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► To cite this version:

Thomas Thiebault, Laëtitia Fougère, Emilie Destandau, Maxime Réty, Jérémy Jacob. Impact of meteorological and social events on human-excreted contaminant loads in raw wastewater: From daily to weekly dynamics. *Chemosphere*, 2019, 230, pp.107-116. <10.1016/j.chemosphere.2019.04.221>. <insu-02125305>

HAL Id: insu-02125305

<https://insu.hal.science/insu-02125305v1>

Submitted on 10 May 2019

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

3
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25 **Abstract**

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

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

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

43

44 **1. Introduction**

45 The occurrence of drug target residues (DTRs) of pharmaceutically active compounds and illicit
46 drugs in numerous environmental compartments (Da Silva et al., 2011; Pal et al., 2013; Tamtam et
47 al., 2008) raises serious concerns about their potential hazard for living beings (Brodin et al., 2013;
48 Richmond et al., 2018). Hence, a significant part of the current literature focuses on both assessing
49 the removal of organic contaminants in classical wastewater treatment plants (Subedi and Kannan,
50 2014; Thiebault et al., 2017a; Verlicchi et al., 2013), and on optimizing their removal based on
51 tertiary treatments (Altmann et al., 2015; Rattier et al., 2014; Thiebault et al., 2016).

52 However, wastewater treatment plant influents (WWI) could also represent a tremendous source
53 of information, due to the link between their chemical composition and the excretion of various
54 chemical compounds by the population in the catchment (Castiglioni et al., 2014; Gracia-Lor et al.,
55 2017a; Kasprzyk-Hordern and Baker, 2012). Several studies have demonstrated the consistency of
56 such analyses on illicit drugs and pharmaceutically active compounds in order to back-calculate
57 the consumption of the population (Baker et al., 2014; Jones et al., 2014; van Nuijs et al., 2009).
58 In the case of illicit drugs, this type of analysis reduces the uncertainty of classical consumption
59 studies based on sociological surveys (Baz-Lomba et al., 2016; Ort et al., 2014), even if ethical
60 questions remain prominent (Lancaster et al., 2019). This new scientific discipline has been called
61 wastewater-based epidemiology and currently investigates not only chemicals consumed as
62 pharmaceuticals, but also passive exposure to other markers such as industrial chemicals and
63 pyrethroid pesticides (Choi et al., 2018; Lopardo et al., 2019; Rousis et al., 2017b).

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

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; Sodr e 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.

90 **2. Material and methods**

91 **2.1. Sample collection and general setting**

92 WWI were collected each day during 84 consecutive days, between March 21st and June 11th 2016
93 except on March 31st, providing a set of 83 samples. Sampling consisted of a flow-enslaved
94 composite with a sampling of 50 mL every 30 m³ of WWI between 0h00 and 23h59. This
95 corresponds to a mix of 167 samples per day for the mean flow value. The chemical parameters of
96 WWI during the study are given in Table S1. Among them, we focused especially on the daily
97 variations in chemical oxygen demand (COxD), suspended solids (SS) and total phosphorus (TP)
98 due to the greater number of analyses (n=24). Mean temperature values were retrieved from the
99 Météo-France database (www.meteofrance.fr). The exact emplacement of the investigated WTP
100 will not be disclosed in this study, in accordance with the request of the local authorities and ethical
101 guidelines (Hall et al., 2012; Prichard et al., 2014).

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

106

107 **2.2. Chemical Reagents**

108 Standards for acetaminophen (ACM), atenolol (ATE), bezafibrate (BZB), carbamazepine (CBZ),
109 codeine (COD), diclofenac (DCF), ibuprofen (IBP), ketoprofen (KET), metoprolol (MET),
110 oxazepam (OXA), salicylic acid (SCA), sulfamethoxazole (SUL), tramadol (TRA) and
111 trimethoprim (TMP) were purchased from Sigma-Aldrich with a purity > 98%. The standards for
112 6-monoacetylmorphine (6MAM), amphetamine (AMP), benzoylecgonine (BZE), buprenorphine

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 (%) |
| <i>Antibiotics</i> | | | | | | | | |
| <i>SUL</i> | Sulfamethoxazole | 91 ± 1.58 | 79.7 ± 9.00 | 0.2 | 0.5 | 0.9998 | 2.1 | 2.6 |
| <i>TMP</i> | Trimethoprim | 109 ± 0.43 | 71.4 ± 3.81 | 0.1 | 0.4 | 0.9999 | 2.8 | 1.5 |
| <i>NSAIDs</i> | | | | | | | | |
| <i>IBP</i> | Ibuprofen | 108 ± 4.28 | 78.9 ± 3.63 | 0.9 | 2.8 | 0.9972 | 6.8 | 3.2 |
| <i>DCF</i> | Diclofenac | 188 ± 0.40 | 62.9 ± 2.00 | 0.3 | 0.8 | 0.9994 | 2.4 | 6.1 |
| <i>KET</i> | Ketoprofen | 123 ± 1.73 | 67.4 ± 5.36 | 0.6 | 1.9 | 0.9998 | 4.6 | 0.9 |

| | | | | | | | | | |
|--------------------------------|------------------|------------|--------------|-----|------|--------|------|-----|--|
| <i>Analgesics</i> | | | | | | | | | |
| <i>SCA</i> | Salicylic Acid | 188 ± 0.70 | 22.1 ± 9.24 | 0.4 | 1.3 | 0.9997 | 2.1 | 1.1 | |
| <i>ACM</i> | Acetaminophen | 349 ± 0.29 | 99.6 ± 9.99 | 0.6 | 1.7 | 0.9998 | 4.6 | 3.1 | |
| <i>Others</i> | | | | | | | | | |
| <i>ATE</i> | Atenolol | 117 ± 1.38 | 68.3 ± 3.56 | 0.3 | 0.8 | 0.9998 | 2.8 | 1.8 | |
| <i>MET</i> | Metoprolol | 113 ± 1.67 | 79.4 ± 2.62 | 0.1 | 0.2 | 0.9998 | 2.4 | 1.4 | |
| <i>OXA</i> | Oxazepam | 168 ± 1.42 | 103.5 ± 1.15 | 2.3 | 6.4 | 0.9994 | 2.0 | 1.5 | |
| <i>CBZ</i> | Carbamazepine | 142 ± 0.48 | 101.1 ± 4.75 | 1.6 | 4.6 | 0.9975 | 1.0 | 3.2 | |
| <i>BZB</i> | Bezafibrate | 112 ± 2.79 | 80.5 ± 6.09 | 0.5 | 1.3 | 0.9998 | 3.1 | 2.9 | |
| <i>THC</i> | THC-COOH | 124 ± 2.51 | 43.6 ± 16.6 | 8.5 | 20.2 | 0.9987 | 3.4 | 4.2 | |
| <i>Opioids and derivatives</i> | | | | | | | | | |
| <i>MOR</i> | Morphine | 108 ± 1.05 | 52.3 ± 5.14 | 3.1 | 8.9 | 0.9996 | 6.1 | 2.0 | |
| <i>6MAM</i> | 6-Acetylmorphine | 171 ± 3.78 | 59.7 ± 4.72 | 1.0 | 2.8 | 0.9996 | 1.6 | 4.0 | |
| <i>HER</i> | Heroin | 112 ± 2.56 | 68.9 ± 6.72 | 6.4 | 17.3 | 0.9937 | 9.7 | 3.1 | |
| <i>METD</i> | Methadone | 235 ± 0.69 | 65.8 ± 13.6 | 2.2 | 7.8 | 0.9985 | 3.8 | 1.6 | |
| <i>COD</i> | Codeine | 111 ± 0.59 | 58.1 ± 2.88 | 0.5 | 1.4 | 0.9998 | 6.8 | 2.3 | |
| <i>BUP</i> | Buprenorphine | 241 ± 2.50 | 53.9 ± 12.4 | 0.8 | 2.6 | 0.9988 | 10.1 | 7.2 | |
| <i>TRA</i> | Tramadol | 171 ± 1.54 | 99.0 ± 2.46 | 2.1 | 6.5 | 0.9997 | 3.9 | 6.4 | |
| <i>Stimulants</i> | | | | | | | | | |
| <i>COC</i> | Cocaine | 80 ± 2.23 | 78.0 ± 5.47 | 1.6 | 4.9 | 0.9989 | 8.9 | 2.7 | |
| <i>BZE</i> | Benzoylcegonine | 109 ± 1.36 | 82.8 ± 3.15 | 1.8 | 5.4 | 0.9996 | 4.3 | 1.9 | |
| <i>CET</i> | Cocaethylene | 096 ± 1.54 | 83.6 ± 3.59 | 0.6 | 2.0 | 0.9996 | 6.6 | 2.6 | |
| <i>MDMA</i> | Ecstasy | 108 ± 0.47 | 72.0 ± 11.5 | 1.0 | 3.2 | 0.9996 | 5.6 | 3.8 | |
| <i>AMP</i> | 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 $\mu\text{g}\cdot\text{L}^{-1}$ 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:

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

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

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.

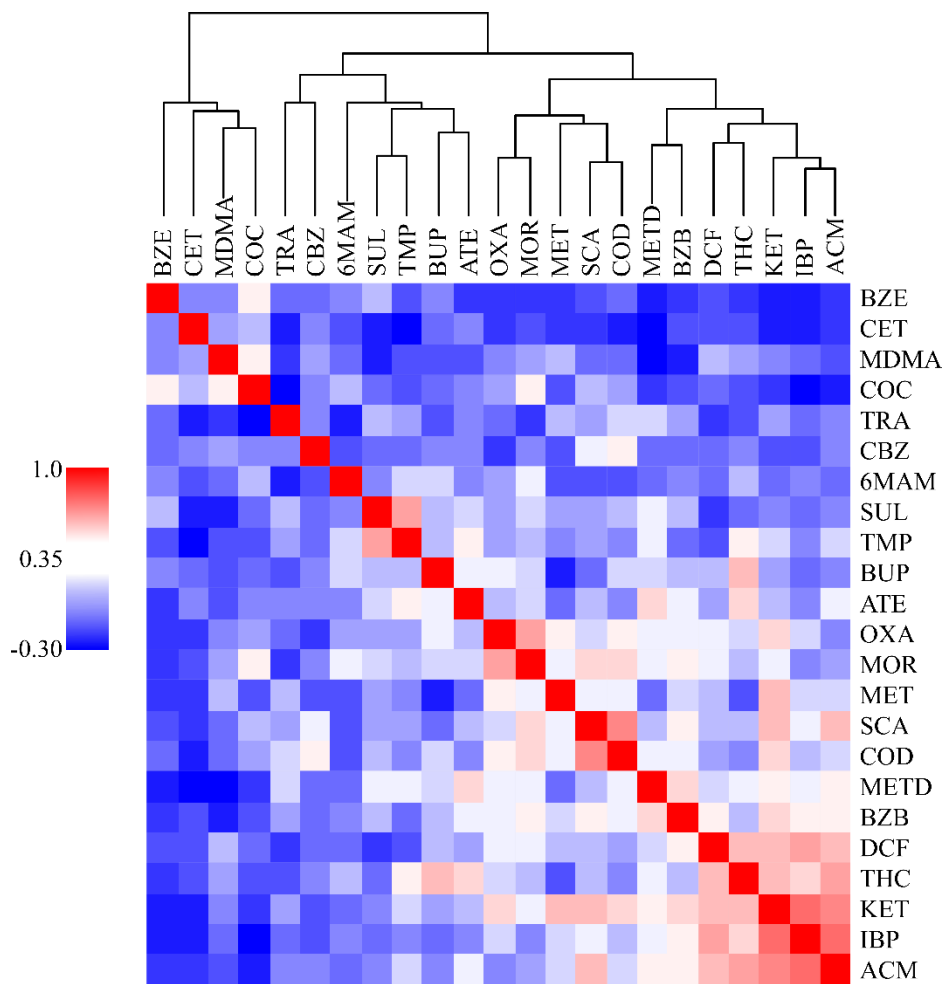
151 **3. Results and Discussion**

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.

163 **3.1. Daily variations of DTRs**

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



168
169 Figure 1: Heat map analysis based on the daily loads of each DTR analyzed

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

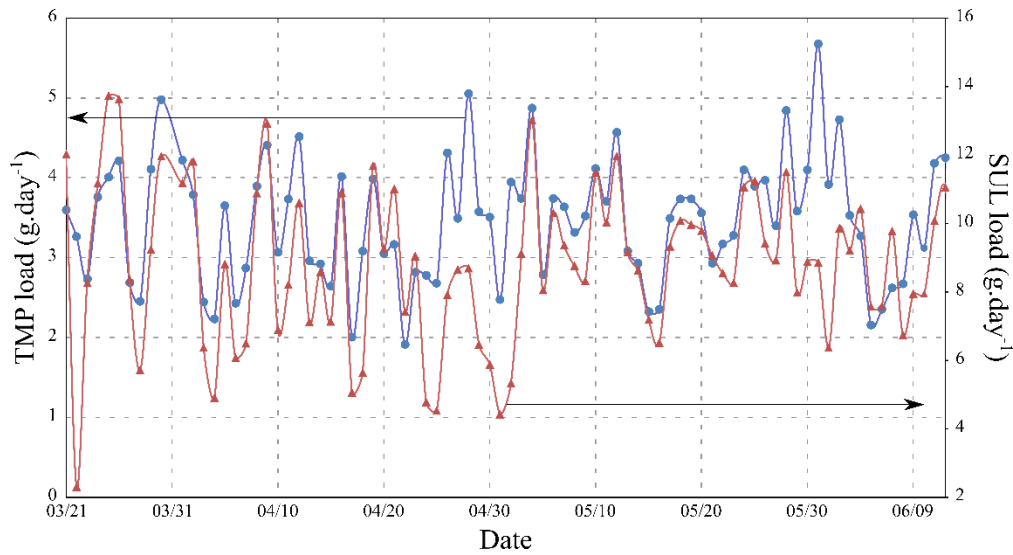
173 MOR. Hence, stimulants exhibit a different daily pattern in comparison with other DTRs, largely
174 generated by the noticeable increase in their loads during weekends (Thiebault et al., 2017b). This
175 weekly pattern is the most significant for stimulants thus resulting in the constitution of this 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.

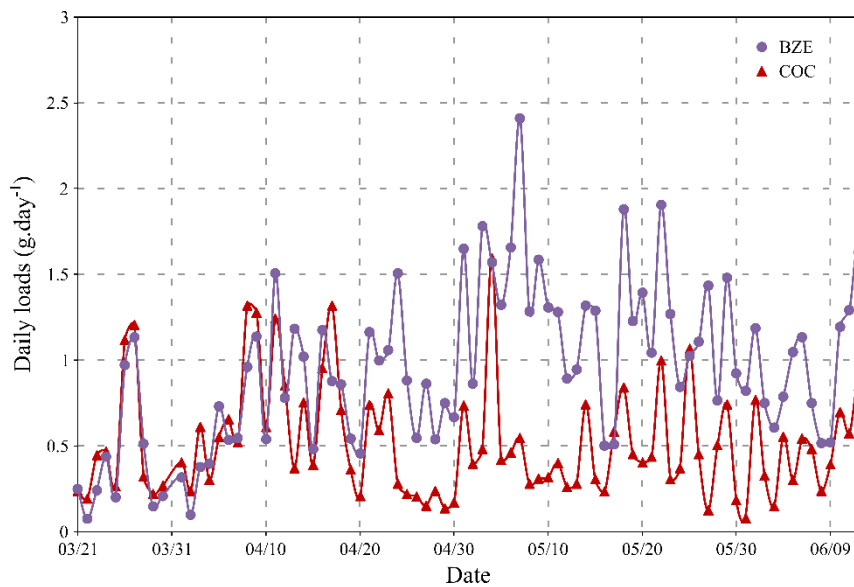
184 Based on this correlation plot, it is therefore difficult to distinguish between year-long medications
185 such as BZB, MET, ATE and the use of painkillers such as ACM, SCA and IBP, which are
186 occasionally consumed. The significant consumption of the latter appears to result in daily load
187 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

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)

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.

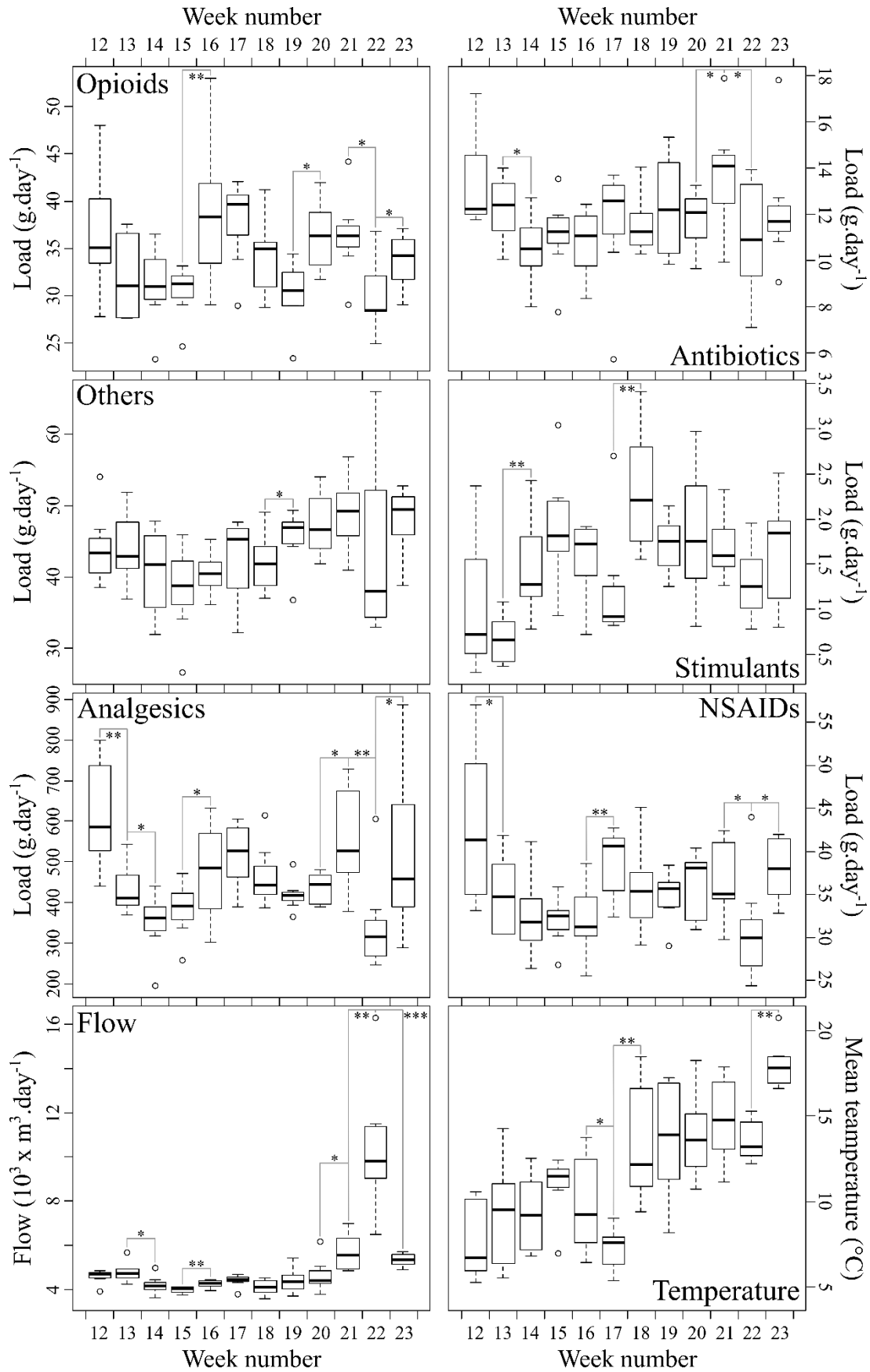
236 *3.3.1. Social and meteorological events in the catchment during the monitoring period*

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

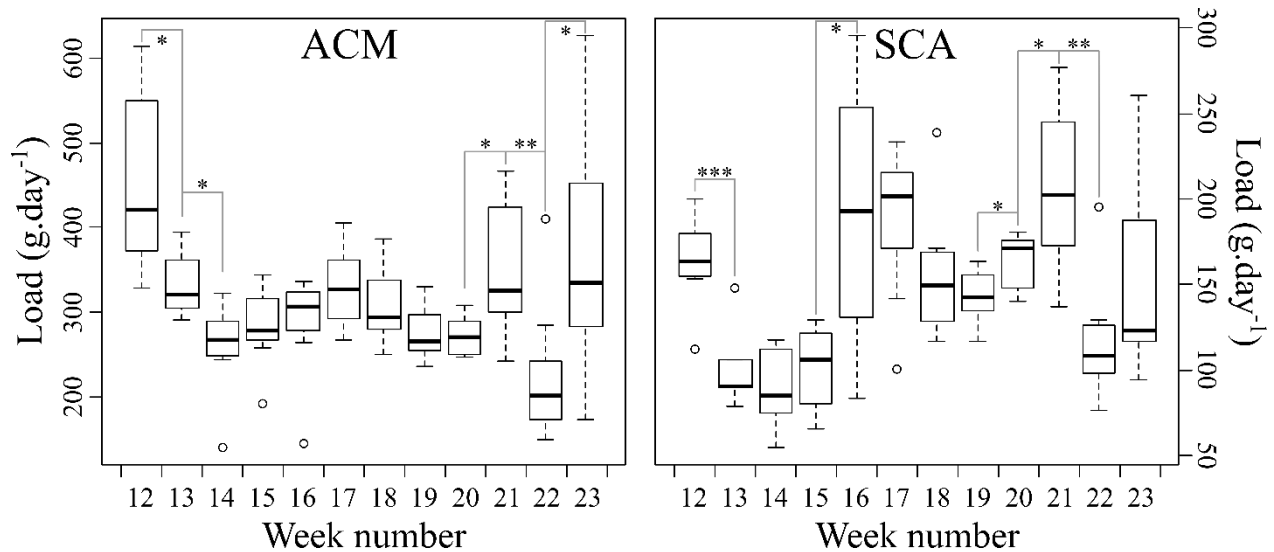
248 rainwaters with wastewaters, although the sewer system is supposed to be unitary, due to leaks.
249 Hence, the WWI flow was strongly impacted by rainfall during weeks 21 and 22.
250 A precise calendar with each specific event is presented in Figure S3.
251 The temperature within the catchment increased 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 $\pm 1.5 \sigma$ 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).



267
 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 1.5σ 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,

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*

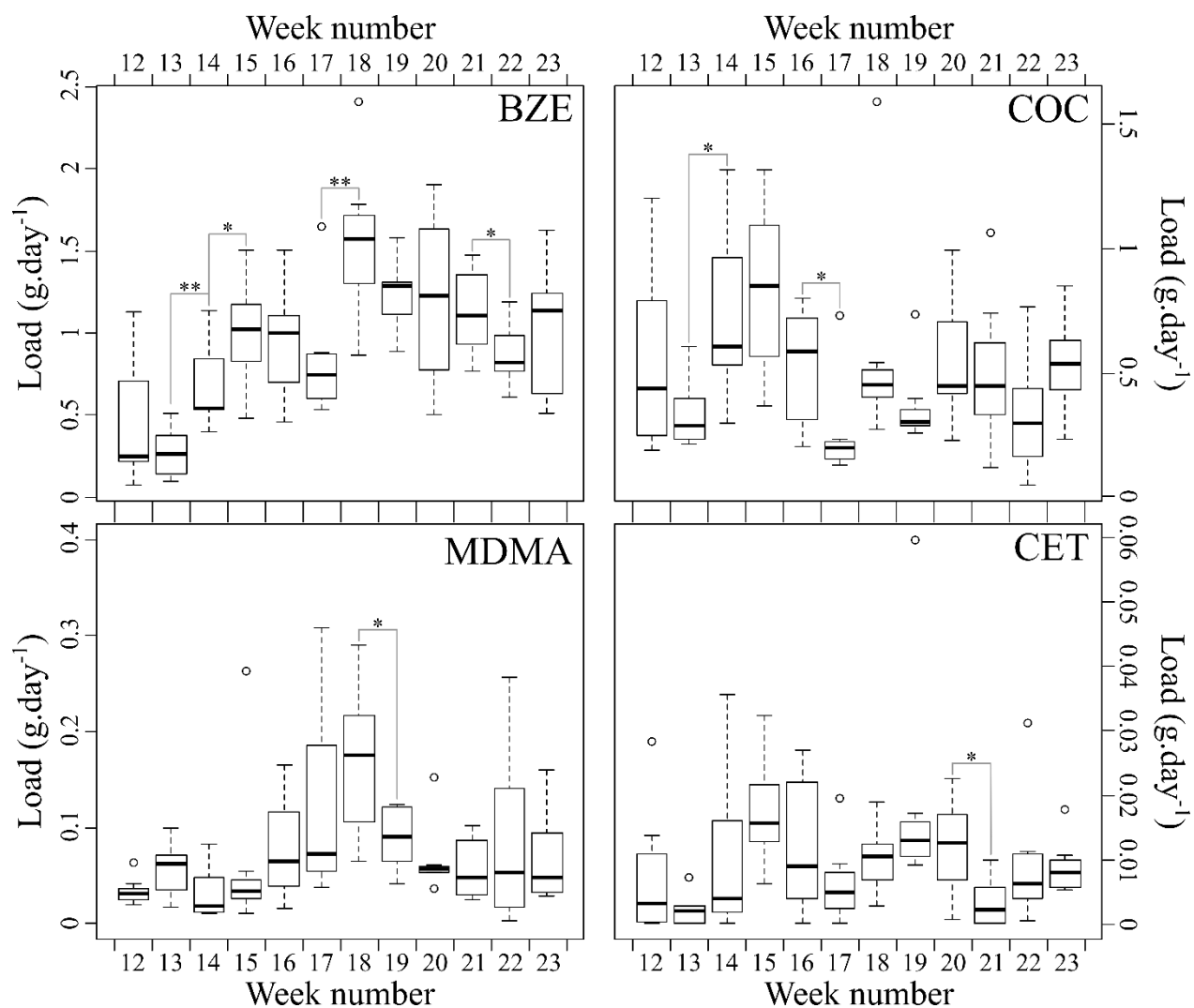
310 This group comprises year-long pharmaceuticals such as CBZ, MET, ATE, BZB and OXA, and
311 one illicit drug, THC, which is considered to be mainly consumed year-long. A significant variation
312 can be observed between weeks 17 and 18 (Figure 4). From a general point of view, the loads of
313 this 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).



342
 343 Figure 6: Loads of BZE, COC, MDMA and CET, for each sampled week. The line within the box marks
 344 the median, boundaries indicate the 25th and 75th percentiles, error bars indicate the maximum and minimal
 345 value in $\pm 1.5 \sigma$ variations and circles indicate individual values outside this range. Gray lines mark
 346 statistically significant variations with *p*-values < 0.05, 0.01 and 0.001 for *, ** and *** respectively
 347
 348 For example, a significant increase in BZE and COC loads occurred during the Easter holidays, as
 349 well as a significant increase at the end of the examination study period, especially for MDMA
 350 (Figure 6).
 351 Even if CET can be considered as a metabolite of COC, its excretion necessitates the consumption
 352 of both ethanol and COC. As a result, the offset between these two DTRs is not surprising.
 353 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.

365 **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.

384 **Acknowledgements**

385 The authors gratefully acknowledge Cedric Morio and Olivier Cantaloube for sampling
386 authorization and Pascale Moret for both the analysis of physico-chemical parameters of
387 wastewater influents and the sample delivery. Sara Karolak is thanked for providing illicit drug
388 standards. This work was supported by the French national program EC2CO-Biohefect Golden
389 Spike and the Labex VOLTAIRE (NR-10-LABX-100-01) is acknowledged for providing a grant
390 to M.R.

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