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Impact of meteorological and social events on human-excreted contaminant loads in raw wastewater: From daily to weekly dynamics

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Abstract

The temporal dynamics of the wastewater influent loads of 25 drug target residues (DTR, both pharmaceuticals and illicit drugs) was assessed during 84 consecutive days. This monitoring scale enables longer temporal patterns than weekday/weekend patterns to be explored. In this study, we focus on day to day variations and the potential statistical correlation of each DTR analyzed in order to better understand the potential forcings that lead to the load variation of DTRs (alone or in clusters). The weekly patterns based on the weekly loads of DTRs were also analyzed and the impact of social and meteorological events on their variations was investigated.

Two cold events occurred during the monitoring period and were associated with the highest loads of analgesics and non-steroidal anti-inflammatory drugs, as well as the lowest loads of stimulants. During the Easter holidays, a significant decrease in some year-long medication as well as analgesics was found, consistent with the demographic decrease within the catchment during this period. Lastly, a good correlation between the academic calendar and the loads of stimulants was found, emphasizing the overrepresentation of students in the consumption of recreational drugs.

This study furnishes new insights in order to better understand the variations in DTR loads in wastewater influents, beyond the weekday/weekend pattern and the seasonal effect. Further investigations remain necessary, especially a real-time monitoring of the population figures within the catchment in order to improve our understanding of these results.

1. Introduction

The occurrence of drug target residues (DTRs) of pharmaceutically active compounds and illicit drugs in numerous environmental compartments (Da Silva et al., 2011; Pal et al., 2013; Tamtam et al., 2008) raises serious concerns about their potential hazard for living beings (Brodin et al., 2013; Richmond et al., 2018). Hence, a significant part of the current literature focuses on both assessing the removal of organic contaminants in classical wastewater treatment plants (Subedi and Kannan, 2014; Thiebault et al., 2017a; Verlicchi et al., 2013), and on optimizing their removal based on tertiary treatments (Altmann et al., 2015; Rattier et al., 2014; Thiebault et al., 2016).

However, wastewater treatment plant influents (WWI) could also represent a tremendous source of information, due to the link between their chemical composition and the excretion of various chemical compounds by the population in the catchment (Castiglioni et al., 2014; Gracia-Lor et al., 2017a; Kasprzyk-Hordern and Baker, 2012). Several studies have demonstrated the consistency of such analyses on illicit drugs and pharmaceutically active compounds in order to back-calculate the consumption of the population (Baker et al., 2014; Jones et al., 2014; van Nuijs et al., 2009). In the case of illicit drugs, this type of analysis reduces the uncertainty of classical consumption studies based on sociological surveys (Baz-Lomba et al., 2016; Ort et al., 2014), even if ethical questions remain prominent (Lancaster et al., 2019). This new scientific discipline has been called wastewater-based epidemiology and currently investigates not only chemicals consumed as pharmaceuticals, but also passive exposure to other markers such as industrial chemicals and pyrethroid pesticides (Choi et al., 2018; Lopardo et al., 2019; Rousis et al., 2017b).

While analyses of passive exposure provide useful information about the chemical quality of the environment (air, soil, water, etc.) (Rousis et al., 2017a), analyses of chemicals consumed as pharmaceuticals are useful to determine the behavior of a target population (Causanilles et al.,

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67 2018; Gracia-Lor et al., 2017b). Many studies have been carried out to characterize this type of

68 specific behavior, especially from a geographical point of view, on a regional to a worldwide scale

69 (Nefau et al., 2013; Thomas et al., 2012; Vuori et al., 2014; Yan et al., 2019). As a result, a

70 significant amount of data is now available to distinguish different consumption behaviors around

71 the world, but few studies have focused on the temporal dynamics of human-excreted pollutants.

72 Among these temporal dynamics the weekly pattern of stimulants (*i.e.* cocaine, ecstasy) that are

73 significantly more excreted/consumed during the weekend than on weekdays is nevertheless well-

74 established (Gatidou et al., 2016; Papageorgiou et al., 2016; van Nuijs et al., 2011). Beyond this

75 pattern, studies have especially focused on special events, such as sport events, in order to assess

76 the specific behavior associated with this type of event (Gerrity et al., 2011; Sodré et al., 2017), or

77 on the seasonality in the use of antibiotics or anti-influenza drugs (Azuma et al., 2013; Coutu et al.,

78 2013; Golovko et al., 2014).

79 However, no studies have explored the daily variations in pharmaceutically active compounds and

80 illicit drugs, and the impact of external parameters on these daily loads. An initial exploration is

81 the recent study by O'Malley et al. (2019) which found a relationship between latitude, temperature

82 and the use of organic UV filters. Hence, in the present study, we propose to assess the external

83 forcings that could impact the daily/weekly evolution of the loads of 25 DTRs (both illicit drugs

84 and pharmaceuticals) which were analyzed in WWI during 84 consecutive days in 2016. Based on

85 the knowledge of some variations in the catchment (*i.e.* holidays, temperature) and intrinsic

86 variations in the WWI parameters, this study aims to advance our understanding of the temporal

87 dynamics of DTR loads during long term monitoring by: (i) characterizing the statistical correlation

88 between DTR loads, (ii) assessing the correlation between classical WWI parameters and DTR

89 loads and (iii) determining the impact of external forcings on DTR load variations.

2. Material and methods

2.1. Sample collection and general setting

WWI were collected each day during 84 consecutive days, between March 21st and June 11th 2016 except on March 31st, providing a set of 83 samples. Sampling consisted of a flow-enslaved composite with a sampling of 50 mL every 30 m^3 of WWI between 0h00 and 23h59. This corresponds to a mix of 167 samples per day for the mean flow value. The chemical parameters of WWI during the study are given in Table S1. Among them, we focused especially on the daily variations in chemical oxygen demand (COxD), suspended solids (SS) and total phosphorus (TP) due to the greater number of analyses (n=24). Mean temperature values were retrieved from the Météo-France database (www.meteofrance.fr). The exact emplacement of the investigated WTP will not be disclosed in this study, in accordance with the request of the local authorities and ethical guidelines (Hall et al., 2012; Prichard et al., 2014).

The same dataset was used as in our previously published paper which aimed to characterize the consumption of pharmaceuticals and illicit drugs within the catchment (Thiebault et al., 2017b). In the present article, the data processing focuses on the temporal dynamics rather than on the back-calculation of consumption.

2.2. Chemical Reagents

Standards for acetaminophen (ACM), atenolol (ATE), bezafibrate (BZB), carbamazepine (CBZ), codeine (COD), diclofenac (DCF), ibuprofen (IBP), ketoprofen (KET), metoprolol (MET), oxazepam (OXA), salicylic acid (SCA), sulfamethoxazole (SUL), tramadol (TRA) and trimethoprim (TMP) were purchased from Sigma-Aldrich with a purity > 98%. The standards for 6-monoacetylmorphine (6MAM), amphetamine (AMP), benzoylecgonine (BZE), buprenorphine

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113 (BUP), cocathylene (CET), cocaine (COC), heroin (HER), 3,4-methylene-dioxy-N-

114 methylamphetamine (MDMA), methadone (METD), morphine (MOR) and 11-nor-delta-9-

115 hydroxytetrahydrocannabinol (THC) were purchased from LGC Standards. Extraction and

116 separation solvents, methanol (MeOH) and acetonitrile (AcN) were purchased from Fisher-

117 Scientific, assuming an analytical grade (purity up to 99.95 %).

118 **2.3. Sample Preparation**

119 After collection, WWI were filtered with glass-fiber filters (GF/F, Whatman) prior to solid-phase

120 extraction (SPE). SPE was carried out using Chromabond HR-X cartridges (6 mL x 500 mg,

121 Macherey-Nagel). Cartridges were conditioned with 6 mL of MeOH followed by 6 mL of ultra-

122 pure water. Then, the cartridges were filled with 250 mL of WWI prior to flushing with 6 mL of

123 ultra-pure water before drying for 30 minutes under vacuum. Finally, elution of DTR was

124 performed with 6 mL of MeOH before drying under nitrogen flow and storage at -10°C.

125 **2.4. Quantification and validation**

126 The quantification and validation procedures were already presented in detail (Thiebault et al.,

127 2017b). The equipment and analytical procedures are detailed in the supplementary material.

128 Quantification performances are given in Table 1. Further information on the analytical setup can

129 be found in Table S2.

Abbreviation	DTR	Matrix Effect ± SD (%)	Recovery Ratio ± %SD (%)	MDL ng.L^{-1}	MQL ng.L^{-1}	Linearity	Instrument Performance	
							Intra-day (%)	Inter-day (%)
Antibiotics								
SUL	Sulfamethoxazole	91 ±1.58	79.7 ± 9.00	0.2	0.5	0.9998	2.1	2.6
TMP	Trimethoprim	109 ± 0.43	71.4 ± 3.81	0.1	0.4	0.9999	2.8	1.5
NSAIDs								
IBP	Ibuprofen	108 ± 4.28	78.9 ± 3.63	0.9	2.8	0.9972	6.8	3.2
DCF	Diclofenac	188 ± 0.40	62.9 ± 2.00	0.3	0.8	0.9994	2.4	6.1
KET	Ketoprofen	123 ± 1.73	67.4 ± 5.36	0.6	1.9	0.9998	4.6	0.9

Analgesics								
SCA	Salicylic Acid	188 ± 0.70	22.1 ± 9.24	0.4	1.3	0.9997	2.1	1.1
ACM	Acetaminophen	349 ± 0.29	99.6 ± 9.99	0.6	1.7	0.9998	4.6	3.1
Others								
ATE	Atenolol	117 ± 1.38	68.3 ± 3.56	0.3	0.8	0.9998	2.8	1.8
MET	Metoprolol	113 ± 1.67	79.4 ± 2.62	0.1	0.2	0.9998	2.4	1.4
OXA	Oxazepam	168 ± 1.42	103.5 ± 1.15	2.3	6.4	0.9994	2.0	1.5
CBZ	Carbamazepine	142 ± 0.48	101.1 ± 4.75	1.6	4.6	0.9975	1.0	3.2
BZB	Bezafibrate	112 ± 2.79	80.5 ± 6.09	0.5	1.3	0.9998	3.1	2.9
THC	THC-COOH	124 ± 2.51	43.6 ± 16.6	8.5	20.2	0.9987	3.4	4.2
Opioids and derivatives								
MOR	Morphine	108 ± 1.05	52.3 ± 5.14	3.1	8.9	0.9996	6.1	2.0
6MAM	6-Acetylmorphine	171 ± 3.78	59.7 ± 4.72	1.0	2.8	0.9996	1.6	4.0
HER	Heroin	112 ± 2.56	68.9 ± 6.72	6.4	17.3	0.9937	9.7	3.1
METD	Methadone	235 ± 0.69	65.8 ± 13.6	2.2	7.8	0.9985	3.8	1.6
COD	Codeine	111 ± 0.59	58.1 ± 2.88	0.5	1.4	0.9998	6.8	2.3
BUP	Buprenorphine	241 ± 2.50	53.9 ± 12.4	0.8	2.6	0.9988	10.1	7.2
TRA	Tramadol	171 ± 1.54	99.0 ± 2.46	2.1	6.5	0.9997	3.9	6.4
Stimulants								
COC	Cocaine	80 ± 2.23	78.0 ± 5.47	1.6	4.9	0.9989	8.9	2.7
BZE	Benzoylecgonine	109 ± 1.36	82.8 ± 3.15	1.8	5.4	0.9996	4.3	1.9
CET	Cocaethylene	096 ± 1.54	83.6 ± 3.59	0.6	2.0	0.9996	6.6	2.6
MDMA	Ecstasy	108 ± 0.47	72.0 ± 11.5	1.0	3.2	0.9996	5.6	3.8
AMP	Amphetamine	105 ± 0.14	73.5 ± 9.42	1.6	4.6	0.9975	5.8	3.9

130 Table 1: Analytical parameters and performance of the selected contaminants with NSAIDs for non-
131 steroidal anti-inflammatory drugs, SD the standard deviation, MDL and MQL the method detection limit
132 and method quantification limit respectively

133

134 The three analytical runs (30 samples for each) were conducted at different times. The between-

135 run drift was also determined, by comparing the calibration curves and analyzing the same sample

136 in two different runs.

137 Relative standard deviation was determined by analyzing the same sample three times. SPE

138 recovery values were calculated for each compound by comparing the concentration of a standard

139 with and without SPE (at 0.2 and 50 µg.L^{-1} respectively). Matrix effect was assessed for each

140   compound by comparing the concentration of standards spiked in ultra-pure water and spiked in

141   the WWI matrix. All further details can be found in Table 1.

142   **2.5. Processing of results**

143   Concentrations were converted into mass load (load) in order to take into account the irregularity

144   of the flow. The load of each DTR in WWI each day was calculated as follows:

145                                $$\text{Load} = 10^3 \; x \; C \; x \; F$$

146   with the load of DTR in g.day^{-1}, C, the concentration in µg.L^{-1}, and F, the flow in m^3.day^{-1}

147   Heatmap, correlation matrix and pairwise p-values were performed using the packages corrplot

148   and FactoMineR of the R software (Lê et al., 2008). Statistical analyses were performed on

149   normalized load and raw load values. The Pearson correlation was used to assess both the

150   correlation matrix and p-values.

3. Results and Discussion

152   Hereafter, daily loads will be used to assess the statistical correlation between DTRs themselves or

153   with some classical WWI parameters. In order to enhance the statistical reliability of the

154   correlation, DTRs were grouped in 6 clusters based on their theoretical therapeutic use (except for

155   THC which is here considered as a daily-consumed compound in accordance with previous

156   studies). The six clusters are: Analgesics, which resulted from the addition of ACM and SCA loads,

157   Antibiotics from the addition of SUL and TMP, Non-steroidal anti-inflammatory drugs (NSAIDs)

158   from the addition of DCF, IBP and KET loads, Opioids from the addition of COD, BUP, METD,

159   MOR, OXA and 6MAM loads, Others from the addition of ATE, BZB, CBZ, MET, OXA and

160   THC loads and Stimulants from the addition of BZE, CET, COC and MDMA loads.

161   In a second phase, loads will be presented in boxplots for each French calendar week (from Monday

162   to Sunday) of the monitoring period.

8

3.1. Daily variations of DTRs

Among the DTRs analyzed, HER (as DTR) and AMP are not shown in Figure 1, nor in the rest of the study because they were never detected. The statistical correlation between normalized daily loads of each DTR is presented in Figure 1. This presentation as a heatmap highlights the statistical correlation and justifies clustering the DTRs in several statistical groups.
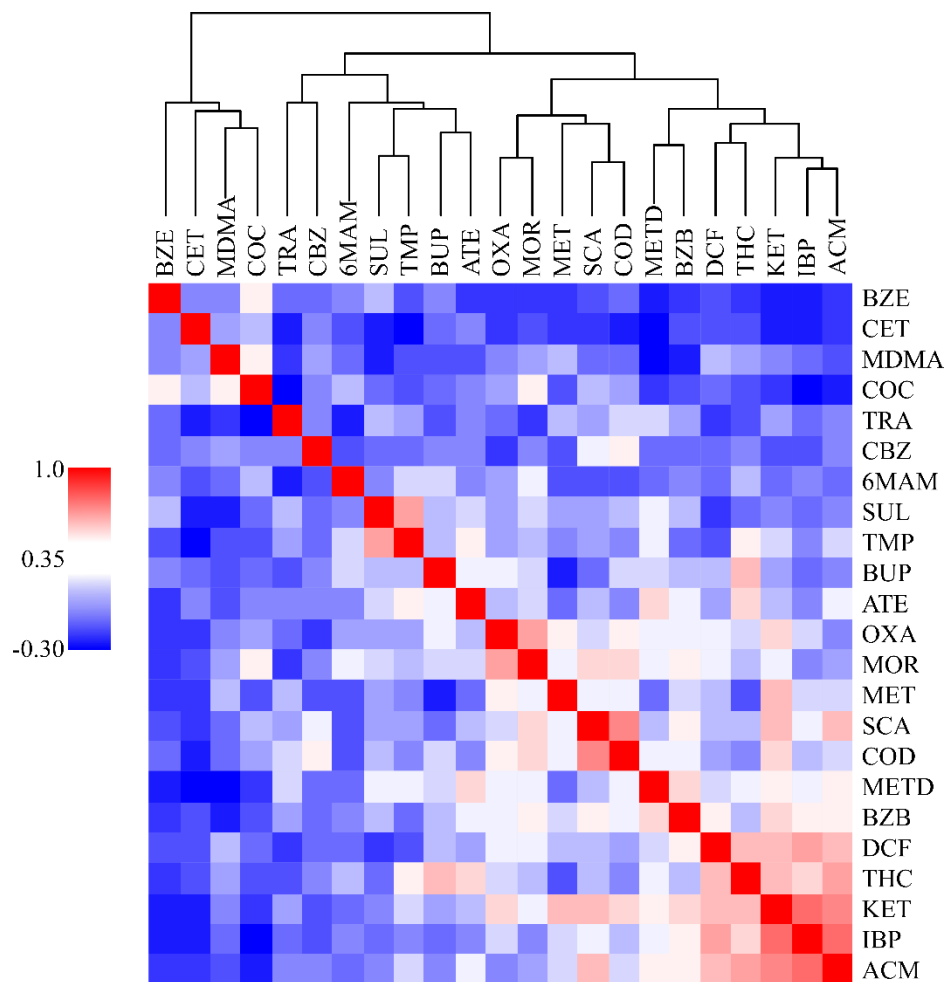

Figure 1: Heat map analysis based on the daily loads of each DTR analyzed

From a clustering point of view, the four stimulants (i.e. COC, BZE, CET and MDMA) constitute a distinct statistical group. This can be explained by the very weak correlation between these DTRs and other compounds if we except the non-statistically significant correlation between COC and

173 MOR. Hence, stimulants exhibit a different daily pattern in comparison with other DTRs, largely

174 generated by the noticeable increase in their loads during weekends (Thiebault et al., 2017b). This

175 weekly pattern is the most significant for stimulants thus resulting in the constitution of this cluster.

176 This appears consistent with their use as recreational drugs, in comparison with other DTRs.

177 Among the other DTRs, the statistical clusters are not especially related to the therapeutic classes

178 of DTR. For example, the most statistically significant cluster includes ACM, THC, KET, DCF

179 and IBP (Figure 1), i.e. a cluster that includes one analgesic, all the three NSAIDs and one illicit

180 drug. However, these DTRs are both highly consumed in the catchment area (Thiebault et al.,

181 2017a, 2017b), and their daily loads seem to be impacted by the same forcings. This cluster is

182 completed with METD and BZB, which are both year-long medications and their excretion pattern

183 appears to be close to that of convenience DTRs such as ACM and IBP.

184 Based on this correlation plot, it is therefore difficult to distinguish between year-long medications

185 such as BZB, MET, ATE and the use of painkillers such as ACM, SCA and IBP, which are

186 occasionally consumed. The significant consumption of the latter appears to result in daily load

187 variations that are comparable to those of year-long medication.

188 The daily loads of the two antibiotics, SUL and TMP, are significantly correlated (Figures 1 and

189 S1). In order to assess the temporal dynamics of these two DTR, their daily load variations are

190 plotted in Figure 2. The significant statistical correlation between the loads of SUL and TMP is

191 obvious from Figure 2, and both DTRs were previously reported to have the highest loads amongst

192 the DTRs analyzed (Thiebault et al., 2017b), resulting in a linear regression determination

193 coefficient of 0.39 (Figure S1). This can be explained by the fact that these two compounds are

194 often associated in a single medicinal product (Dan et al., 2013). There is a perfect fit between the

10

195   two curves throughout the monitoring period, except between 04/23 and 05/02. During this period,

196   the SUL load was significantly lower than expected.
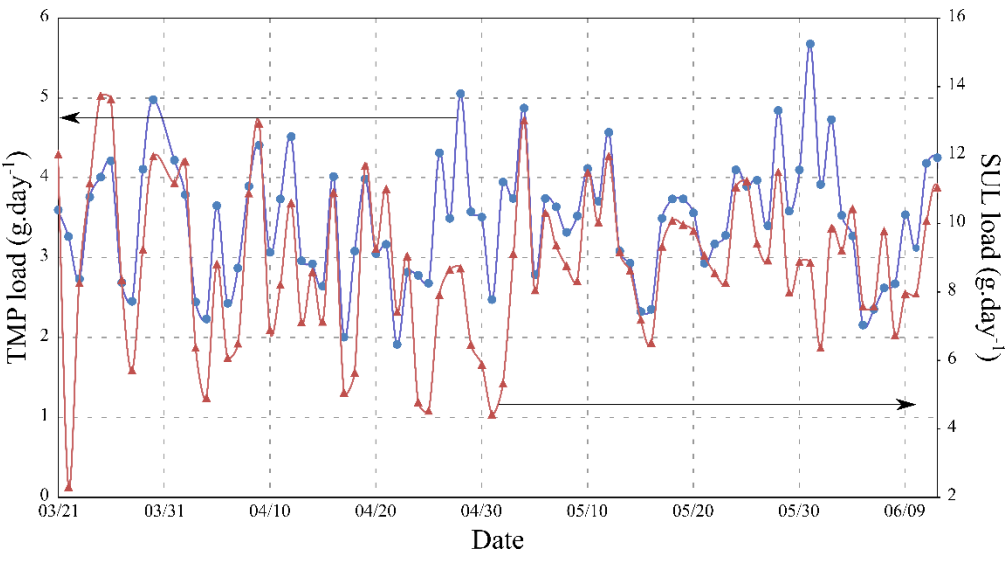

197

198   Figure 2: Daily loads of TMP (blue circles) and SUL (red triangles)

199   This punctual absence of correlation was unexpected since SUL and TMP are consumed in

200   association. It could result from variations in the respective stability of these compounds during

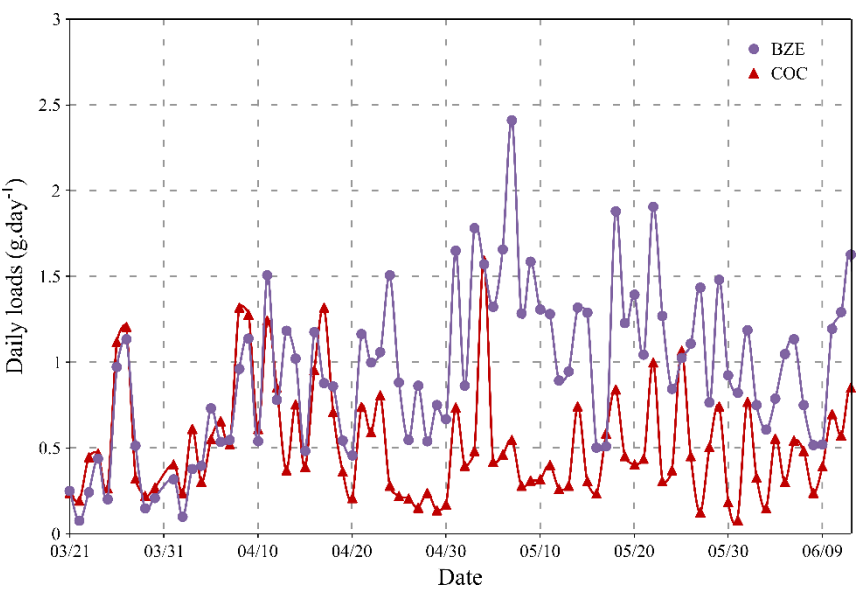201   their transport through sewers.

202

203   Figure 3: Daily loads of COC (red triangles) and BZE (blue circles)

11

204 COC and BZE are relevant DTRs to assess the co-evolution of their loads as BZE is the main

205 metabolite of COC and is considered as more stable than COC (McCall et al., 2016). During the

206 monitoring period, BZE loads were higher than those of COC, in agreement with the literature on

207 the subject (Ort et al., 2014; van Nuijs et al., 2009). However, the ratio between BZE and COC

208 was not constant throughout the monitoring period, as displayed in Figure 3. The loads of both

209 BZE and COC were very similar during the first few weeks but then a significant discrepancy

210 between the two can be observed. This increasing discrepancy indicates some variations in the

211 WWI composition that could impact the in-sewer stability of COC (which is more sensitive to

212 degradation than BZE as described by Gheorghe et al. (2008)) and simultaneously increases the

213 concentration of its metabolite BZE, whereas their excretion rate remains stable (Gracia-Lor et al.,

214 2016).

215 In order to verify this hypothesis and also to better constrain the origin of the variation in DTR

216 loads, a correlation matrix was performed between therapeutic class loads and classical WWI

217 parameter loads recorded during the study. The results are presented in Table 2.

218 Table 2: Correlation coefficients describe the statistical relationship between cumulative normalized loads
219 of each therapeutic class and normalized loads of several classical wastewater parameters, namely Chemical
220 Oxygen demand (CoxD), Suspended Solids (SS) and Total Phosphorus (TP). [*], [**], [***] correspond to p-values
221 < 0.05, 0.01 and 0.001 respectively, n=24.

	Analgesics	Antibiotics	Others	Opioids	Stimulants	COxD	SS	TP
NSAIDs	0.79[***]	0.32	0.67[***]	0.40	-0.10	-0.25	-0.16	-0.21
Analgesics		0.23	0.61[*]	0.39	-0.04	-0.07	-0.00	-0.15
Antibiotics			0.29	0.42	-0.57	-0.42	-0.39	-0.25
Others				0.26	-0.00	-0.50	-0.44	-0.56
Opioids					-0.18	-0.15	-0.02	-0.02
Stimulants						0.27	0.26	-0.03
COxD							0.89[***]	0.88[***]
SS								0.82[***]

222
223 Two clusters emerge from this correlation matrix. First, a very significant positive correlation is

224 found between TP, SS and COxD, indicating that the daily variations in these three classical

225 parameters are correlated. Then, NSAIDs, Analgesics and Others loads are also significantly

226 correlated, indicating that several external forcings impact their daily variations. However, no

227 correlation was found between the daily loads of DTRs and those of classical WWI parameters

228 (Table 2). As a result, the daily variations in DTR loads are expected to be different from the

229 variations in the operating conditions of the sewer system alone.

230 **3.3. Weekly variations of DTR loads**

231 Overall, the scientific literature seeking to improve the understanding of the temporal dynamics of

232 DTRs in WWI has focused on the daily dynamics, and especially the weekday/weekend pattern.

233 However, several forcings on these loads, such as meteorological or social events, may also present

234 a weekly pattern. We therefore focus in this section on weekly variations, and especially those that

235 are statistically significant.

236 *3.3.1. Social and meteorological events in the catchment during the monitoring period*

237 During the monitoring period, several social and climatic events with a potential weekly effect

238 occurred. Weeks 14 and 15 were the Easter holidays (from school to university). According to

239 official figures, the number of university students in the catchment is approximately 15,000 and

240 accounts for ~ 20 % of the total catchment population (*i.e.* 70,000). The mobility of French people

241 during holidays was assessed by a recent report (Houbian, 2010), which revealed that between 10

242 and 35 % of people are likely to go on holiday outside the catchment (the targeted area is not

243 especially touristic).

244 Week 17 and the beginning of week 18 were the examination period at the university, followed by

245 the end of the university year during week 21 (except for students who failed the first session).

246 From a meteorological point of view, the monitoring period was characterized by heavy rainfall

247 episodes during weeks 21 and 22 (Figure S2). This heavy rainfall period resulted in the mix of

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248   rainwaters with wastewaters, although the sewer system is supposed to be unitary, due to leaks.

249   Hence, the WWI flow was strongly impacted by rainfall during weeks 21 and 22.

250   A precise calendar with each specific event is presented in Figure S3.

251   The temperature within the catchment increased regularly between March and June, which is

252   expected under such latitudes. However, during week 17, a cold snap occurred, resulting in

253   significantly lower mean temperatures during week 17 in comparison with weeks 16 and 18 (Figure
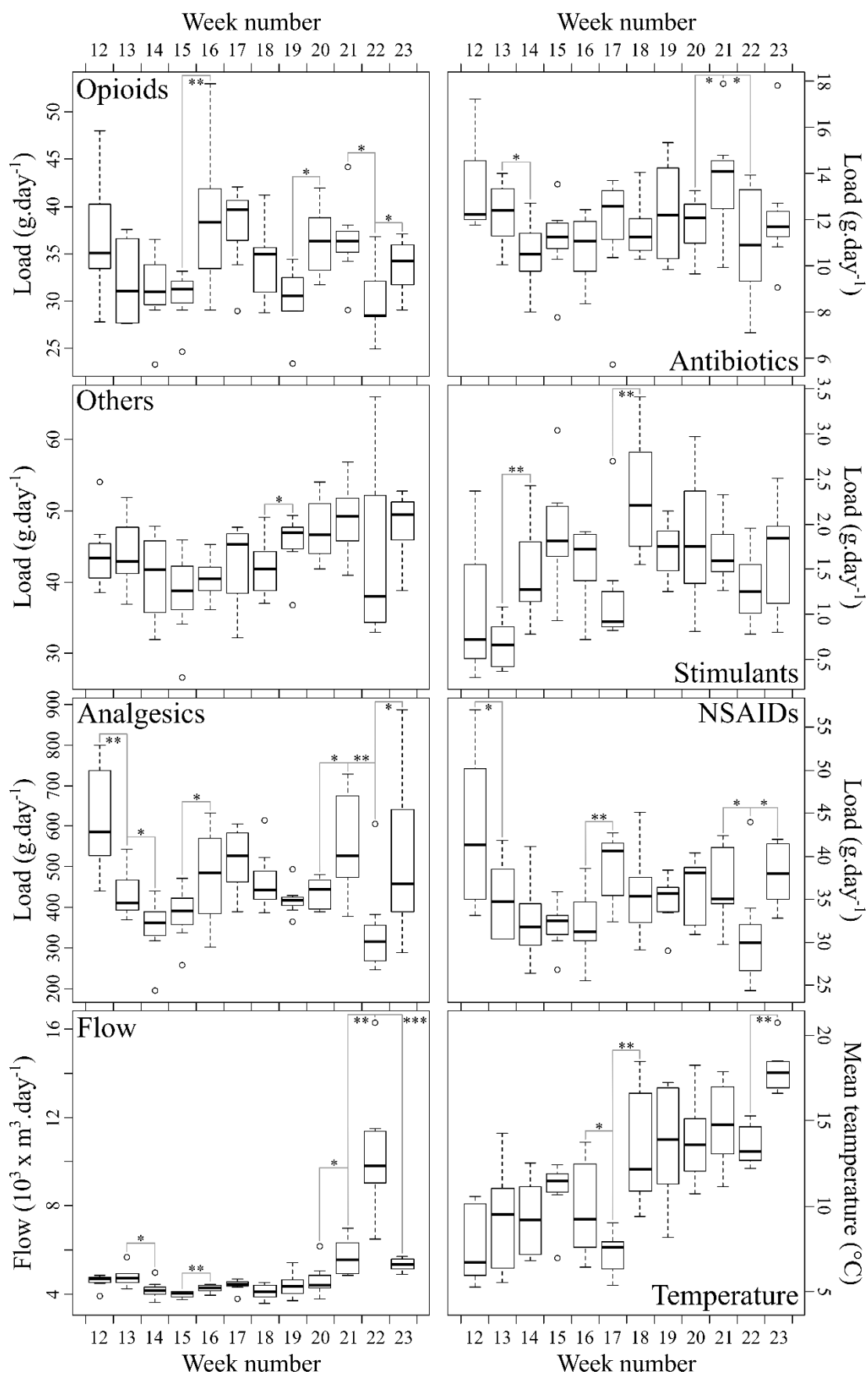
254   4).

256   Figure 4: Loads of therapeutic classes, mean temperature and flow for each sampled week. The line within
257   the box marks the median, boundaries indicate the 25th and 75th percentiles, error bars indicate the maximum
258   and minimal value in $\pm$ 1.5 σ variations and circles indicate individual values outside this range. Gray lines
259   mark statistically significant variations with p-values < 0.05, 0.01 and 0.001 for *, ** and *** respectively.
260

261   *3.3.2. Analgesics*

262   ACM and SCA were the two most abundant DTRs detected during this study. Their cumulative

263   loads, grouped as "Analgesics", ranged from 194.7 to 887.5 g.day^{-1}. A significant decrease in the

264   loads of Analgesics was observed between weeks 12, 13 and 14. A significant increase was then

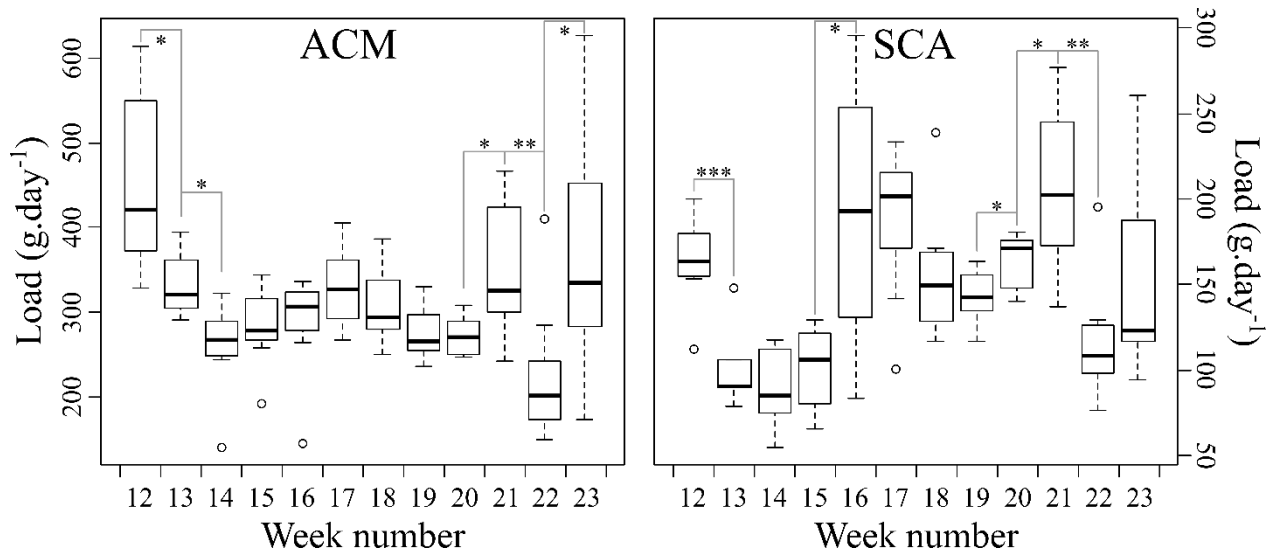265   observed between weeks 15 and 16, before marked variations between weeks 19, 20 and 21 (Figure

266   4).

268   Figure 5: Loads of ACM and SCA, for each sampled week. The line within the box marks the median,
269   boundaries indicate the 25th and 75th percentiles, error bars indicate the maximum and minimal value in $\pm$
270   1.5 σ variations and circles indicate individual values outside this range. Gray lines mark statistically
271   significant variations with p-values < 0.05, 0.01 and 0.001 for *, ** and *** respectively
272

273   The Analgesic loads during the Easter holidays (weeks 14 and 15) were the lowest and are

274   statistically significant in comparison with the previous and following weeks. Hence, the decrease

275   in these loads can be interpreted as a significant demographic decrease in the catchment during the

276   vacation. This decrease is also visible in the significant decrease of the flow values during weeks

277   14 and 15 (Figure 4). Similarly, the two highest weekly loads were found during weeks 12 and 17,

16

278   corresponding to the two coldest weeks of the monitoring period, even if the pattern is
279   systematically visible for each analgesic (Figure 5). However, meteorological conditions may
280   significantly impact the excretion of these compounds within the catchment, resulting from a
281   relative increase in their consumption during cold episodes (Roumie and Griffin, 2004). Lastly, the
282   pronounced disturbance in the WWI flow during the heavy rainfall events (i.e. weeks 21 and 22,
283   Figure S2) strongly impacted both ACM and SCA loads (Figure 5), with a sudden increase in week
284   21 followed by a sudden decrease in week 22. These variations are unexpected at this time of the
285   year, but major modifications in the operating conditions in the sewers due to the mix with
286   rainwaters could be the main reason for these variations.

287   *3.3.2. NSAIDs*

288   The weekly loads of NSAIDs result from the addition of DCF, IBP and KET loads. Among them,
289   KET is the most abundant DTR, representing 65% of the whole load on average. Significant
290   variations were found in NSAID loads, with higher loads during weeks 12 and 17 in comparison
291   with weeks 13 and 16 respectively, and a lower load during week 22 in comparison with weeks 21
292   and 23 (Figure 4). The latter case is comparable to that observed for Analgesics and can be related
293   to the strong rainfall events, which disturbed the operating conditions in the sewer system.
294   Concerning NSAID loads during weeks 12 and 17, it is worthwhile noting that they coincided with
295   the two coldest weeks of the monitoring period. Hence, these cold weeks appear to favor the
296   excretion of NSAIDs in the catchment, resulting in a significant increase during these weeks for
297   IBP and KET (Figure S4). The use of this type of medication as both a painkiller and for anti-
298   inflammatory purposes is probably the main reason for the excretion (*i.e.* consumption) increase
299   during cold events (ter Laak et al., 2010).

300   *3.3.3. Antibiotics*

301 This cluster is composed by SUL and TMP, between which the significant correlation has already

302 been discussed (Figure 2). Whereas the analysis of individual compounds does not show any

303 statistically significant variations (except between week 17 and 18 for SUL, Figure S5), their

304 cumulative loads display a significant decrease between week 13 and 14 and a significantly higher

305 load in week 21 in comparison with weeks 20 and 22 (Figure 4). The former pattern can be

306 attributed to the beginning of the Easter holidays in week 14, as previously discussed on

307 Analgesics. For the latter, the disturbance generated by rainfall events is yet again the only logical

308 explanation that we can propose.

309 *3.3.4. Others*

310 This group comprises year-long pharmaceuticals such as CBZ, MET, ATE, BZB and OXA, and

311 one illicit drug, THC, which is considered to be mainly consumed year-long. A significant variation

312 can be observed between weeks 17 and 18 (Figure 4). From a general point of view, the loads of

313 this cluster globally increase during the monitoring period, although this type of evolution is

314 unexpected based on their posology. A demographic shift due to the end of the university year

315 could be a possible explanation (Vatovec et al., 2016). However, no correction of the population

316 was performed here. Looking at the load evolution of single compounds, this global increase is not

317 common and is not statistically significant. Yet, both CBZ and THC present a pattern impacted by

318 the Easter holidays, whereas the loads of ATE, BZB and MET, like the other therapeutic classes,

319 are only affected by the strong rainfall events (Figure S6). This different impact of social and

320 meteorological events on the weekly load variations of DTRs that are presumably consumed

321 identically (i.e. all year long) raises questions about the sociological profile of such consumers.

322 However, the present study did not provide any clues to elucidate this issue.

323 *3.3.5. Opioids*

324 The weekly loads of opioids were calculated by summing the loads of COD, TRA, 6MAM, BUP,

325 METD and MOR. These compounds have several different therapeutic purposes. 6MAM is an

326 exclusive DTR of heroin consumption, whereas MOR results from both licit and illicit uses (Baker

327 et al., 2014). COD and TRA are both used for their analgesic properties and can be used (partially)

328 in association with analgesics such as ACM. Finally, METD and BUP are two substitutes for illicit

329 substances. In view of these differences, we will focus on the pattern of individual loads rather than

330 cumulative ones. TRA and BUP loads did not exhibit any significant pattern throughout the

331 monitoring period (Figure S7). MOR and COD appear to be impacted both by the Easter holidays

332 and the cold snap during week 17, as previously described for NSAIDs and Analgesics (Figure 4).

333 For COD, this pattern can be explained by its consumption in association with ACM (i.e. COD was

334 significantly correlated with ACM and SCA, Figure 1), whereas for MOR this pattern is more

335 surprising. Another surprising significant variation was observed for 6MAM, with higher loads

336 during the Easter holidays. Due to the very weak loads of 6MAM (*i.e.* the lowest among the

337 analyzed DTRs, between 0.1 and 73 mg.day^{-1}), any hypothesis can only be speculative.

338 *3.3.6. Stimulants*

339 Consumption of this type of illicit drugs is considered to be related to recreational uses. Hence, the

340 daily loads of Stimulants (i.e. the addition of BZE, COC, CET and MDMA loads) exhibit a

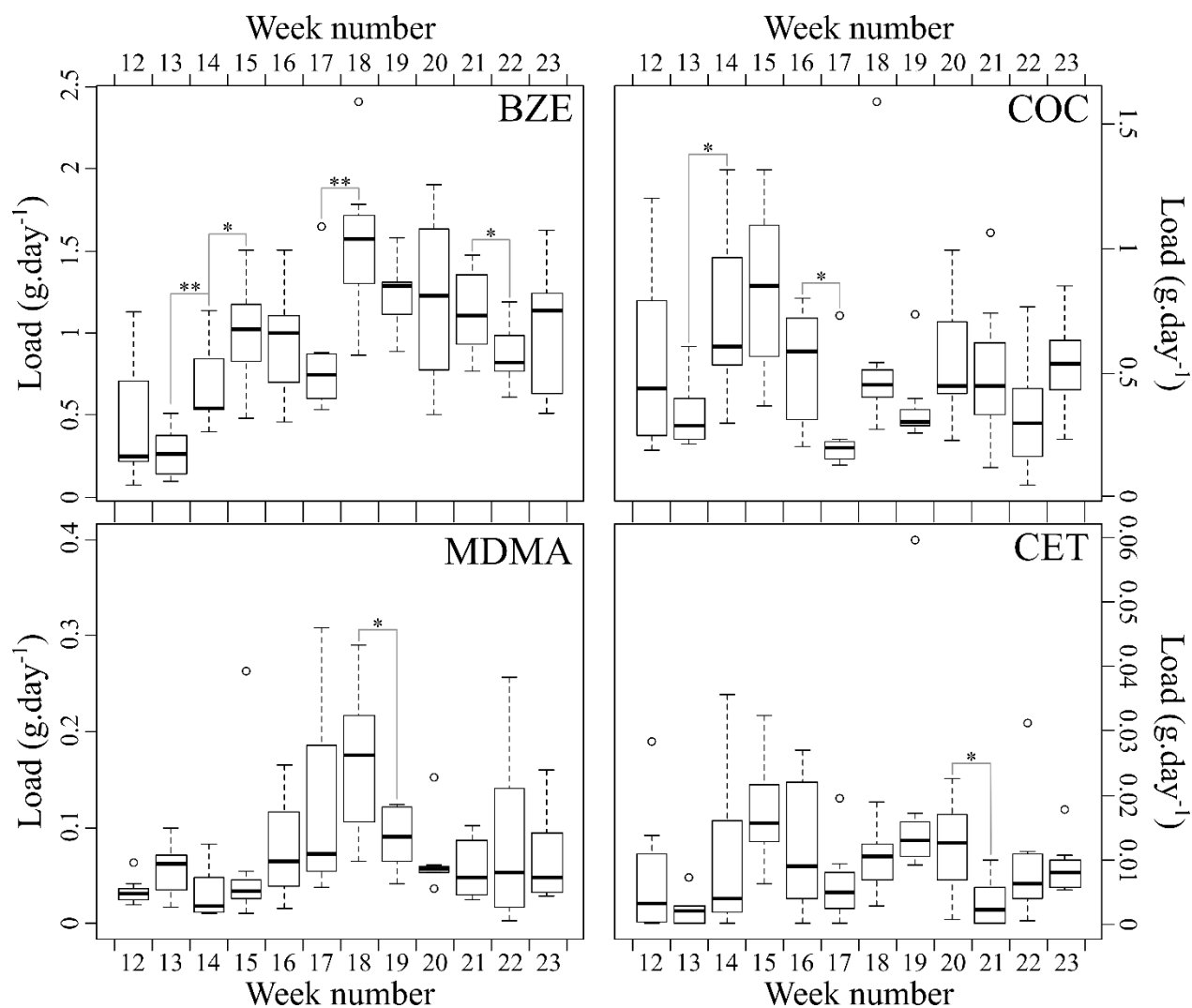341 completely different pattern from that of the other clusters (Figure 1).

Figure 6: Loads of BZE, COC, MDMA and CET, for each sampled week. The line within the box marks the median, boundaries indicate the 25th and 75th percentiles, error bars indicate the maximum and minimal value in ± 1.5 σ variations and circles indicate individual values outside this range. Gray lines mark statistically significant variations with *p*-values < 0.05, 0.01 and 0.001 for *, ** and *** respectively

For example, a significant increase in BZE and COC loads occurred during the Easter holidays, as

well as a significant increase at the end of the examination study period, especially for MDMA

(Figure 6).

Even if CET can be considered as a metabolite of COC, its excretion necessitates the consumption

of both ethanol and COC. As a result, the offset between these two DTRs is not surprising.

However, due to the very weak CET loads and poor weekly variations, no further conclusions can

354 be drawn about this DTR. In the same way, BZE is the main metabolite of COC (Figure 3), and

355 during the first weeks of the monitoring period, the variations in these DTRs were very close. From

356 week 18, the weekly loads of BZE decreased whereas no variation occurred in the COC weekly

357 loads. This could suggest that although BZE and COC can both serve as DTRs to estimate the

358 consumption of cocaine, their potential is not equivalent. The greater stability of BZE makes it

359 more reliable for use as a DTR.

360 From week 18 on, a general but statistically non-significant decrease in all stimulants was observed.

361 The use of these substances seems to be correlated with the academic calendar, and students are

362 known to be among the consumers of such substances (van der Poel et al., 2009). This result is

363 especially interesting and makes a new type of contribution to our understanding of the temporal

364 dynamics of Stimulants, beyond the weekday/weekend pattern.

4. Conclusion

366 Twenty-five DTRs were monitored during 84 consecutive days to assess daily and weekly load

367 variations as a function of external forcings in the catchment.

368 Findings show that the daily variations of stimulants are very different from those of the other

369 DTRs analyzed. The impact of the pronounced increase during weekends is probably the most

370 important factor in this statistical clustering. The loads of Analgesics and NSAIDs also exhibit a

371 very significant correlation, emphasizing the presence of external factors that could lead to their

372 consumption/excretion within the catchment. Thus, both meteorological (*e.g.* cold snap) and social

373 (*e.g.* holidays) events involve sudden and significant variations. Other therapeutic classes such as

374 Opioids are less concerned by this type of temporal pattern. A good fit between the academic

375 calendar and the loads of Stimulants was found, consistent with the overrepresentation of students

376 in the consumption of recreational drugs.

377 This type of monitoring improves our understanding of the impact of external forcings on the

378 consumption behavior (*i.e.* temperature, academic calendar) or mobility of people out of the

379 catchment (*i.e.* holidays). However, a strong disturbance of the loads was observed during heavy

380 rainfall events. The mixing between wastewaters and rainwaters considerably modified the loads

381 of DTRs in WWI without any logical pattern. Such results suggest that while this study provides

382 initial insights into the temporal dynamics of DTRs in WWI, further work remains necessary to

383 deepen our comprehension of daily load variations.

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