^{-1}$ . Other compounds, such as MET and DIC, presented occurrences

197 up to  $\mu\text{g.L}^{-1}$  but the median concentrations remained below 0.2  $\mu\text{g.L}^{-1}$ . Unsurprisingly, the

198 frequency of detection in effluent samples was lower than in influents, as illustrated for example

199 by ACM ( $n = 11$ ), the most abundant compound in influents. However, the frequency of

200 detection for most compounds, such as CBZ and DIC, was 100% in both influent and effluent

201 (Table 2).

### 202 **3.2. Load assessment**

203 Apart from some extreme values (e.g. DOX) or significant variations in concentration for DIC

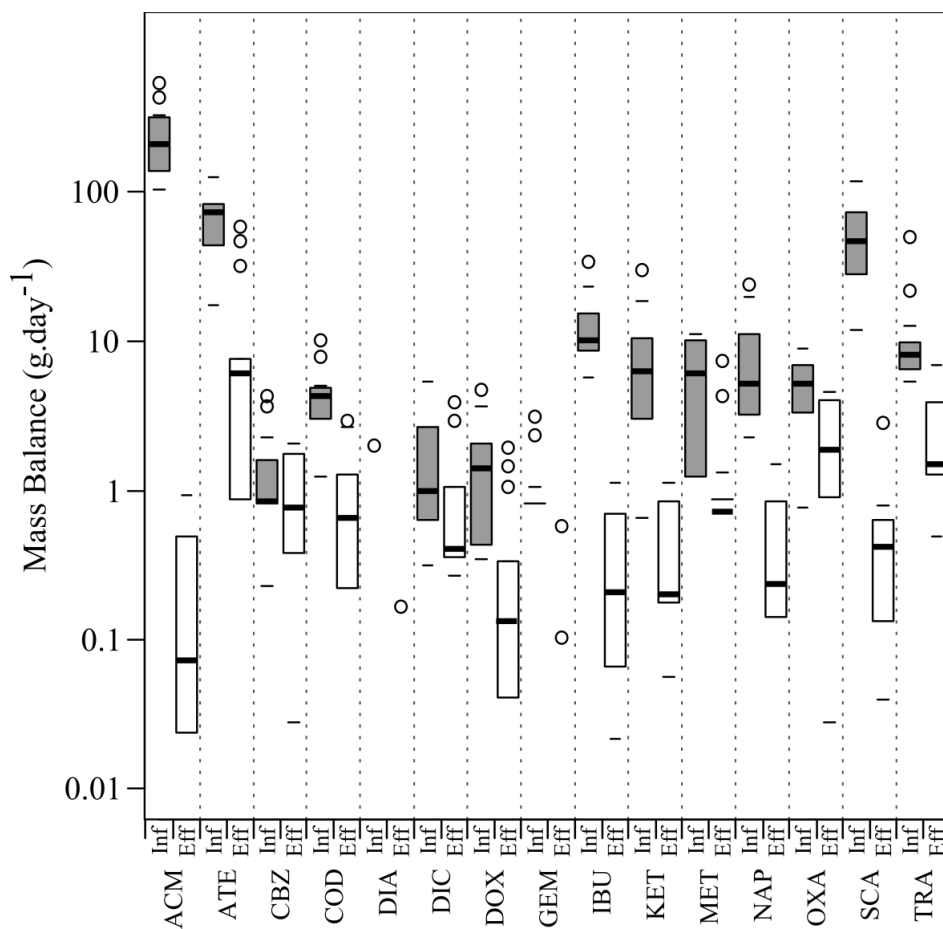
204 and MET (i.e. above one order of magnitude), the influent mass balances varied only slightly

205 during this seasonal monitoring, confirming several studies (Birošová et al., 2014; Sui et al.,

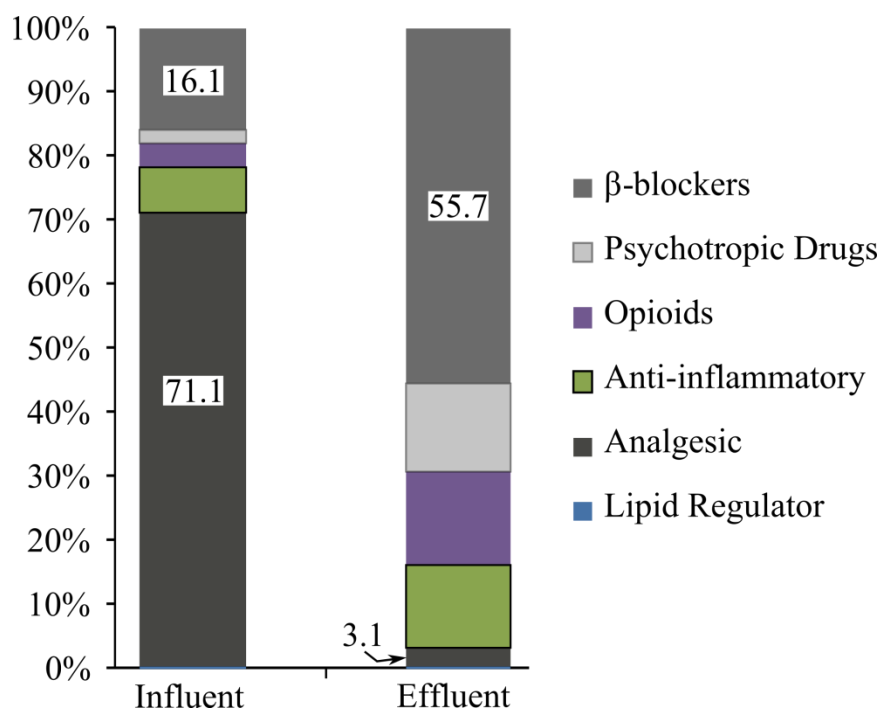
206 2011; Thiebault et al., 2017). However, the variability rarely exceeds one order of magnitude

207 (Figure 1).

208 Conversely, significant variations were observed in effluent concentrations and removal  
 209 efficiency, two interdependent values, with effluent concentrations extending over two or three  
 210 orders of magnitude. For example the effluent load of ATE varied from <MQL to 59 g.day<sup>-1</sup>  
 211 (Figure 1).



212  
 213 Figure 1: Boxplots of loads for each PAC in influent and effluent samples. The line within the box marks  
 214 the median, boundaries indicate the 25<sup>th</sup> and 75<sup>th</sup> percentiles, error bars indicate the maximum and the  
 215 minimum load  $\pm 1.5$  standard deviation and white squares indicate values outside this range



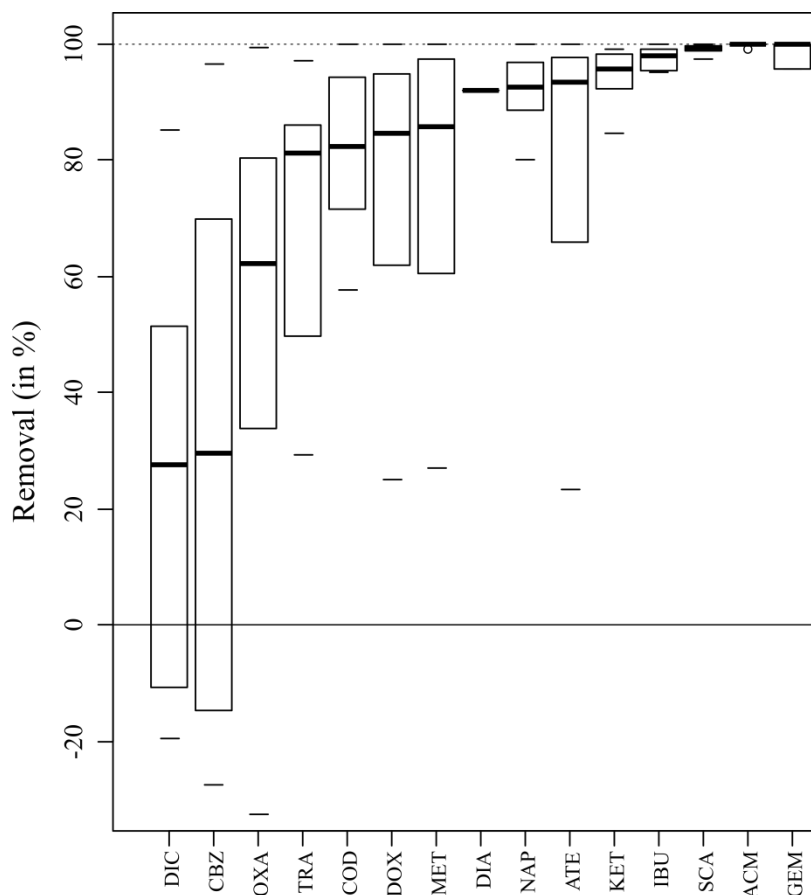
216

217 Figure 2: Relative percentage of each therapeutic class in both influent and effluent based on the mean  
 218 load value

219 Raw data give mean loads of 448.5 and 26.3 g.day<sup>-1</sup> in influent and effluent respectively,  
 220 corresponding to a mean removal of 94% when adding the load of each selected PAC. By  
 221 separating the total load values into therapeutic classes, it is possible to assess the relative  
 222 contribution of each class to the influent and effluent composition (Figure 2).

223 It can be seen that whereas analgesics predominate in influents with a relative percentage of 71%,  
 224 their contribution drops to 3.1% of the total load of PACs in effluents. The opposite trend is  
 225 observed for other classes whose contribution significantly increases between influent and  
 226 effluent. beta-blockers are especially concerned, with a relative percentage of 16.1% in influent  
 227 which increases to 55.7% in effluent, indicating that this class represents the predominant load in  
 228 effluents of this WWTP, a case already mentioned in other plants (Behera et al., 2011).

229 It should be mentioned that some therapeutic classes, such as antibiotics, are not present in this  
230 study due to the methodology employed. These classes may potentially make a significant  
231 contribution to the total load.



232 Figure 3: Removal efficiencies of each PAC for all samples calculated on load values. The line within the  
233 box marks the median, boundaries indicate the 25<sup>th</sup> and 75<sup>th</sup> percentiles and error bars indicate the  
234 maximum and the minimum removal values

### 235 3.3. Removal of PACs

236 As noted in previous studies, the removal efficiency was variable in time, especially for low  
237 concentrations of PACs for which the analytical error is proportionally higher. For the lower  
238 removal efficiencies such as DIC, the values varied between -20 % and 50 % (Figure 3). This is  
239 consistent with literature data, even in the same WWTP (Verlicchi et al., 2012). For the most  
240 concentrated compounds, the removal varied from 95 to 100 % (e.g. ACM and SCA).

241 These results revealed that beyond a seasonal effect regularly pointed out in the literature as  
242 impacting the removal efficiency (Sui et al., 2011; Zhang et al., 2015), there is also a significant  
243 removal variability within the same season. Thus, it seems risky to estimate the removal  
244 efficiency in a particular season based on the analysis of only one or two samples.

245 This high variability could be caused by changes in the chemical parameters of the influent water  
246 that could potentially affect the water-treatment efficiency, since while the influent  
247 concentrations of PACs remained fairly stable, the chemical parameters of the raw waters  
248 changed (Table S1).

249 The removal of classical wastewater parameters was also calculated to assess the stability of the  
250 removal quality during the tracking (Table S2). Their removal is stable, especially concerning the  
251 carbonaceous organic matter, whereas the removal of nitrogen is far more variable (i.e. between  
252 30 and 99%; Table S2).

## 253 **4. Discussion**

### 254 **4.1. Fate of PACs during treatment**

255 The considerable variation in the removal efficiency of PACs in the selected WWTP raises  
256 questions about the regularity in time of the removal mechanisms (Figure 3). In activated sludge  
257 treatment, two main mechanisms remove PACs. Firstly, biodegradation generated by several  
258 types of bacteria (i.e. for the removal of carbonaceous organic matter or nitrogen) and then,  
259 flocculation/precipitation that is mostly responsible of the removal of phosphorus (Joss et al.,  
260 2005).



261 The statistical correlation between the removal efficiency of PACs and the removal efficiency of  
262 classical wastewater quality parameters (Table S2) could therefore point out the mechanism  
263 which is responsible for the degradation of each PAC (Table 3).

264 Table 3: Correlation coefficients describe the relationship between removal efficiencies of each detected  
 265 PAC and removal efficiencies of classical parameters of water treatment, DIA and GEM are not presented  
 266 due to their low frequency of detection <sup>1</sup>

	ACM	ATE	CBZ	COD	DIC	DOX	IBU	KET	MET	NAP	OXA	SCA	TRA
<b>BOD<sub>5</sub></b>	-0.02	-0.04	0.60**	-0.13	-0.22	-0.49**	-0.17	0.09	0.57**	-0.24	-0.11	0.03	-0.35
<b>COD</b>	-0.09	0.00	0.21	-0.27	-0.21	-0.43*	-0.47*	-0.22	0.68***	-0.50**	-0.30	-0.35	-0.50***
<b>SS</b>	-0.23	0.29	0.06	0.24	0.35	0.15	-0.39*	0.08	0.09	0.05	0.00	-0.06	0.01
<b>GLN</b>	-0.10	0.75***	-0.13	0.61**	0.39*	0.64***	0.07	-0.05	-0.35	0.49*	0.77***	0.10	0.59*
<b>NH<sub>4</sub><sup>+</sup></b>	0.14	0.76***	-0.14	0.09	-0.12	0.10	-0.22	-0.09	-0.01	0.12	0.51**	-0.21	0.18
<b>NO<sub>2</sub><sup>-</sup></b>	0.20	0.55**	0.16	0.01	-0.05	-0.12	-0.32	0.00	0.39*	-0.01	0.25	-0.16	-0.06
<b>NO<sub>3</sub><sup>-</sup></b>	-0.09	0.33	0.08	0.20	0.53**	0.26	-0.19	-0.01	0.27	0.48*	0.45*	0.05	0.45*
<b>TKN</b>	-0.15	0.69***	-0.19	0.35	0.17	0.33	-0.25	-0.02	-0.21	0.24	0.48*	-0.10	0.23
<b>TP</b>	-0.26	0.00	-0.38	0.22	0.02	0.46*	0.20	-0.07	-0.53**	-0.04	-0.14	-0.03	0.02

267 Highly removed PACs such as ACM and SCA (i.e. > 99.9%, Figure 1) do not exhibit any  
 268 statistically significant correlation with other parameters. Yet, these two PACs are known be  
 269 highly biodegradable and photodegradable micropollutants and variations in the WWTP  
 270 operating conditions should not affect their removal (Andreozzi et al., 2003; Petrie et al., 2015).  
 271 Moderately removed PACs such as ATE, MET and TRA (i.e. median removal between 80 and  
 272 99%) exhibit several statistically significant correlations that could indicate the process which is  
 273 responsible for their removal (Miège et al., 2009). MET is known to be sensitive to the  
 274 biodegradation induced by various type of bacteria (Velázquez and Nacheva, 2017), and the  
 275 correlation with both the removal of BOD<sub>5</sub> and NO<sub>2</sub><sup>-</sup> indicates that the quality of oxic processes  
 276 (i.e. oxic degradation of carbonaceous organic matter, and oxidation of nitrites into nitrates)  
 277 impacts the removal of MET. Global nitrogen removal is also presented as a key factor  
 278 concerning the removal efficiency of several PACs such as ATE (Miège et al., 2009; Vieno et al.,  
 279 2007). This assumption is verified by the statistically significant correlation between the removal  
 280 of ATE and the removal of global nitrogen (i.e. GLN) in our results (Table 3).

\* \*\*, \*\*\* correspond to *p*-values < 0.05, 0.01 and 0.001 respectively

281 Tracking the removal of nitrogen in a plant could therefore be a solution in order to estimate the  
282 removal of several PACs such as ATE but also COD, DOX, NAP, OXA, DIC and TRA,  
283 respectively (Table 3).

284 CBZ is considered as a persistent compound in conventional wastewater treatment (Bahlmann et  
285 al., 2014; Clara et al., 2005). The results presented in this study are in accordance with this, as  
286 one of the lowest removal values was found for CBZ (Figure 3). However, the limited removal of  
287 CBZ would be caused by aerobic biodegradation (Kosjek et al., 2009; Petrie et al., 2013). This  
288 assumption is confirmed by the statistically significant correlation between the removal of CBZ  
289 and the removal of BOD<sub>5</sub> (Table 4). Although low, the removal of CBZ remains significant and  
290 is probably enhanced by the selected season (i.e. end of spring and summer) which maximized  
291 biological activity (Collado et al., 2014).

292 Lastly, the flocculation/precipitation could impact the removal of PACs. Even if the sorption of  
293 PACs is recognized as minor in the treatment process (Jones et al., 2006; Luo et al., 2014;  
294 Radjenović et al., 2009), some hydrophobic PACs could be impacted by this mechanism, mainly  
295 responsible for the removal of phosphorus. Only the removal of DOX demonstrates a statistically  
296 significant correlation with the removal of phosphorus. DOX is one of the most hydrophobic  
297 contaminants among the selected PACs with DIC and IBU (Table 1). But unlike DIC and IBU  
298 (i.e. anionic forms), DOX is in cationic form due to the slightly alkaline pH (Table S1). Yet, the  
299 sorption of cationic pollutants onto negatively charged surfaces of microorganisms and sludge is  
300 proposed as an efficient removal factor especially for hydrophobic compounds (Giebułtowicz and  
301 Nałęcz-Jawecki, 2014; Ternes et al., 2004). This difference of charge state between DOX, DIC  
302 and IBU therefore explains the difference in the statistical correlation between the removal of  
303 these PACs and the removal of phosphorus.

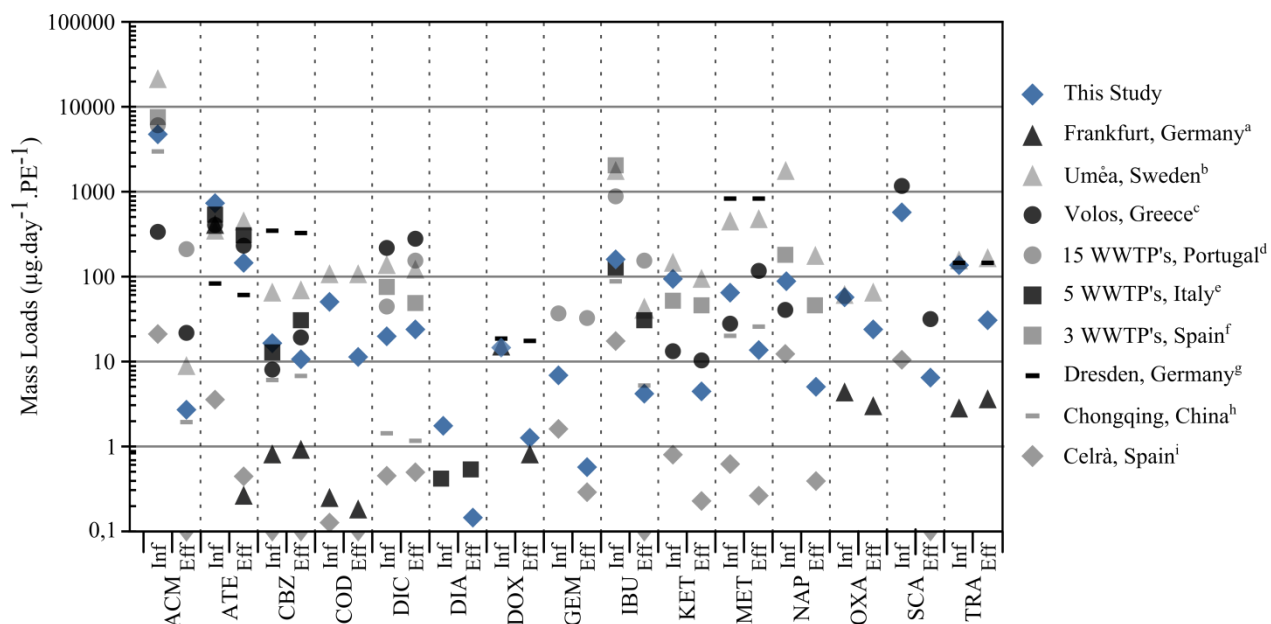
304

305 Beyond the link between the removal efficiencies of PACs and chemical parameters, negative  
306 removal values also raise questions. The PACs concerned are DIC, CBZ and OXA. Negative  
307 removal values for these PACs are frequently observed but can be attributed to various reasons.  
308 For both DIC and CBZ, the most common reason given is that they are partially excreted in  
309 conjugated form. Yet, they can be transformed back to parent compound during treatment  
310 explaining their negative removal values (Bahlmann et al., 2014; Ternes, 1998). Concerning the  
311 negative removal values of OXA, the main reason put forward for its persistence is its position at  
312 the end of the degradation pattern of benzodiazepines such as DIA and temazepam (Hummel et  
313 al., 2006), which may artificially increase the concentration of this product. Although we  
314 analysed the occurrence of DIA in this study, only one occurrence was found, mainly due to the  
315 high MQL (Table 1). However, concentrations of OXA were greater than those of DIA (Table 2).

#### 316 **4.2. Daily mass loads of PACs**

317 The mean DML obtained in this study can be compared with those obtained in previous ones to  
318 assess the average impact per inhabitant in Orléans with respect to other places in the world.  
319 Another possibility is to assess the type of influents by comparing their PAC loads. For example,  
320 the study by Collado et al. (2014) was carried out in a WWTP drained mainly by industrial  
321 influents. The account of PE was therefore difficult and probably overestimated. This is the  
322 probable reason why DML influents in this study are systematically the lowest among the  
323 selected literature (Figure 4).

324



325  
 326 Figure 4: Mean DML in influent (Inf) and effluent (Eff) samples from the selected WWTP  
 327 compared with other studies; triangles indicate values below  $0.1 \mu\text{g}\cdot\text{day}^{-1}\cdot\text{PE}^{-1}$

328 Data from:

329 Gurke et al. (2015)<sup>a</sup>

330 Lindberg et al. (2014)<sup>b</sup>

331 Papageorgiou et al. (2016)<sup>c</sup>

332 Pereira et al. (2016)<sup>d</sup>

333 Castiglioni et al. (2006)<sup>e</sup>

334 Gracia-Lor et al. (2012)<sup>f</sup>

335 Wick et al. (2009)<sup>g</sup>

336 Yan et al. (2014)<sup>h</sup>

337 Collado et al. (2014)<sup>i</sup>

338

339 In the present study, the industrial impacts on influents were withdrawn for the calculation of the

340 DML. The results are consistent with the literature published on the subject. By comparison with

341 other predominantly domestic WWTPs, the DML are often in the same order of magnitude

342 (Figure 4). However, some extreme values were observed, depending on the location of the

343 WWTP, indicating variations at different scales.

344 Except data from Collado et al. (2014), the WWTPs studied in the selected literature served

345 medium-sized towns to large cities (i.e. from  $10^5$  to  $10^6$  inhabitants) characterized by a

346 prevalence of domestic waste. No systematic rule can be drawn for the comparison of DML

347 (Figure 4). SCA and ACM are the most loaded PACs in influent whatever the studied WWTP  
348 (between 320 to 21,456  $\mu\text{g}\cdot\text{day}^{-1}\cdot\text{PE}^{-1}$  in Greece and Sweden, respectively for ACM) and are also  
349 highly removed in all cases (i.e. two orders of magnitude, Figure 4). For these two PACs, the  
350 results of this study are in the same order of magnitude for both influent and effluent load. The  
351 influent loads of DIC and CBZ are not particularly high, but their effluent load remains close to  
352 their influent load (i.e. in the same order of magnitude), whatever the studied plant. This indicates  
353 that the difficulty in removing these specific PACs is not limited to the WWTP investigated in  
354 this study. By contrast, MET and TRA are moderately removed in the present work whereas they  
355 are poorly removed in other studies such as in Germany or Sweden indicating that the removal of  
356 some PACs can vary strongly depending on the WWTP investigated.

357 However, the influent DML of several PACs varies between and within each country. For  
358 example, while France is one of the largest consumers of PACs in weight, there are some  
359 differences in the consumption behavior of particular classes of medication. The influent loads  
360 should therefore be valuable in order to assess the consumption of PACs.

### 361 **4.3. Consumption assessment**

362 The back-calculation of the mean consumption in the targeted site is given in Table 4.  
363 These values were compared with published data on the amount of sold PACs in France in  
364 2014. There is a lack of consumption data on a national scale for three contaminants,  
365 GEM, COD and DOX.

366 The comparison between experimental and theoretical values for other PACs shows two  
367 trends. For widely consumed PACs, the estimated experimental and theoretical  
368 consumption gives values in the same order of magnitude, with for example an estimated  
369 consumption of 117 and  $0.887 \text{ mg}\cdot\text{day}^{-1}\cdot\text{PE}^{-1}$  and a theoretical consumption of 137 and  
370  $0.761 \text{ mg}\cdot\text{day}^{-1}\cdot\text{PE}^{-1}$  for ACM and ATE respectively (Table 4). While there is a good

371 correlation between experimental and theoretical consumption for several PACs, such as  
 372  $\beta$ -blockers or analgesics, considerable variations can be observed for other PACs such as  
 373 CBZ, DIC and IBU. For these three compounds, the estimated consumption values are  
 374 significantly lower than theoretical ones (i.e. up to one order of magnitude). These  
 375 variations could come from two factors.

376 Firstly, the comparison is between national scale and local scale data for theoretical and  
 377 experimental values respectively. This change in the scale could explain the significant  
 378 variation in consumption, especially for CBZ. As CBZ is often used to treat chronic  
 379 diseases, the seasonal impact on consumption can be considered negligible.

380 Then, the consumption of anti-inflammatory drugs (e.g. IBU and DIC) differs greatly  
 381 between cold and hot seasons (Sui et al., 2011; Vieno et al., 2005). As the sampling  
 382 campaign was carried out only in the hot season (end of spring and summer), the low  
 383 consumption of anti-inflammatory drugs when compared with yearly consumption may  
 384 result from the significant seasonal differences in their consumption. However, the  
 385 consumption of IBU has already been noticed as significantly lower than theoretical one  
 386 in the same region (Thiebault et al., 2017).

387

388 Table 4: Excretion Rate of targeted pharmaceuticals, calculation of the mean amount consumed and  
 389 comparison with the theoretical estimation with ExR the excretion rate, SSP, the sorption on suspended  
 390 solids, the estimated consumption, based on the effluent mean DML value, the theoretical consumption  
 391 data in France in 2014 according to the literature, and n.d corresponding to a lack of data

PAC	ExR (%)	SSP (%)	Estimated Consumption mg.day <sup>-1</sup> .PE <sup>-1</sup>	Theoretical Consumption in France <sup>h</sup> mg.day <sup>-1</sup> .PE <sup>-1</sup>
<i>Analgesics</i>				
ACM	4 <sup>a</sup>	0.0	117	137
SCA	8 <sup>a</sup>	-	7.22	16.4

<i>β-blockers</i>				
ATE	83 <sup>a</sup>	9.0 <sup>f</sup>	0.887	0.761
MET	11 <sup>a</sup>	0.0 <sup>g</sup>	0.599	0.364
<i>Psychotropic drugs</i>				
CBZ	16 <sup>b</sup>	0.0 <sup>f</sup>	0.099	1.39
DIA	8 <sup>a</sup>	42.0 <sup>g</sup>	0.037	0.022
DOX	25	-	0.072	n.d
OXA	75 <sup>d</sup>	5.4 <sup>c</sup>	0.105	0.257
<i>Anti-inflammatory drugs</i>				
DIC	16 <sup>a</sup>	0.0 <sup>f</sup>	0.125	1.62
IBU	30 <sup>a</sup>	5.0 <sup>f</sup>	0.492	9.97
KET	10 <sup>c</sup>	0.0 <sup>g</sup>	0.950	0.900
NAP	10 <sup>e</sup>	0.0 <sup>g</sup>	0.895	1.55
<i>Lipid regulator</i>				
GEM	76 <sup>e</sup>	0.0 <sup>g</sup>	0.009	n.d
<i>Opioids</i>				
COD	64 <sup>c</sup>	1.0 <sup>c</sup>	0.079	n.d
TRA	32 <sup>g</sup>	1.0 <sup>g</sup>	0.420	1.07

392 Data from:  
393 Lienert et al. (2007)<sup>a</sup>  
394 Bahlmann et al. (2014)<sup>b</sup>  
395 Baker et al. (2014)<sup>c</sup>  
396 Carballa et al. (2008)<sup>d</sup>  
397 Khan and Ongerth (2004)<sup>e</sup>  
398 Hörsing et al. (2011)<sup>f</sup>  
399 Jelic et al. (2011)<sup>g</sup>  
400 Chiffre et al. (2016)<sup>h</sup>  
401  
402



## 403        **5. Conclusion**

404        This work has demonstrated that the quantification of PACs by GC-MS is feasible and  
405        reproducible at field-relevant concentrations, making it possible for numerous laboratories  
406        to practice this type of screening. Among the selected PACs, the majority exhibited  
407        detection frequencies of 100 %. However, the pollutants with the highest concentrations in  
408        influents are not necessarily the most problematic after treatment. ATE, TRA and DIC are  
409        respectively the three PACs with the highest concentrations in effluents and should be  
410        closely monitored to track pollution in the natural environment.

411        Significant variations in removal efficiencies were found throughout the tracking. Three  
412        groups can be distinguished among the selected PACs: highly removed (ACM, GEM,  
413        SCA), moderately removed (ATE, MET, DOX, COD, IBU, NAP, KET and TRA) and  
414        poorly removed (OXA, CBZ and DIC) PACs. These groups are in good agreement with  
415        other studies, showing that the removal capacity of current treatment plants is limited,  
416        whatever the plant studied. The removal efficiencies of some specific compounds are  
417        higher than those reported in previous studies, e.g. for CBZ with a median removal of 30  
418        %. However, for poorly removed compounds, some negative removal efficiencies are also  
419        recorded. The chosen season (i.e. summer) could have an impact on the yield of biological  
420        degradation processes. Summer is considered to be favourable to a high biological  
421        activity, correlated with the removal of several PACs except ACM and SCA. Moreover,  
422        we propose that the removal efficiency of various PACs can be assessed by tracking the  
423        removal of nitrogen and/or BOD<sub>5</sub>, as their removal is statistically correlated with the  
424        removal efficiency of various PACs.

425 Finally, the impact and the behaviour of the population were assessed from the back-  
426 calculation of DML and consumption. The experimentally calculated consumption was  
427 generally on the same order of magnitude as the theoretical one especially for year-long  
428 medication (psychotropic drugs,  $\beta$ -blockers). Conversely for some therapeutic classes  
429 (such as anti-inflammatory drugs) that are highly season-dependent, the experimental  
430 consumption was significantly lower than the theoretical one.

431 Lastly, this work has demonstrated that significant variations in removal efficiency occur  
432 within the same season, indicating that the seasonal effect is not a satisfactory explanation  
433 to assess removal variations throughout the year.

434

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440

441

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