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1 Dynamics and sources of pharmaceutically active compounds in a coastal 2 Mediterranean river during heavy rains

3 Brice Reoyo-Prats^{1,2}, Dominique Aubert^{1,2}, Amélie Sellier³, Benoit Roig³, Carmen Palacios^{1,2,*}

4 ¹CEFREM, Univ. Perpignan Via Domitia (UPVD), Perpignan, France

5 ²CEFREM, CNRS UMR5110, Perpignan, France

6 ³CHROME (EA7352), Université de Nîmes, Nîmes, France

7 *Corresponding author: UPVD, CEFREM, UMR5110, F-66860 Perpignan, France. E-mail address:
8 carmen.palacios@univ-perp.fr. Phone: + 33 (0) 464662083. Fax: + 33 (0) 468662096.

10 Abstract

11 Concentrations of Pharmaceutically Active Compounds (PACs) in freshwater systems
12 depend on numerous factors such as land use and hydrometeorological conditions. In the
13 Mediterranean, heavy rain events are of particular importance as they highly influence the
14 concentration of micropollutants found in freshwater and are a source of recurrent first foul flushes
15 due to Combined Sewer Overflows (CSOs). In this study, we seek to assess the dynamics of
16 pharmaceuticals during storm events in coastal Mediterranean rivers at a fine scale and to determine
17 their contribution to multicontamination phenomena owing to CSOs. Our results showed that, while
18 dissolved PACs followed the same trend as other contaminants *i.e.* they increased significantly during
19 CSOs, PACs in the total fraction did not peak yet maintained their already high concentrations for
20 slightly longer due to their release via CSOs. Pharmaceutical concentrations for both the dissolved
21 and the total fraction were dramatically diluted during the peak river flow. A fine-scale follow-up of
22 PACs dynamics in the total fraction, including the differentiation of sewer overflows from both the
23 right and left river banks, as well as the analyses of a large amount of PACs molecules, allowed us to
24 clearly identify their major sources. While domestic inputs were dominated by nicotine and caffeine,
25 the use of gadolinium (an MRI contrast agent) as a marker, attributed the main source of medical
26 drugs such as tramadol, ibuprofen and diclofenac to the major public hospital of the region. Thus,
27 identifying major sources of PACs and implementing adapted water treatments directly at those
28 sources would be the most cost-efficient alternative to cope with pharmaceutical drugs in coastal
29 Mediterranean aquatic environments. Moreover, PACs behavior differed depending on the
30 molecules considered and the source of these molecules, but we could not establish a direct link
31 between their behavior and their chemical or physical properties. Our study highlights the
32 importance of monitoring at strategic locations and with a high frequency sampling in order to better
33 understand fate, sources and behavior of pharmaceuticals in aquatic environments.

34

35 **Keywords:** pharmaceutically active compounds, water quality, multicontamination phenomena, coastal rivers,
36 Mediterranean climate, storm events, multiple stressors.

1 **1. Introduction**

2

3 Two decades ago the European Environment Agency, the scientific community and the
4 public started to be concerned about the environmental and health effects of chemically bioactive
5 substances used in human and veterinary medicine found at trace levels (micropollutants) in aquatic
6 environments (EEA 2010). Still, these Pharmaceutically Active Compounds (PACs) were not
7 monitored in the European Union until 2015 and today, only three substances are regularly
8 monitored including diclofenac, 17 α -ethinylestradiol, 17 β -estradiol and estrone (EC 2015). PACs, like
9 other micropollutants such as pesticides or metal elements, are released in the aquatic environment
10 via point sources of pollution such as WasteWater Treatment Plants (WWTP) and hospitals (Pal et al.
11 2010). Furthermore, human and veterinary-use drugs accumulate in superficial soils through the use
12 of sewage sludge or manure as fertilizers in farm fields. The remobilization of PACs from soils
13 through runoff and leaching is therefore a potential diffuse source for these compounds (Halling-
14 Sorensen et al. 1998; Gielen et al. 2009). Thus, the concentration of PACs in surface waters will
15 depend on both watershed land use and rainfall regimes in the study area.

16 In the Mediterranean, long dry periods alternate with short but intense seasonal rainfalls
17 (Miller 1983; Cowling et al. 2005). During the summer, contaminants from human activities tend to
18 concentrate in soils and in river sediments as water resources decrease through evaporation (Gasith
19 and Resh 1999; Olías et al. 2004). During heavy rain events in the Mediterranean, flow
20 augmentation, surface soil runoff, river sediments and the resuspension of sewer solids from
21 Combined Sewer Overflows (CSOs) lead to a modification in the level of contaminants in surface
22 waters (Coynel et al. 2007; Sakrabani et al. 2009; Taghavi et al. 2010; Dumas et al. 2015) and in
23 particular, an increase in the level of pharmaceutical products (Escher et al. 2011; Osorio et al.
24 2012a; Backhaus 2014; LaLone et al. 2014; Osorio et al. 2014). Drought/flood hydrodynamics of
25 coastal Mediterranean rivers have been identified as the major factor affecting the presence of
26 micropollutants in these environments (Pailler et al. 2009; Osorio et al. 2012a; Fairbairn et al. 2016).
27 While Ashley et al. (1992) predicted the release of high concentrations of contaminants during first
28 foul flushes from CSOs at the start of a wet weather flow, studies of pollutant dynamics during heavy
29 rains and high flows are scarce in the literature (Pailler et al. 2009). Reoyo-Prats et al. 2017
30 performed a high frequency follow-up of six families of contaminants, including pesticides, nutrients,
31 heavy metals and fecal indicators, during a flood event. They demonstrated that floods and perhaps
32 even more importantly, recurrent heavy Mediterranean rain events, are responsible for chronic
33 multicontamination phenomena under this climate. Such micropollutant mixtures are potentially
34 highly toxic for living organisms of the land-sea continuum, even at small concentrations

1 (Schwarzenbach et al. 2006). Determining the importance of PACs compared to other pollutants is
2 therefore fundamental to assess their environmental risk (Boxall et al. 2012), particularly during first
3 flush multicontamination phenomena. Moreover, few environmental studies detail the fate and the
4 way pharmaceuticals are transported along well-characterized river watersheds during different
5 seasons (Pal et al. 2010), particularly in conjunction with other micropollutants (Biales et al. 2015;
6 Fairbairn et al. 2016; Garrido et al. 2016) and during storm events and floods (Pailler et al. 2009). The
7 lack of information regarding their sources, seasonal occurrence and potential environmental risk
8 might be the reason why medical and veterinary drugs are not yet properly regulated and thoroughly
9 included in monitoring lists of priority pollutants.

10 In this study, our first goal was to finely assess the dynamics of PACs concentrations during
11 first foul flushes from CSOs from heavy rainfalls on the Têt River, a coastal Mediterranean
12 watercourse situated in the Southeast of France. This river was previously used as a model to study
13 the transfer of suspended matter, associated nutrients and pollutants to the Mediterranean Sea
14 (Roussiez et al. 2005; Garcia-Esteves et al. 2007; Dumas et al. 2015; Reoyo-Prats et al. 2017). Our
15 second goal was to identify the different sources of PACs and their contribution to river water
16 contamination. Because no animal farming activities exist along the Têt River, all drugs are derived
17 from human consumption and their sources are thus easier to identify. Our final goal, though less
18 significant than the others, was to determine how concentrations of PACs changed relative to a
19 variety of other contaminants, particularly during typical Mediterranean heavy rainfall events.

21 **2. Material and Methods**

23 *2.1 Sampling*

25 *2.1.1 Stations*

26 To follow the dynamics of medical residues, we focused our efforts on the most urbanized
27 section of the Têt River, from Perpignan, the biggest city in the Pyrénées-Orientales department, to
28 the river mouth (Fig. 1). Stations were chosen according to two criteria: for safety reasons, sampling
29 had to be done from bridges during flood risk events and sampling locations had to be close enough
30 to the laboratory to be sampled at high frequency. The first station, R2, was located in the city of
31 Perpignan, downstream the Basse River (Conseil Général des Pyrénées Orientales (CG66) 2009;
32 Conseil Général des Pyrénées Orientales (CG66) 2012), a tributary highly polluted by agriculture and
33 urban activities and downstream Perpignan city's right bank sewage-overflow system, but upstream
34 main WWTP inputs (Fig. 1). The second station, R0, was located 9 km downstream from R2 at the
35 first bridge downstream from all Perpignan's sewage-overflow system and WWTP (350,000

1 Population Equivalent, PE) and the WWTPs for the Sainte-Marie-la-Mer and Canet-en-Roussillon
2 vacation resorts (24,000 PE and 66,000 PE, respectively). Both R0 and R2 received inputs from
3 extensive gardening and vineyard culturing activities from the last portion of the catchment area (Fig.
4 1, main figure and inlet).

5

6 *2.1.2 Campaigns*

7 A campaign comprised three sampling periods including one autumnal storm event with high
8 frequency sampling, and two punctual samplings on either side of this event, during summer and
9 winter droughts.

10 The first campaign was a pilot study that aimed to describe pharmaceutical trends for a
11 limited number of molecules to determine if a more thorough study would be relevant. Sampling was
12 conducted at the R0 station of the Têt River during periods of drought in summer 2013 (17th of
13 September) and winter 2014 (13th of February). Eleven additional samples were collected from the
14 16th to the 21st of November 2013 during an autumnal flood event, with a total follow-up time of 109
15 h. This campaign also compared the behavior of PACs with that of other contaminants' reported in
16 [Reoyo-Prats et al. 2017](#) during the same flood event.

17 Based on the results from the first campaign, a second campaign was carried out in 2015-16
18 to follow the temporal dynamics of a larger number of drugs, upstream and downstream WWTPs, at
19 R2 and R0 respectively (Fig. 1). Punctual samplings during periods of drought were conducted in
20 summer 2015 (18th of August) and winter 2016 (10th of February). In addition, a total of 10 samplings
21 were done from the 2nd to the 4th of November 2015 at R2 and R0 stations, with a total of 5
22 samplings per station and a total follow-up of 53 h.

23

24 *2.1.3 Heavy rains and flood sampling strategy*

25 Perpignan city's sewer system is designed to overflow according to the 2-month return
26 period as defined by the maximum precipitation distribution curves for the Têt River (Online
27 resource 1). Therefore, in order to determine the level of contaminants before and after the
28 Perpignan sewer system overflowed, sampling began when precipitation approached the 2-month
29 return period distribution curve and continued at a high frequency thereafter. Sampling time
30 frequency during first heavy rains was controlled by the "live" monitoring of precipitation on the
31 Perpignan hydrological station's webpage, which is located within the Ministère de la Transition
32 Écologique et Solidaire website (<http://www.rdbmrc.com/hydroreel2/station.php?codestation=459>).
33 Once we estimated that the sewer system had overflowed, sampling frequency was determined by
34 either changes in precipitation or river water flow levels, which are available at this same webpage.
35 Reported final river flow was retrieved at the Banque Hydro (<http://www.hydro.eaufrance.fr>).

1

2 *2.2 Medical, veterinary and emerging drugs analyses*

3

4 River water was sampled with 10 L capacity polyethylene terephthalate (PET) tanks
5 previously cleaned with 1.5 L of 1 M HCl and rinsed with 2 L of distilled water. Plastic tanks were
6 required for field sampling during the heavy rainfalls and for the flood, as crude weather conditions
7 did not allow for sampling with independent bottles for each contaminant. In the field, tanks were
8 rinsed three times with river water before they were filled. Once in the laboratory, 0.8 L of sampled
9 water was transferred to an uncontaminated 1 L bottle and put at -20°C for future pharmaceutical
10 analyses. The use of plastic bottles instead of glass bottles was necessary for safety reasons as glass
11 containers explode when stored at freezing temperatures. This constraint requires that results are
12 interpreted with caution, particularly with respect to comparative studies of absolute concentrations
13 of molecules.

14 PACs analyses from the 2013-14 pilot campaign were conducted in the dissolved fraction
15 using internally validated methods. The pharmaceuticals chosen for analyses were four medical
16 residues commonly found in waters: sulfamethoxazole, carbamazepine, ibuprofen and diclofenac.
17 The Solid Phase Extraction (SPE) was performed using PolyClean™ 2H (60 µm, 70 Å), 200 mg / 6 mL
18 (Interchim, Montluçon, France) and a vacuum manifold from phenomenex (Torrance, CA, USA). After
19 cartridge conditioning with 20 mL of methanol followed by 6 mL of reagent water, samples were
20 loaded onto the cartridge at a flow rate of 5-10 mL/min. The cartridge was then dried under vacuum
21 for approximately 5 min. The cartridge was eluted with 5 mL of methanol and the extract was filtered
22 through a 0.45 µm PolyTetraFluoroEthylene (PTFE) filter (VWR, Radnor, PA, USA), concentrated until
23 dry under a gentle stream of nitrogen in a dry bath at 50 ± 5 °C and reconstituted in a volume of 200
24 µL of methanol. HPLC analyses were performed by Liquid Chromatography-Mass Spectrometry (LC-
25 MS). The chromatography was done in a Waters Alliance 2695 separation module (Waters, Milford,
26 MA, USA) equipped with a reversed phase C18 analytical column of 100 mm × 2.2 mm and 3.5 µm
27 particle size (XTerra MS C18). The mobile phases used were ultrapure water and acetonitrile at
28 different percentages ([Table 1](#)). The injected sample volume and flow-rate was 5 µL and 0.25 mL/min
29 respectively. The mass spectral analysis was performed on a Waters micromass ZQ (Waters, Milford,
30 MA, USA) equipped with a Z-Spray™ ElectroSpray Ionization (ESI) source ([Table 2](#)). Detection and
31 quantification limits are also reported in [Table 2](#).

32 During the 2015-16 campaign, a more thorough monitoring of pharmaceutical products was
33 conducted on a total of 89 molecules. For this purpose, the total fraction was analyzed by COFRAC
34 accredited laboratory Groupe CARSO, via Liquid Chromatography-tandem Mass Spectrometry (LC-
35 MS/MS) using a Thermo Scientific TSQ Quantum (Waltham, MA, USA) connected to an API 5500 mass

1 spectrometer (Applied Biosystems-Sciex, Foster City, CA, USA) or an Agilent 6460 (Santa Clara, CA,
2 USA). Ionization was performed in the switch positive/negative mode for all runs. Chromatographic
3 analyses were achieved using a C18 analytical column of 100 mm × 2.2 mm and 3.5 μm particle size
4 (XTerra MS C18) with a non-polar elution gradient at a flow rate of 0.4 mL/min while the injected
5 sample volume varied from 30 to 5,000 μL depending on the method. Direct injection was performed
6 for diclofenac. Direct injection and EDTA treatment were used for tetracycline, chlortetracycline,
7 doxycycline, oxytetracycline, ciprofloxacin, danofloxacin, norfloxacin, ofloxacin, enrofloxacin,
8 marbofloxacin and sulfamethoxazole. The same instrument was used with on-line SPE injection with
9 methanol on a C18 cartridge for trimethoprim, lincomycin, clindamycin, chloramphenicol,
10 clenbuterol, erythromycin, clarithromycin, spiramycin, monensin, virginiamycin M1 (pristinamycin
11 IIA), roxithromycin, irbesartan, indomethacin, fenoprofen, antipyrine (phenazone), propyphenazone,
12 dexamethasone, naproxen, ibuprofen, ibuprofen 1-hydroxy, ibuprofen 2-hydroxy, piroxicam,
13 ketorolac (Macril), hydrocortisone, fenofibric acid, clofibrac acid, simvastatine, aminopyrine,
14 tramadol, desmethyltramadol, dihydrocodeine, oxycodone, morphine, cyclophosphamide,
15 methotrexate, ifosfamide, prilocaine, mepivacaine, bupivacaine, atenolol, propranolol, acebutolol,
16 metoprolol, bisoprolol, sotalol, timolol, diltiazem, ticlopidine, pentoxifylline, fluoxetine, doxepine,
17 imipramine, amitriptyline, zolpidem, norfluoxetine, lorazepam, oxazepam, bromazepam, diazepam,
18 alprazolam, carbamazepine, phenytoin (Dilantin), caffeine, salbutamol, progesterone, testosterone,
19 4-androstenedione, norethindrone, ranitidine, cotinine and nicotine. Again, the same instrument was
20 used but with off-line SPE injection with methanol on an ion exchange cartridge according to ISO
21 25101 ([International Organization for Standardization 2009](#)) for estrone, ethinylestradiol, estradiol
22 17 alpha, estradiol 17 beta, estriol, dienestrol and diethylstilbestrol. Detection limit and the method
23 used for different analytes analysis are summarized in [Table 3](#).

24 Mass fluxes (g/h) were calculated for the 2015-16 campaign as mass concentrations (g/L)
25 multiplied by river flow (L/h). Flow data were only available at R2 station but as R0 station was only 9
26 km downstream from R2 and is at the very end of the catchment area, we assumed the same flow
27 for both.

28 In order to better discern the relationship of PACs with positive concentrations at R0 station
29 during the rain event of the 2015-16 campaign, a multivariate analyses using Principal Component
30 Analysis (PCA) was conducted using *rda* function from *vegan* package ([Oksanen et al. 2017](#)) in R
31 freeware ([R Core Team 2017](#)).

32

33 2.3. Rare Earth Element (REE) analyses

34

35 REE concentrations were measured by Inductively Coupled Plasma Mass Spectrometry (ICP-

1 MS, Agilent 7700X) at CEFREM laboratory. REE concentrations followed an intercalibration exercise
2 conducted on river water certified reference material SLRS-6 developed for the analysis of trace
3 metals and other constituents (Yeghicheyan et al. 2017). This exercise demonstrated that REE
4 concentrations provided by CEFREM were consistent with other participants. REE patterns were
5 determined by using the Upper Continental Crust (UCC) elemental composition of rock standards in
6 order to normalize sample concentrations of these elements (Piper and Bau 2013).

8 **3. Results**

10 *3.1. Pilot study on pharmaceutical trends in the Têt River during the 2013-14 sampling campaign*

12 Our qualitative study during the 2013-14 campaign sought to estimate major trends of
13 dissolved pharmaceuticals for the R0 station (Fig. 1) located in the Têt River downstream of
14 Perpignan, Canet and Sainte-Marie-la-Mer WWTPs, during a typical autumnal flood event as
15 compared to summer and winter droughts. Four dissolved pharmaceuticals (carbamazepine,
16 sulfamethoxazole, ibuprofen and diclofenac) were studied as representatives of three families of
17 pharmaceuticals (anticonvulsants, antibiotics and anti-inflammatories, respectively) that are
18 frequently found in river waters. Pharmaceutical levels for all seasons, in parallel with changes in the
19 river flow during the storm event, are summarized in figure 2. Maximum levels of dissolved PACs,
20 with the exception of ibuprofen which was not detected, were attained at 20 h sampling time.

22 *3.2. Exhaustive monitoring of medical, veterinary and emerging drugs on the total fraction during the* 23 *2015-16 sampling campaign over several seasons*

25 Given the encouraging results of our pilot study, a more extensive study was conducted
26 during the 2015-16 campaign. A total of 89 molecules were analyzed in the total fraction at both R0
27 and R2 sampling stations located upstream and downstream of the primary WWTPs in urbanized
28 areas of the Têt River (Fig. 1). Twenty-one molecules were identified and their concentrations are
29 plotted together with river flow for the 2015 autumnal storm event, and for the summer and winter
30 droughts at both stations, R2 (Fig. 3a) and R0 (Fig. 3b). These results are also summarized in the
31 Online Resource 2. In parallel, figures 3c and d show discharges of the main Sewer-Overflows (SO) for
32 the city of Perpignan, river flow and precipitations along sampling time during the same storm event.
33 All molecules detected in 2013-14 (Fig. 2) were also found in 2015-16, except for sulfamethoxazole,
34 detected only in 2013-14 with a peak concentration of 4.4 ng/L, well beneath the 2015-16
35 quantification limit (20 ng/L, Table 3). For both stations, the highest drug concentrations were found

1 for the winter drought (right axes in [Fig. 3a&b](#)) and at the start of sampling during the autumnal
2 storm event (0 h sampling time in [Fig. 3a&b](#)). At R2, seven molecules were detected but nicotine and
3 caffeine were dominant at the beginning of the autumnal storm event ([Fig. 3a](#)), with concentrations
4 of 217 ng/L and 175 ng/L, respectively ([Online Resource 2](#)). These values were at least 2.5 times
5 higher than those of other molecules for all seasons for this station. At R0, however, a total of 20
6 molecules were detected, corresponding to 11 PACs families ([Fig. 3b](#) and [Online Resource 2](#)). Top
7 concentrations for nicotine and caffeine were less important with 149 ng/L and 59 ng/L, respectively.
8 But analgesics, represented by tramadol and desmethyltramadol, had the highest cumulated
9 concentrations with 382 ng/L at 0 h and 289 ng/L at 18 h sampling time for the storm event and with
10 297 ng/L and 224 ng/L for the winter and summer droughts respectively, with tramadol as the most
11 abundant molecule in this family ([Online Resource 2](#)). Anti-inflammatories (ibuprofen and diclofenac)
12 were also dominant in our study with 93 ng/L and 293 ng/L cumulated concentrations at 0 h and 18 h
13 respectively and 171 ng/L in winter while only 30 ng/L in summer. Anti-hypertensives, only
14 represented by irbesartan, also had important concentrations, 195 ng/L at 0 h and 85 ng/L at 18h
15 during the autumnal storm event, and 182 ng/L and 132 ng/L in winter and summer droughts
16 respectively. With a total of five (see [Fig. 3](#)), beta blockers were the most significant family in terms
17 of the number of molecules found in the river, with cumulated concentrations of 146 ng/L at 0 h, 130
18 ng/L at 18 h, 112 ng/L in the summer drought and 144 ng/L in the winter drought.

19 Pharmaceuticals were also monitored at a high frequency during the autumnal heavy rain
20 event. At R2, all six molecules detected at 0 h sampling time decreased remarkably after this first
21 sampling and were at their lowest concentration at the flow peak ($144 \text{ m}^3/\text{s}$) that occurred at around
22 23 h sampling, except for irbesartan, which increased slightly at this point ([Fig. 3a](#) and [Online](#)
23 [Resource 2](#)). In contrast to R2, at R0, most PACs remained at high concentration during the first rains
24 until 18 h ([Fig. 3b](#) and [Online Resource 2](#)), when the major overflows of the sewer systems occurred
25 ([Fig. 3c&d](#)). They then decreased sharply and found their lowest levels around the flow peak.
26 Exceptions to this rule existed for irbesartan which showed a linear dramatic decrease similar to
27 emerging drugs in R2, and ibuprofen and fenofibric acid whose concentrations peaked sharply at 18
28 h and then decreased rapidly at the flow peak. A principal component analysis to explore the
29 relationships among PACs concentrations throughout the rain event in the R0 station was also
30 conducted. The ordination plot showed that all PACs were negatively correlated with respect to the
31 first axis and therefore to initial moments of the rain event, at 0 h and 18 h sampling times (PCA,
32 [Online Resource 3](#)). The second axis discriminated amongst PACs correlated to 0 h and those
33 correlated to 18 h. While fluoxetine and irbersartan were very positively correlated to axis 2 and had
34 indeed the highest concentrations at 0 h sampling time (see also [Online Resource 2](#)), fenofibric acid
35 and ibuprofen were very negatively correlated to axis 2 and had their highest concentrations at 18 h

1 sampling time.

2 In order to consider the influence of the river flow, we calculated instantaneous mass fluxes
3 at both stations, R2 (Fig. 4a) and R0 (Fig. 4b). Considering seasonal variations, most PACs fluxes were
4 higher in winter than in summer at both R2 and R0 stations, although some were 0 g/L for both
5 seasons. Exceptions to this rule were nicotine at R2, and acebutolol at R0 with the opposite behavior.
6 During the autumnal heavy rain event at R2 station, cotinine and bisoprolol fluxes were always
7 around 0 g/h and so was the case for caffeine except from a flux of 2.1 g/h at the very beginning of
8 the event (Fig. 4a). Tramadol and irbesartan fluxes were also near 0 g/h throughout the rain event
9 with the exception of peaks of 1.8 and 4.1 g/h, respectively, but at different times. While tramadol
10 peaked at 18 h, irbesartan did so at 23 h. Nicotine had two high peak fluxes, one of 14.8 g/h at 18 h,
11 followed by a dramatic decrease to 0 g/h at 23 h and a second peak at 11.2 g/h at 29 h before a soft
12 decrease to 5.8 g/h at 51 h. At R0 station, all top flux peaks were attained at 22 h with the highest
13 fluxes of 30.6 g/h for caffeine, 21.3 g/h for diclofenac and nicotine, 19.2 g/h for ibersartan and 18.7
14 g/h for tramadol. All these four molecules decreased sharply after 22 h but never reached 0 g/h with
15 the exception of diclofenac. All other molecules that peaked at 22 h showed a rapid decrease to 0
16 g/h after 22 h. Finally, ibuprofen, sotalol, clarithromycin, atenolol, acebutolol, diltiazem,
17 clarithromycin, erythromycin and trimethoprim had their peak fluxes at 18 h followed by a sharp
18 decrease immediately after, and remained at near 0 g/h during the rest of the rain event.

19

20 *3.3. Rare earth element patterns during a heavy rain in autumn 2015*

21

22 Rare Earth Element (REE) patterns were defined at R2 and R0 stations to determine the
23 contribution of hospitals as sources of PACs in the Têt River. Upstream station R2 showed a generally
24 flat pattern of REEs along different sampling times, except for europium (Eu) with small peaks at 0
25 and 18 h sampling times (Fig. 5a), probably due to the mineral origin of this element in the Têt River
26 catchment area. However, the downstream station R0 showed mostly large peaks of gadolinium (Gd)
27 during the same sampling times (Fig. 5b). Indeed, at 0 and 18 h, Gd values were respectively 6 and 18
28 times higher at R0 than at R2.

29

30 **4. Discussion**

31

32 *4.1 Dissolved PACs contribute to chronic risk multicontamination phenomena for coastal* 33 *Mediterranean rivers*

34

35 In 2013-14, we conducted an exploratory qualitative study whose main purpose was to

1 compare pharmaceutical dynamics with those of other pollutants during heavy rainfalls and floods in
2 the Têt River, a typical coastal Mediterranean watercourse. We studied the dissolved fraction
3 because it allows for comparisons to be made with the only other known published study on PACs
4 during storm events and sewer overflows (Pailler et al. 2009). Although our results were only
5 internally validated and should be interpreted with caution, they showed a simultaneous increase of
6 dissolved pharmaceuticals just before the increase in river flow during the first heavy rains at 20 h
7 sampling time (Fig. 2). Pailler et al. 2009 obtained the same results for dissolved PACs dynamics
8 during storm events in Luxembourg. Reoyo-Prats et al. 2017 demonstrated that multiple pollutants
9 (nutrients, metals, pesticides and fecal indicators) reached concentrations never before recorded for
10 the Têt River at exactly the same time during this rain event in 2013. They linked this pollutant
11 cocktail to first foul flush of Combined Sewer Overflows (CSO). First flushes of wastewater and in-
12 sewer cumulated sediments are a source of major pollutants (Gromaire et al. 2001; McLellan et al.
13 2007; Phillips and Chalmers 2009; Weyrauch et al. 2010; Passerat et al. 2011). Because heavy
14 rainfalls are recurrent under a Mediterranean climate, Reoyo-Prats et al. 2017 argued that first flush
15 multicontamination phenomena constitute a chronic risk in Mediterranean coastal environments
16 and, according to our results, dissolved PACs are no exception.

17

18 *4.2. A fine-scale study of PACs dynamics during the 2015 rain event allowed for identification of*
19 *sources, fate and transport of PACs in surface waters*

20

21 A higher number and concentration of pharmaceutical compounds in the total fraction was
22 found downstream (R0 station, Fig. 3b) than upstream WWTPs (R2, Fig. 3a) at all seasons, indicating
23 their constant release by WWTPs, which are recognized as major sources of pharmaceuticals in the
24 environment (Santos et al. 2007; Fernández et al. 2010; López-Roldán et al. 2010; Vazquez-Roig et al.
25 2011; Barber et al. 2013). The highest concentrations of PACs in the Têt River were found at the
26 beginning of the autumnal heavy rain event (0 h sampling time on Fig. 3) and during the winter
27 drought. This result could be explained by the higher river flow during these seasons leading to a
28 higher resuspension of suspended matter, in contrast to the summer drought. Other studies of
29 Mediterranean rivers also reported higher PACs levels during this season (Osorio et al. 2012a; Osorio
30 et al. 2012b). Another possible explanation is the decrease in the attenuation of PACs during winter
31 and autumn due to the decline of phototransformation processes at these seasons (Daneshvar et al.
32 2010), which largely contribute to PACs elimination in WWTPs (Vieno et al. 2005). However, in order
33 to compare seasonal variations, it is best to use mass fluxes of organic pollutants such that river flow
34 can be accounted for (Bernot et al. 2013; Moreno-González et al. 2013). Our flux results indicated
35 that for most PACs, levels were slightly higher in winter than in summer. This result differs from the

1 study of [Bernot et al. \(2013\)](#), which only found caffeine and paraxanthine more abundant in winter
2 whereas the abundance of some personal care products actually increased in summer because they
3 were consumed at this time (*i.e.* DEET from insect repellents). This result is not captured in [Fig. 4](#),
4 because summer and winter drought fluxes were negligible in comparison to the high fluxes of PACs
5 observed for the rain event. To the best of our knowledge no study on total PACs mass flux loads
6 during a rain event has ever been conducted. Due to the high recurrence of heavy rains under a
7 Mediterranean climate, these events largely contribute to PACs release into aquatic environments.

8 The most abundant PACs families encountered at R0 were analgesics, anti-inflammatories
9 and beta blockers ([Fig. 2](#)), which are known to be the most resistant to wastewater treatments with a
10 removal rate of only 30-40% (reviewed in [Deblonde et al. 2011](#)). Analgesics had the highest
11 cumulated concentrations. In France, analgesics are the most popular prescription drugs with
12 tramadol, a drug found in high concentrations in the Têt River, as the fourth most sold analgesic
13 ([Agence Nationale de la Sécurité du Médicament et des produits de santé \(ANSM\) 2014](#)). Analgesics
14 are also found in high abundance in other freshwater systems in Europe ([Kasprzyk-hordern et al.](#)
15 [2008](#); [Rúa-Gómez et al. 2012](#); [Loos et al. 2013](#); [Osorio et al. 2015](#)). Anti-inflammatories were also
16 predominant in our study, a result similar to other Mediterranean European countries such as Italy
17 ([Patrolecco et al. 2013](#)) and Spain ([Moreno-González et al. 2014](#); [Osorio et al. 2015](#)), as well as in
18 other developed countries around the world ([Stumpf et al. 1999](#); [Tixier et al. 2003](#); [Bendz et al. 2005](#);
19 [Roberts and Thomas 2006](#); [Palmer et al. 2008](#)). Beta blocker levels were also significant in the Têt
20 River. Among them, sotalol was predominant at our study site as well as at another nearby coastal
21 river ([Osorio et al. 2012a](#)), although atenolol, metoprolol and propranolol are typically the most
22 common beta blockers found in aquatic environments (revised in [Godoy et al. 2015](#)).

23 At R2 station, however, only nicotine and caffeine were found in abundance at the
24 beginning of the storm event. As they are common urban contaminants coming from human
25 consumption of cigarettes and coffee, their presence was either due to discharges from WWTPs from
26 small towns situated upstream R2, or to illicit sanitary inputs, *i.e.* houses not connected to the
27 wastewater collection system that directly and illegally release their untreated wastewaters in rivers.
28 Illicit sanitary inputs were reported to us by locals at the Basse River tributary, which is directly
29 upstream R2. The hypothesis of a nearby discharge of these drugs by illicit sanitary inputs is
30 supported by the presence of nicotine and caffeine at higher concentrations at R2 compared to R0,
31 where these molecules must be buffered by the WWTPs. If this hypothesis is confirmed, the rapid
32 release of these emerging drugs during the first hours of a heavy rain could therefore serve as
33 markers of illicit sanitary inputs.

34 Regarding PACs dynamics during the storm event at 2015-16 campaign, only two samplings
35 were done at the beginning of the rain event, at 0 and 18 h respectively, but we are confident that

1 our second sampling point is fully representative of the CSO phenomena and no major changes in
2 pollutants occurred in between for two major reasons. Firstly, although a CSO occurred at 10 h, it
3 was minor, with $\sim 2,000 \text{ m}^3$ of untreated water released into the river, while the major CSO at 16 h
4 represented a volume of approximately $7,000 \text{ m}^3$. Secondly, a higher frequency follow-up during the
5 flood event of the 2013-14 campaign included a sampling point during first CSO of approximately
6 $18,000 \text{ m}^3$, which did not lead to other contaminants increase. Only at the second CSO ($\sim 50,000 \text{ m}^3$)
7 pollutants peaked (Reoyo-Prats et al., 2017) including dissolved PACs (see above). Coming back to
8 the 2015 storm event, at R0 station the great majority of PACs remained at a constant concentration
9 during first flush events (18 h sampling time in Fig. 3b), resembling their concentration in winter
10 (vertical right axis in Fig. 3b). This result can be explained by CSO during first flushes (Fig. 1 and Fig.
11 3d). However, right bank sewer overflows SO11, SO64 and SO50 situated upstream R2 (Fig. 1) also
12 overflowed during this flood (Fig. 3c), but concentrations of medical drugs decreased rapidly at this
13 station (Fig. 3a) as is usually expected because of the rapid dilution of molecules with increased
14 water flow during first rains. First, the absence of pharmaceuticals other than caffeine and nicotine
15 at 0 h sampling time at R2 indicate that, in spite of numerous agricultural areas around our sampling
16 stations (Fig. 1), diffuse sources of PACs via runoff from potential sewage sludge used as fertilizers
17 did not occur during intense rainfalls. Our study therefore supports previous findings that diffuse
18 sources are less important than point sources for pharmaceutical products in surface waters (López-
19 Roldán et al. 2010; Vazquez-Roig et al. 2011; Barber et al. 2013). Second, the prevalence of
20 prescribed drugs at first flushes at R0 but not at R2 demonstrate that major sources of prescribed
21 medical drugs along the Têt River are situated on the left bank (Fig. 1). The public hospital of
22 Perpignan city lies on this bank and is, with 1,183 bed-places, the largest hospital in the Pyrénées-
23 Orientales department and the third of its category in the Languedoc-Roussillon region.

24 To determine if hospitals are the source of pharmaceuticals, we conducted an analysis of
25 the trace metal gadolinium (Gd). This element is used as a contrast agent in Magnetic Resonance
26 Imaging (MRI) and is not removed by sewage water treatments, and thus produces positive
27 anthropogenic anomalies in Rare Earth Element (REE) patterns in rivers (Rabiet et al. 2009; Kulaksiz
28 and Bau 2011; Piper and Bau 2013). A general flat pattern of REEs was observed at R2 station (Fig.
29 5a), which received discharges of only right bank SOs, i.e. SO11, SO64 and SO50 (Fig. 1). In contrast,
30 R0 station, which also received left bank discharges from SO09 and SO10 (Fig. 1), showed sharper
31 peaks of Gd REE element in autumn (Fig. 5b). Both right and left bank SOs collect urban water, but
32 left bank SOs discharged vast quantities of pharmaceutical compounds compared to the right bank.
33 Worth noting is that the left bank collects public hospital wastewaters. These results indicate that
34 the public hospital is responsible for the origin of the high concentration of medical drugs detected in
35 the Têt River at R0 station.

1 When looking at fluxes at R0 station ([Fig. 4.b](#)), three different behaviors were observed.
2 Firstly, ibuprofen, sotalol, clarithromycin, atenolol, acebutolol, diltiazem, clarithromycin,
3 erythromycin and trimethoprim had their peak fluxes at 18 h during the CSOs while they remained
4 near 0 g/h during the rest of the rain event. Therefore, these compounds seemed to come mostly
5 from CSOs while under normal circumstances they are eliminated by WWTPs. Secondly, diclofenac,
6 desmethyltramadol, oxazepam, fenofibric acid, carbamazepine propranolol and bisoprolol reached
7 their highest fluxes during the flow peak at 22 h but their fluxes were nearly as high during the CSOs
8 at 18 h while they decreased sharply to 0 g/h just after the flow peak at 27 h. These second group of
9 compounds were therefore released through direct discharges from CSOs as well as by the
10 remobilization of the riverbed sediments. Thirdly, caffeine, nicotine, irbesartan and tramadol
11 increased during the CSOs at 18 h before they attained their highest values (top levels among all
12 PACs) during the flow peak at 22 h, then they sharply decreased until 27 h before they decreased
13 softly until the end of the rain event, never attaining a null flux value. This dynamic seemed to
14 characterize compounds predominantly remobilized from river sediments at the flow peak, but also
15 those punctually discharged by CSOs and constantly released into the river by WWTPs. Interestingly,
16 these compounds are those that are predominantly found at R2 station ([Fig. 4.b](#)) and are not
17 released by the hospital but are entirely derived from urban discharges. At the flow peak in R2, all
18 compounds had a null flux except for irbesartan. This proves that river sediments in R2 are not as
19 heavily contaminated as those in R0, which is the station downstream main urban WWTPs.
20 Irbesartan's unique behavior can be explained by its physicochemical characteristics that are
21 discussed hereafter.

22 As the 2015-16 pharmaceutical campaign was conducted on the total fraction,
23 corresponding to both the dissolved and the suspended water fractions, hydrophilic and hydrophobic
24 properties of PACs had an important impact on their fate and transport. While at R0 most molecules
25 remained at a constant concentration during CSOs first flush event at 18 h ([Fig. 3b](#)), several of them
26 behaved differently, especially fluoxetine, irbesartan, fenofibric acid and ibuprofen, which were also
27 more highly correlated to axis 2 in the PCA ordination plot ([Online resource 3](#)). Fluoxetine had a null
28 concentration throughout the rain event, and before the event it had a concentration of 1 ng/L
29 ([Online resource 2](#)), which explains its particular position in the PCA ([Online resource 3](#)). Irbesartan
30 was also highly positively correlated with axes 2 and its highest concentration occurred at the
31 beginning of the rain event, and then rapidly decreased ([Fig. 3.b](#)). This rapid dilution behavior is
32 typical of hydrophobic molecules that are primarily attached to suspended matter. Irbesartan has a
33 logarithm of octanol-water partition coefficient ($\log K_{ow}$) of 5.31 ([Table 4](#)) and a very high organic
34 carbon-based sorption coefficient ($K_{oc} = 1,300,000$), and together these properties confirmed its
35 hydrophobic nature. A $\log K_{ow}$ higher than 5 and a high molecular weight (irbesartan weights 428.53

1 g/mol) are properties typical of molecules easily sorbed to sediments according to [Pal et al. 2010](#) and
2 sorption has been identified as one of the predominant attenuation mechanisms for PACs ([Riml et al.](#)
3 [2013](#); [Acuña et al. 2015](#)). These characteristics also explain why irbesartan peaked slightly at R2 at
4 the flow peak (23 h, [Fig. 3a](#)), when suspended solids reached their maximum load (data not shown).
5 On the contrary, ibuprofen and fenofibric acid dramatically increased at first flushes, peaking at 18 h
6 at R0 ([Fig. 3b](#)), just as PACs of the dissolve fraction behaved in our 2013-14 study. They were also
7 highly negatively correlated with axis 2 in the PCA plot. These pharmaceuticals therefore behaved as
8 highly hydrophilic molecules, even though their molecular weights are 206.28 g/mol and 360.83
9 g/mol, respectively, their log K_{ow} are 5.19 and 3.97, and their K_{oc} are higher (3,800 and 3,400) than
10 those of the molecules that maintained their concentration levels during first flush ([Table 4](#)). Thus, it
11 does not seem PACs behavior can be fully explained by the parameters described by [Pal et al. 2010](#),
12 particularly for hydrophilic compounds which are known to be affected principally by the variation of
13 environmental conditions, such as temperature or dissolved oxygen ([Acuña et al. 2015](#)). In this case,
14 other attenuation processes besides sorption should be taken into consideration, such as
15 biotransformation or photolysis ([Radke et al. 2010](#); [Riml et al. 2013](#); [Baena-Nogueras et al. 2017](#)).

16

17 **5. Conclusions and Perspectives**

18

19 First foul flush multicontamination events are known to occur during heavy rainfalls due to
20 Combined Sewer Overflows (CSO), which are recurrent phenomena largely impacting the water
21 quality of coastal Mediterranean rivers. As expected, dissolved Pharmaceutical Active Compounds
22 (PACs) follow the same trend as other contaminants increasing rapidly during first flushes. However,
23 we have demonstrated for the first time that CSOs will actually have little impact on PACs in the total
24 fraction. First flush events during heavy Mediterranean rainfalls will maintain high drug
25 concentrations for slightly longer, counteracting their dilution due to increased river flow. Our high
26 frequency sampling at two strategically located river stations during a heavy rainfall event allowed
27 for the precise identification of pharmaceutical sources, fate and transport. Our results support
28 previous studies on the major contribution of point sources (WWTPs, illicit discharges and hospitals)
29 compared to diffuse sources (runoffs) of PACs. Moreover, we could attribute the origin of medical
30 residues downstream urban areas to CSOs from the left river bank and, with the use of gadolinium (a
31 MRI contrast agent) as a specific marker, and pinpoint the heavy discharge of medical drugs on this
32 side of the river to a nearby public hospital. PACs behavior could not be fully explained by their
33 chemical properties or their molecular weight, highlighting the need to conduct studies at a fine scale
34 on well-characterized river models to better track the fate of PACs in natural environments. A
35 comparison of fluxes at different seasons highlighted the comparatively high contribution of

1 recurrent heavy rain events in the Mediterranean to pharmaceuticals in aquatic environments.
2 Finally, if our hypothesis of illicit sanitary inputs upstream from Perpignan rejects is confirmed,
3 release of emerging drugs during heavy rainfalls could be a good marker for these inputs.

4 River water quality could clearly be improved by implementing quaternary water treatment
5 processes in WWTPs; such processes include ozonation (Ternes et al. 2003; Rúa-Gómez et al. 2012;
6 Antoniou et al. 2013), photocatalysis (Dalrymple et al. 2007) or activated carbon (Rúa-Gómez et al.
7 2012). Another solution would be to use membrane bioreactors as the primary treatment (Verlicchi
8 et al. 2012; Fernandez-Fontaina et al. 2013), but this would need to be implemented from the time
9 of WWTP construction. According to our results, identifying major PACs sources and enforcing
10 adapted water treatments directly at those sources would be a more cost-efficient alternative in
11 coastal Mediterranean aquatic environments. Although further monitoring at strategic points with
12 high frequency sampling is necessary to better understand the fate, sources and behavior of PACs in
13 aquatic ecosystems, governments must begin to accept responsibility for the presence of at least
14 prescription drugs in the environment, as they can no longer be considered “emerging
15 contaminants”.

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18
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