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

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## 10 Abstract

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

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

In the Mediterranean, long dry periods alternate with short but intense seasonal rainfalls (Miller 1983; Cowling et al. 2005). During the summer, contaminants from human activities tend to concentrate in soils and in river sediments as water resources decrease through evaporation (Gasith and Resh 1999; Olías et al. 2004). During heavy rain events in the Mediterranean, flow augmentation, surface soil runoff, river sediments and the resuspension of sewer solids from Combined Sewer Overflows (CSOs) lead to a modification in the level of contaminants in surface waters (Coyne et al. 2007; Sakrabani et al. 2009; Taghavi et al. 2010; Dumas et al. 2015) and in particular, an increase in the level of pharmaceutical products (Escher et al. 2011; Osorio et al. 2012a; Backhaus 2014; LaLone et al. 2014; Osorio et al. 2014). Drought/flood hydrodynamics of coastal Mediterranean rivers have been identified as the major factor affecting the presence of micropollutants in these environments (Pailler et al. 2009; Osorio et al. 2012a; Fairbairn et al. 2016). While Ashley et al. (1992) predicted the release of high concentrations of contaminants during first foul flushes from CSOs at the start of a wet weather flow, studies of pollutant dynamics during heavy rains and high flows are scarce in the literature (Pailler et al. 2009). Reoyo-Prats et al. 2017 performed a high frequency follow-up of six families of contaminants, including pesticides, nutrients, heavy metals and fecal indicators, during a flood event. They demonstrated that floods and perhaps even more importantly, recurrent heavy Mediterranean rain events, are responsible for chronic multicontamination phenomena under this climate. Such micropollutant mixtures are potentially highly toxic for living organisms of the land-sea continuum, even at small concentrations (Schwarzenbach et al. 2006). Determining the importance of

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

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

## 19 20 **2. Material and Methods**

### 21 22 *2.1 Sampling*

#### 23 24 *2.1.1 Stations*

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

1 (24,000 PE and 66,000 PE, respectively). Both R0 and R2 received inputs from extensive gardening and  
2 vineyard culturing activities from the last portion of the catchment area ([Fig. 1](#), main figure and inlet).

### 3 4 2.1.2 Campaigns

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

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

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

### 21 22 2.1.3 Heavy rains and flood sampling strategy

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

### 34 35 2.2 Medical, veterinary and emerging drugs analyses

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

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

29 During the 2015-16 campaign, a more thorough monitoring of pharmaceutical products was  
30 conducted on a total of 89 molecules. For this purpose, the total fraction was analyzed by COFRAC  
31 accredited laboratory Groupe CARSO, via Liquid Chromatography-tandem Mass Spectrometry (LC-  
32 MS/MS) using a Thermo Scientific TSQ Quantum (Waltham, MA, USA) connected to an API 5500 mass  
33 spectrometer (Applied Biosystems-Sciex, Foster City, CA, USA) or an Agilent 6460 (Santa Clara, CA,  
34 USA). Ionization was performed in the switch positive/negative mode for all runs. Chromatographic  
35 analyses were achieved using a C18 analytical column of 100 mm × 2.2 mm and 3.5 µm particle size

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

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

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

### 30 2.3. Rare Earth Element (REE) analyses

31  
32 REE concentrations were measured by Inductively Coupled Plasma Mass Spectrometry (ICP-  
33 MS, Agilent 7700X) at CEFREM laboratory. REE concentrations followed an intercalibration exercise  
34 conducted on river water certified reference material SLRS-6 developed for the analysis of trace metals  
35 and other constituents ([Yeghicheyan et al. 2017](#)). This exercise demonstrated that REE concentrations

1 provided by CEFREM were consistent with other participants. REE patterns were determined by using  
2 the Upper Continental Crust (UCC) elemental composition of rock standards in order to normalize  
3 sample concentrations of these elements (Piper and Bau 2013).  
4

### 5 **3. Results**

6

#### 7 *3.1. Pilot study on pharmaceutical trends in the Têt River during the 2013-14 sampling campaign*

8

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

#### 19 *3.2. Exhaustive monitoring of medical, veterinary and emerging drugs on the total fraction during the* 20 *2015-16 sampling campaign over several seasons*

21

22 Given the encouraging results of our pilot study, a more extensive study was conducted during  
23 the 2015-16 campaign. A total of 89 molecules were analyzed in the total fraction at both R0 and R2  
24 sampling stations located upstream and downstream of the primary WWTPs in urbanized areas of the  
25 Têt River (Fig. 1). Twenty-one molecules were identified and their concentrations are plotted together  
26 with river flow for the 2015 autumnal storm event, and for the summer and winter droughts at both  
27 stations, R2 (Fig. 3a) and R0 (Fig. 3b). These results are also summarized in the Online Resource 2. In  
28 parallel, figures 3c and d show discharges of the main Sewer-Overflows (SO) for the city of Perpignan,  
29 river flow and precipitations along sampling time during the same storm event. All molecules detected  
30 in 2013-14 (Fig. 2) were also found in 2015-16, except for sulfamethoxazole, detected only in 2013-14  
31 with a peak concentration of 4.4 ng/L, well beneath the 2015-16 quantification limit (20 ng/L, Table 3).  
32 For both stations, the highest drug concentrations were found for the winter drought (right axes in Fig.  
33 3a&b) and at the start of sampling during the autumnal storm event (0 h sampling time in Fig. 3a&b).  
34 At R2, seven molecules were detected but nicotine and caffeine were dominant at the beginning of  
35 the autumnal storm event (Fig. 3a), with concentrations of 217 ng/L and 175 ng/L, respectively (Online

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

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

33 In order to consider the influence of the river flow, we calculated instantaneous mass fluxes at  
34 both stations, R2 (Fig. 4a) and R0 (Fig. 4b). Considering seasonal variations, most PACs fluxes were  
35 higher in winter than in summer at both R2 and R0 stations, although some were 0 g/L for both



1 seasons. Exceptions to this rule were nicotine at R2, and acebutolol at R0 with the opposite behavior.  
2 During the autumnal heavy rain event at R2 station, cotinine and bisoprolol fluxes were always around  
3 0 g/h and so was the case for caffeine except from a flux of 2.1 g/h at the very beginning of the event  
4 ([Fig. 4a](#)). Tramadol and irbesartan fluxes were also near 0 g/h throughout the rain event with the  
5 exception of peaks of 1.8 and 4.1 g/h, respectively, but at different times. While tramadol peaked at  
6 18 h, irbesartan did so at 23 h. Nicotine had two high peak fluxes, one of 14.8 g/h at 18 h, followed by  
7 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 decrease to  
8 5.8 g/h at 51 h. At R0 station, all top flux peaks were attained at 22 h with the highest fluxes of 30.6  
9 g/h for caffeine, 21.3 g/h for diclofenac and nicotine, 19.2 g/h for ibersartan and 18.7 g/h for tramadol.  
10 All these four molecules decreased sharply after 22 h but never reached 0 g/h with the exception of  
11 diclofenac. All other molecules that peaked at 22 h showed a rapid decrease to 0 g/h after 22 h. Finally,  
12 ibuprofen, sotalol, clarithromycin, atenolol, acebutolol, diltiazem, clarithromycin, erythromycin and  
13 trimethoprim had their peak fluxes at 18 h followed by a sharp decrease immediately after, and  
14 remained at near 0 g/h during the rest of the rain event.

### 15 16 *3.3. Rare earth element patterns during a heavy rain in autumn 2015*

17  
18 Rare Earth Element (REE) patterns were defined at R2 and R0 stations to determine the  
19 contribution of hospitals as sources of PACs in the Têt River. Upstream station R2 showed a generally  
20 flat pattern of REEs along different sampling times, except for europium (Eu) with small peaks at 0 and  
21 18 h sampling times ([Fig. 5a](#)), probably due to the mineral origin of this element in the Têt River  
22 catchment area. However, the downstream station R0 showed mostly large peaks of gadolinium (Gd)  
23 during the same sampling times ([Fig. 5b](#)). Indeed, at 0 and 18 h, Gd values were respectively 6 and 18  
24 times higher at R0 than at R2.

## 25 26 **4. Discussion**

### 27 28 *4.1 Dissolved PACs contribute to chronic risk multicontamination phenomena for coastal* 29 *Mediterranean rivers*

30  
31 In 2013-14, we conducted an exploratory qualitative study whose main purpose was to  
32 compare pharmaceutical dynamics with those of other pollutants during heavy rainfalls and floods in  
33 the Têt River, a typical coastal Mediterranean watercourse. We studied the dissolved fraction because  
34 it allows for comparisons to be made with the only other known published study on PACs during storm  
35 events and sewer overflows ([Pailler et al. 2009](#)). Although our results were only internally validated

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

#### 14 *4.2. A fine-scale study of PACs dynamics during the 2015 rain event allowed for identification of sources, 15 fate and transport of PACs in surface waters*

17 A higher number and concentration of pharmaceutical compounds in the total fraction was  
18 found downstream (R0 station, [Fig. 3b](#)) than upstream WWTPs (R2, [Fig. 3a](#)) at all seasons, indicating  
19 their constant release by WWTPs, which are recognized as major sources of pharmaceuticals in the  
20 environment ([Santos et al. 2007](#); [Fernández et al. 2010](#); [López-Roldán et al. 2010](#); [Vazquez-Roig et al.  
21 2011](#); [Barber et al. 2013](#)). The highest concentrations of PACs in the Têt River were found at the  
22 beginning of the autumnal heavy rain event (0 h sampling time on [Fig. 3](#)) and during the winter  
23 drought. This result could be explained by the higher river flow during these seasons leading to a higher  
24 resuspension of suspended matter, in contrast to the summer drought. Other studies of  
25 Mediterranean rivers also reported higher PACs levels during this season ([Osorio et al. 2012a](#); [Osorio  
26 et al. 2012b](#)). Another possible explanation is the decrease in the attenuation of PACs during winter  
27 and autumn due to the decline of phototransformation processes at these seasons ([Daneshvar et al.  
28 2010](#)), which largely contribute to PACs elimination in WWTPs ([Vieno et al. 2005](#)). However, in order  
29 to compare seasonal variations, it is best to use mass fluxes of organic pollutants such that river flow  
30 can be accounted for ([Bernot et al. 2013](#); [Moreno-González et al. 2013](#)). Our flux results indicated that  
31 for most PACs, levels were slightly higher in winter than in summer. This result differs from the study  
32 of [Bernot et al. \(2013\)](#), which only found caffeine and paraxanthine more abundant in winter whereas  
33 the abundance of some personal care products actually increased in summer because they were  
34 consumed at this time (*i.e.* DEET from insect repellents). This result is not captured in [Fig. 4](#), because  
35 summer and winter drought fluxes were negligible in comparison to the high fluxes of PACs observed

1 for the rain event. To the best of our knowledge no study on total PACs mass flux loads during a rain  
2 event has ever been conducted. Due to the high recurrence of heavy rains under a Mediterranean  
3 climate, these events largely contribute to PACs release into aquatic environments.

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

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

30 Regarding PACs dynamics during the storm event at 2015-16 campaign, only two samplings  
31 were done at the beginning of the rain event, at 0 and 18 h respectively, but we are confident that our  
32 second sampling point is fully representative of the CSO phenomena and no major changes in  
33 pollutants occurred in between for two major reasons. Firstly, although a CSO occurred at 10 h, it was  
34 minor, with ~2,000 m<sup>3</sup> of untreated water released into the river, while the major CSO at 16 h  
35 represented a volume of approximately 7,000 m<sup>3</sup>. Secondly, a higher frequency follow-up during the

1 flood event of the 2013-14 campaign included a sampling point during first CSO of approximately  
2 18,000 m<sup>3</sup>, which did not lead to other contaminants increase. Only at the second CSO (~50,000 m<sup>3</sup>)  
3 pollutants peaked (Reoyo-Prats et al., 2017) including dissolved PACs (see above). Coming back to the  
4 2015 storm event, at R0 station the great majority of PACs remained at a constant concentration during  
5 first flush events (18 h sampling time in Fig. 3b), resembling their concentration in winter (vertical right  
6 axis in Fig. 3b). This result can be explained by CSO during first flushes (Fig. 1 and Fig. 3d). However,  
7 right bank sewer overflows SO11, SO64 and SO50 situated upstream R2 (Fig. 1) also overflowed during  
8 this flood (Fig. 3c), but concentrations of medical drugs decreased rapidly at this station (Fig. 3a) as is  
9 usually expected because of the rapid dilution of molecules with increased water flow during first rains.  
10 First, the absence of pharmaceuticals other than caffeine and nicotine at 0 h sampling time at R2  
11 indicate that, in spite of numerous agricultural areas around our sampling stations (Fig. 1), diffuse  
12 sources of PACs via runoff from potential sewage sludge used as fertilizers did not occur during intense  
13 rainfalls. Our study therefore supports previous findings that diffuse sources are less important than  
14 point sources for pharmaceutical products in surface waters (López-Roldán et al. 2010; Vazquez-Roig  
15 et al. 2011; Barber et al. 2013). Second, the prevalence of prescribed drugs at first flushes at R0 but  
16 not at R2 demonstrate that major sources of prescribed medical drugs along the Têt River are situated  
17 on the left bank (Fig. 1). The public hospital of Perpignan city lies on this bank and is, with 1,183 bed-  
18 places, the largest hospital in the Pyrénées-Orientales department and the third of its category in the  
19 Languedoc-Roussillon region.

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

31 When looking at fluxes at R0 station (Fig. 4.b), three different behaviors were observed. Firstly,  
32 ibuprofen, sotalol, clarithromycin, atenolol, acebutolol, diltiazem, clarithromycin, erythromycin and  
33 trimethoprim had their peak fluxes at 18 h during the CSOs while they remained near 0 g/h during the  
34 rest of the rain event. Therefore, these compounds seemed to come mostly from CSOs while under  
35 normal circumstances they are eliminated by WWTPs. Secondly, diclofenac, desmethyltramadol,

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

16 As the 2015-16 pharmaceutical campaign was conducted on the total fraction, corresponding  
17 to both the dissolved and the suspended water fractions, hydrophilic and hydrophobic properties of  
18 PACs had an important impact on their fate and transport. While at R0 most molecules remained at a  
19 constant concentration during CSOs first flush event at 18 h ([Fig. 3b](#)), several of them behaved  
20 differently, especially fluoxetine, irbesartan, fenofibric acid and ibuprofen, which were also more  
21 highly correlated to axis 2 in the PCA ordination plot ([Online resource 3](#)). Fluoxetine had a null  
22 concentration throughout the rain event, and before the event it had a concentration of 1 ng/L ([Online  
23 resource 2](#)), which explains its particular position in the PCA ([Online resource 3](#)). Irbesartan was also  
24 highly positively correlated with axes 2 and its highest concentration occurred at the beginning of the  
25 rain event, and then rapidly decreased ([Fig. 3.b](#)). This rapid dilution behavior is typical of hydrophobic  
26 molecules that are primarily attached to suspended matter. Irbesartan has a logarithm of octanol-  
27 water partition coefficient ( $\log K_{ow}$ ) of 5.31 ([Table 4](#)) and a very high organic carbon-based sorption  
28 coefficient ( $K_{oc} = 1,300,000$ ), and together these properties confirmed its hydrophobic nature. A log  
29  $K_{ow}$  higher than 5 and a high molecular weight (irbesartan weights 428.53 g/mol) are properties typical  
30 of molecules easily sorbed to sediments according to [Pal et al. 2010](#) and sorption has been identified  
31 as one of the predominant attenuation mechanisms for PACs ([Riml et al. 2013](#); [Acuña et al. 2015](#)).  
32 These characteristics also explain why irbesartan peaked slightly at R2 at the flow peak (23 h, [Fig. 3a](#)),  
33 when suspended solids reached their maximum load (data not shown). On the contrary, ibuprofen and  
34 fenofibric acid dramatically increased at first flushes, peaking at 18 h at R0 ([Fig. 3b](#)), just as PACs of the  
35 dissolve fraction behaved in our 2013-14 study. They were also highly negatively correlated with axis

1 2 in the PCA plot. These pharmaceuticals therefore behaved as highly hydrophilic molecules, even  
2 though their molecular weights are 206.28 g/mol and 360.83 g/mol, respectively, their log  $K_{ow}$  are 5.19  
3 and 3.97, and their  $K_{oc}$  are higher (3,800 and 3,400) than those of the molecules that maintained their  
4 concentration levels during first flush (Table 4). Thus, it does not seem PACs behavior can be fully  
5 explained by the parameters described by Pal et al. 2010, particularly for hydrophilic compounds which  
6 are known to be affected principally by the variation of environmental conditions, such as temperature  
7 or dissolved oxygen (Acuña et al. 2015). In this case, other attenuation processes besides sorption  
8 should be taken into consideration, such as biotransformation or photolysis (Radke et al. 2010; Riml et  
9 al. 2013; Baena-Nogueras et al. 2017).

## 11 5. Conclusions and Perspectives

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

33 River water quality could clearly be improved by implementing quaternary water treatment  
34 processes in WWTPs; such processes include ozonation (Ternes et al. 2003; Rúa-Gómez et al. 2012;  
35 Antoniou et al. 2013), photocatalysis (Dalrymple et al. 2007) or activated carbon (Rúa-Gómez et al.



1 2012). Another solution would be to use membrane bioreactors as the primary treatment (Verlicchi et  
2 al. 2012; Fernandez-Fontaina et al. 2013), but this would need to be implemented from the time of  
3 WWTP construction. According to our results, identifying major PACs sources and enforcing adapted  
4 water treatments directly at those sources would be a more cost-efficient alternative in coastal  
5 Mediterranean aquatic environments. Although further monitoring at strategic points with high  
6 frequency sampling is necessary to better understand the fate, sources and behavior of PACs in aquatic  
7 ecosystems, governments must begin to accept responsibility for the presence of at least prescription  
8 drugs in the environment, as they can no longer be considered “emerging contaminants”.

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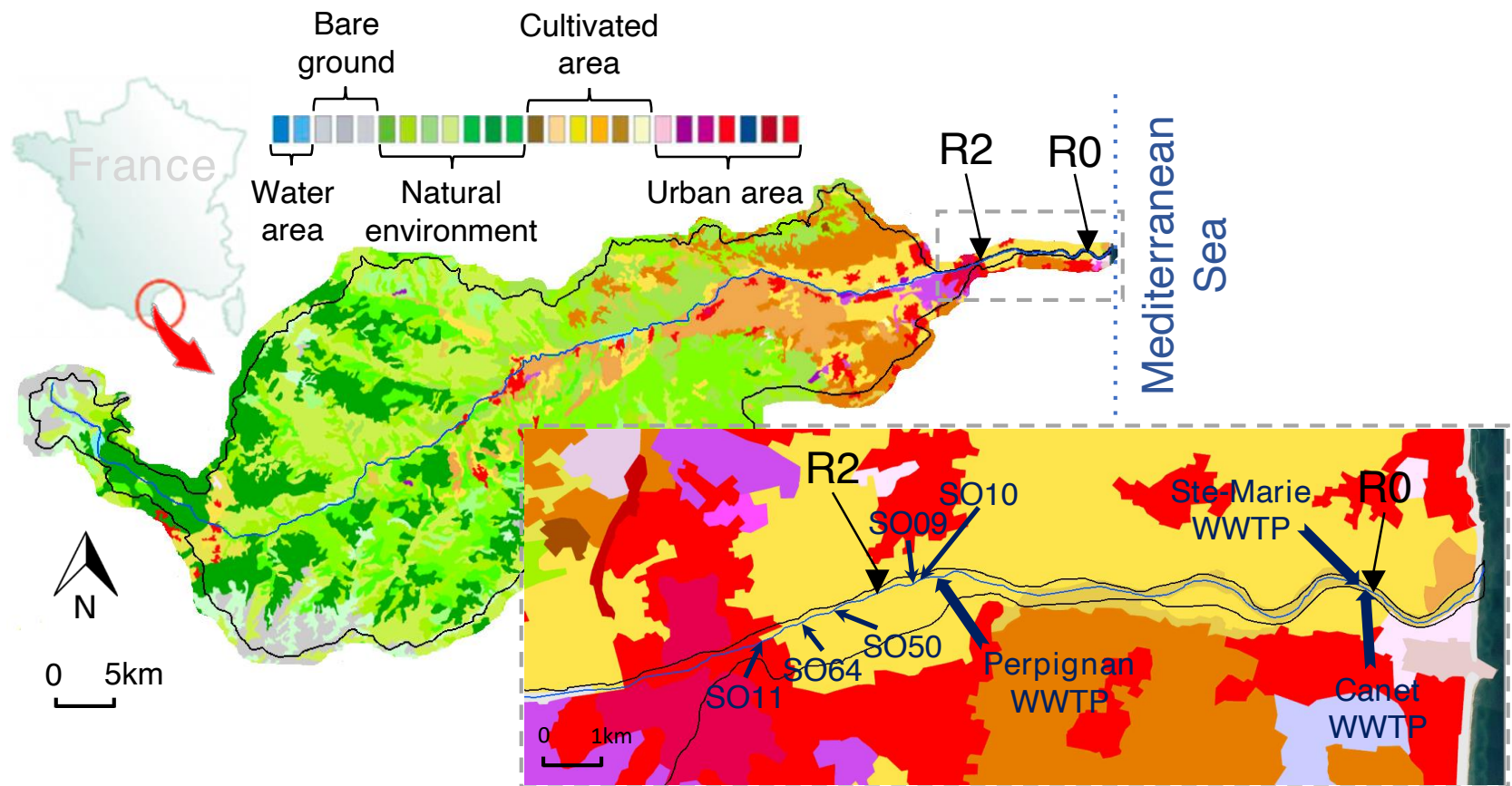
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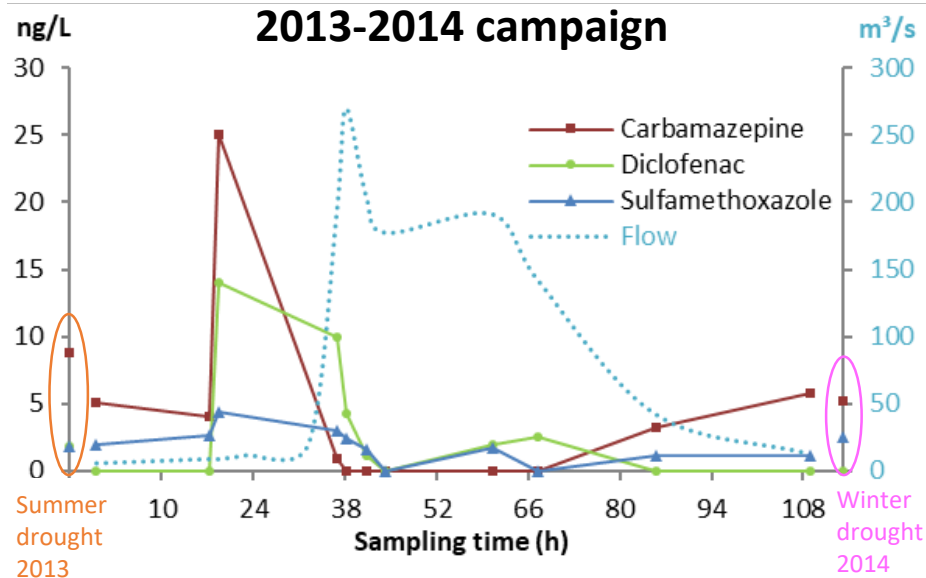
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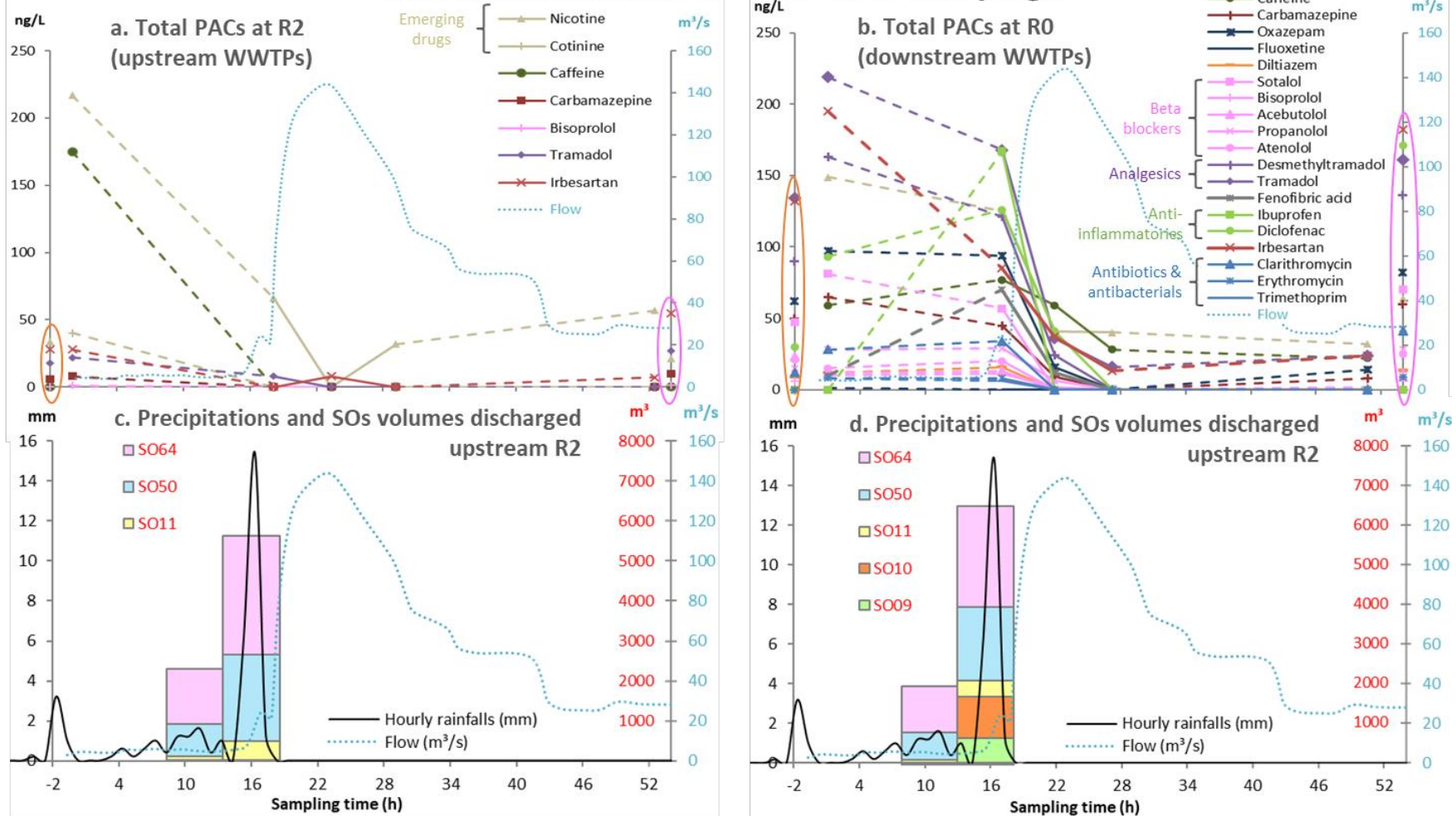
**Fig. 1.** Land-use map from the Corine Land Cover dataset (European Environmental Agency) for the catchment basin of the Têt River situated in the Southeast of France. Downstream section has been zoomed in for better seeing land-use activities responsible of potential contaminant input sources at sampling stations from this study (R2 and R0, black triangles) as well as Sewer Overflows (SO) and WasteWater Treatment Plants (WWTP) in this area.

## Dissolved PACs at R0 station in 2013-2014 campaign



**Fig.2.** Dynamics of pharmaceuticals and flow variations downstream main urban WWTPs that discharge at the Têt River (R0 station, see [figure 1](#)) during the autumn flood 2013. The peak of dissolved pharmaceuticals can be explained by first flush overflow of the combined sewer system of Perpignan (see text for details). PAC concentrations in summer drought 2013 and winter drought 2013 and winter drought 2014 are also reported on left (orange circle) and right (pink circle) vertical axis respectively.

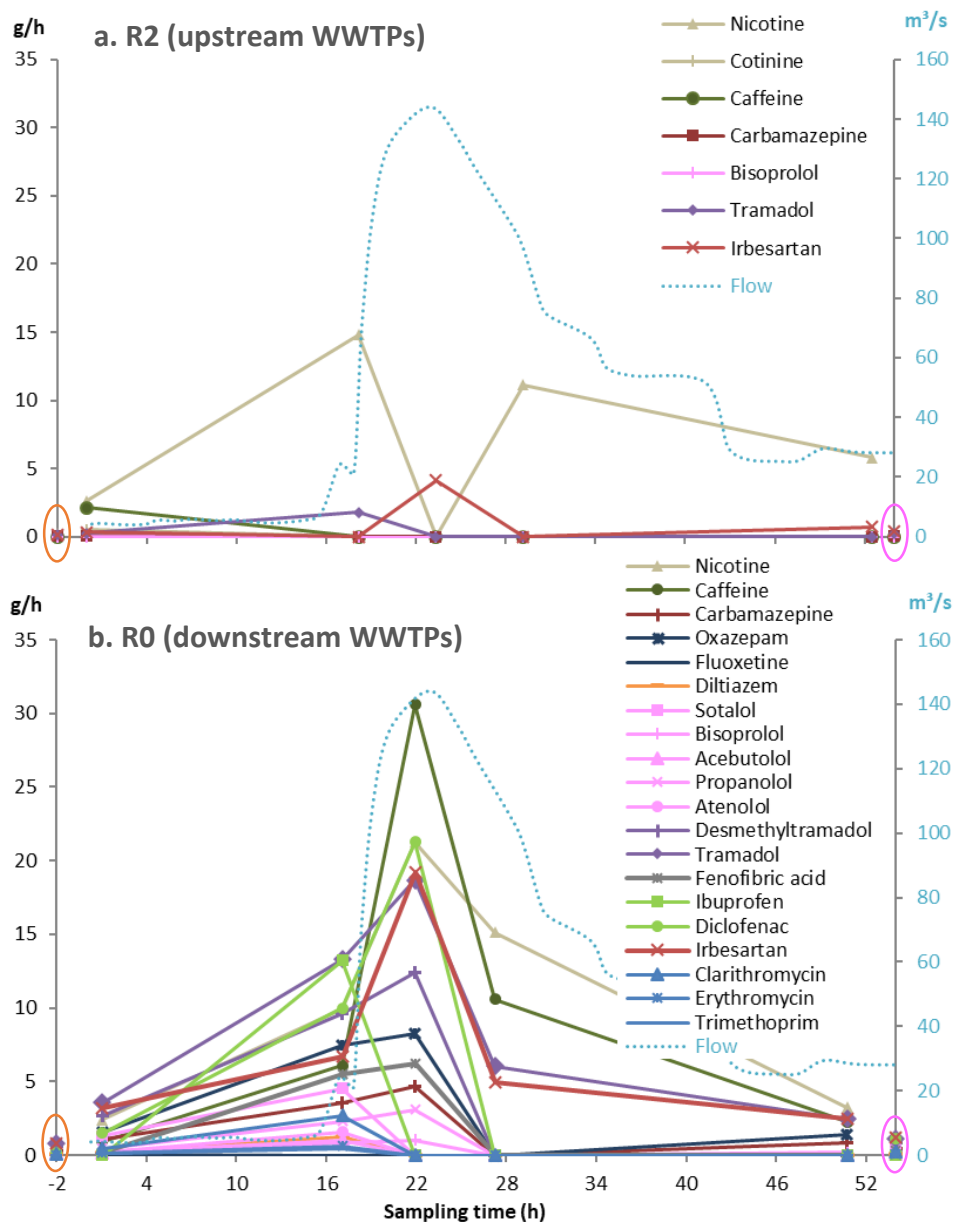
## PAC concentrations in 2015-2016 Campaign



**Fig. 3.** Total PAC concentrations, river flow, precipitations and sewer overflows in 2015-2016 campaign upstream and downstream main WWTPs in urbanized areas of the Têt River. **(a and b)** Dynamics of pharmaceuticals (ng/L) and river flow variations (m<sup>3</sup>/s), **(c and d)** hourly rainfall (mm), flow variations (m<sup>3</sup>/s) and Sewer Overflows (SOs) discharge volumes (m<sup>3</sup>) along sampling time during a typical Mediterranean heavy rain event in 2015 at **(a and c)** upstream and **(b and d)** downstream main urban WasteWater Treatment Plants (WWTP) discharging at the Têt River. **(a and b)** PAC concentrations during the 2015 summer drought and 2016 winter drought are also reported on the left (orange circles) and right (pink circles) vertical axes, respectively. Molecules of the same color belong to the same family. Family names are spelled out when more than one molecule from that family was found. Dash lines connect sampling points at more than 10 h interval. For details on stations and SOs location along the Têt River see [figure 1](#).

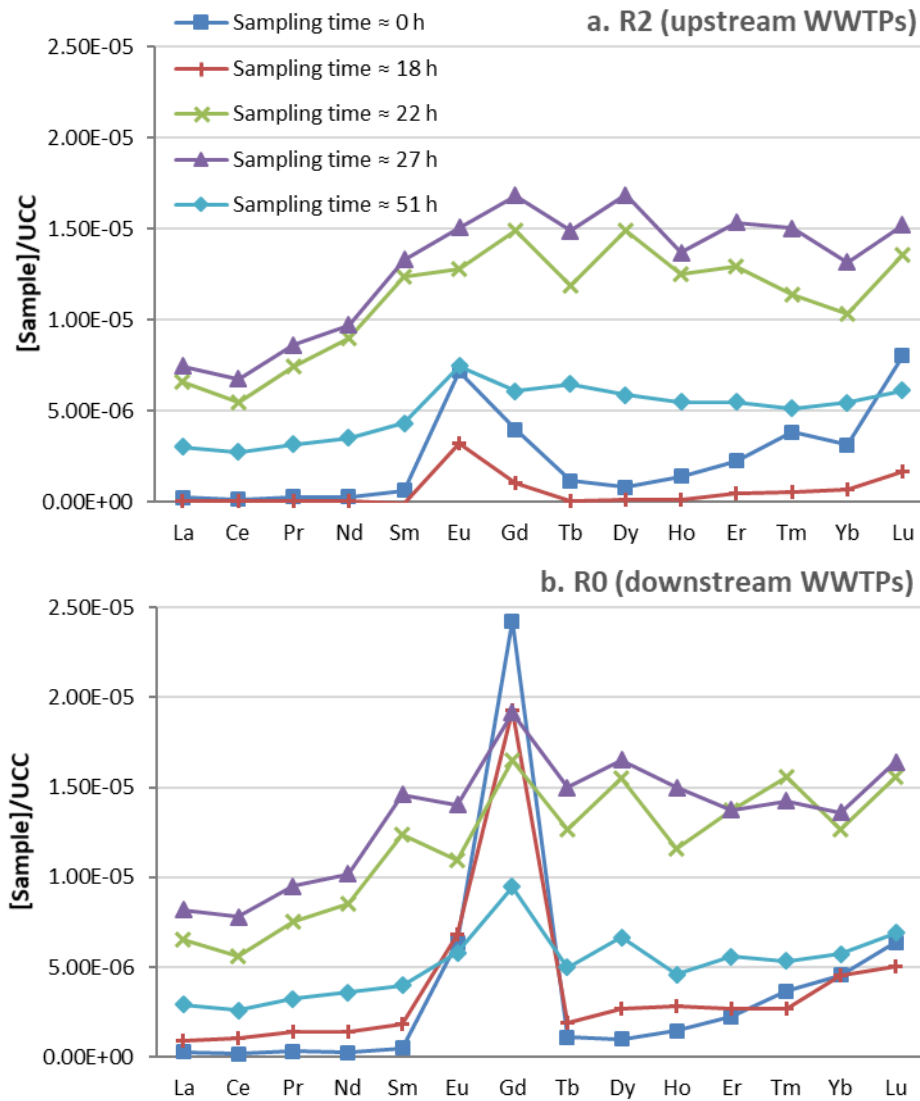


# PACs fluxes in 2015-2016 Campaign



**Fig. 4.** Instantaneous mass PAC fluxes in river water (a) upstream and (b) downstream the main WWTPs in urbanized areas of the Têt River. Fluxes during 2015 summer drought and 2016 winter drought are also reported on the left (orange circles) and right (pink circles) vertical axes, respectively.

## REE patterns at 2015-2016 campaign



**Fig. 5.** Rare Earth Element (REE) patterns of river water (a) upstream and (b) downstream the main WWTPs in urbanized areas. Extremely large positive gadolinium (Gd) values are observed at R0 at first flushes (18h sampling time, Fig. 3d).

Table

**Table 1.** HPLC gradient elution program used by the authors in order to analyze pharmaceutical products studied in the dissolved fraction for the 2013-14 campaign.

Time (min)	Ultrapure water %	Acetonitrile %	Flow (mL/min)	Curve
0.00	90.0	10.0	0.250	1
25.00	10.0	90.0	0.250	6
30.00	10.0	90.0	0.250	1
35.00	90.0	10.0	0.250	6
40.00	90.0	10.0	0.250	1

**Table 2.** Ionization mode, retention times (Rt), m/z, detection and quantification limits of pharmaceutical products studied by the authors for the 2013-14 campaign.

Analyte	Ionization mode	Rt (min)	m/z	Detection limit (ng/L)	Quantification limit (ng/L)
Sotalol	+	1.09	273	0.32	0.68
Atenolol	+	1.09	267	0.09	0.27
Propranolol	+	6.78	260	0.05	0.10
Sulfamethoxazole	+	9.52	254	0.11	0.22
Carbamazepine	+	12.74	237	0.02	0.04
Diclofenac	-	18.9	294	0.30	0.87
Ibuprofen	-	19.7	205.1	0.30	0.86

**Table 3.** Detection limit and analysis method for each pharmaceutical product analyzed by Carso laboratory (COFRAC accredited) for the 2015-16 campaign.

Analyte	Detec. limit (ng/L)	Method	Analyte	Detec. limit (ng/L)	Method	Analyte	Detec. limit (ng/L)	Method
Tetracycline	100	D-I EDTA	Propranolol	5	OnL-SPE-I Meth	Simvastatine	100	OnL-SPE-I Meth
Chlortetracycline	20	D-I EDTA	Acebutolol	5	OnL-SPE-I Meth	Aminopyrine	20	OnL-SPE-I Meth
Doxycycline	5	D-I EDTA	Metoprolol	20	OnL-SPE-I Meth	Tramadol	5	OnL-SPE-I Meth
Oxytetracycline	5	D-I EDTA	Bisoprolol	1	OnL-SPE-I Meth	Desmethyldiamadol	20	OnL-SPE-I Meth
Ciprofloxacin	20	D-I EDTA	Sotalol	20	OnL-SPE-I Meth	Dihydrocodeine	20	OnL-SPE-I Meth
Denofloxacin	100	D-I EDTA	Timolol	5	OnL-SPE-I Meth	Oxycodone	5	OnL-SPE-I Meth
Norfloxacin	100	D-I EDTA	Diltiazem	5	OnL-SPE-I Meth	Morphine	20	OnL-SPE-I Meth
Ofloxacin	20	D-I EDTA	Ticlopidine	10	OnL-SPE-I Meth	Cyclophosphamide	20	OnL-SPE-I Meth
Enrofloxacin	20	D-I EDTA	Pentoxifylline	20	OnL-SPE-I Meth	Methotrexate	50	OnL-SPE-I Meth
Marbofloxacin	100	D-I EDTA	Fluoxetine	1	OnL-SPE-I Meth	Ifosfamide	5	OnL-SPE-I Meth
Sulfamethoxazole	20	D-I EDTA	Doxepine	10	OnL-SPE-I Meth	Phenytoin (Dilantin)	50	OnL-SPE-I Meth
Trimethoprim	5	OnL-SPE-I Meth	Imipramine	20	OnL-SPE-I Meth	Caffeine	20	OnL-SPE-I Meth
Lincomycin	5	OnL-SPE-I Meth	Amitriptyline	20	OnL-SPE-I Meth	Salbutamol	5	OnL-SPE-I Meth
Clindamycin	5	OnL-SPE-I Meth	Zolpidem	5	OnL-SPE-I Meth	Progesterone	5	OnL-SPE-I Meth
Chloramphenicol	100	OnL-SPE-I Meth	Norfluoxetine	20	OnL-SPE-I Meth	Testosterone	5	OnL-SPE-I Meth
Monensin	5	OnL-SPE-I Meth	Lorazepam	10	OnL-SPE-I Meth	4-androstenedione	5	OnL-SPE-I Meth
Virginiamycin M1*	20	OnL-SPE-I Meth	Oxazepam	10	OnL-SPE-I Meth	Norethindrone	20	OnL-SPE-I Meth
Roxithromycin	20	OnL-SPE-I Meth	Bromazepam	20	OnL-SPE-I Meth	Ranitidine	50	OnL-SPE-I Meth
Irbesarta	5	OnL-SPE-I Meth	Diazepam	20	OnL-SPE-I Meth	Cotinine	20	OnL-SPE-I Meth
Indomethacin	20	OnL-SPE-I Meth	Alprazolam	1	OnL-SPE-I Meth	Nicotine	20	OnL-SPE-I Meth
Fenoprofen	20	OnL-SPE-I Meth	Carbamazepine	5	OnL-SPE-I Meth	Estrone	5	OffL-SPE-I Meth
Antipyrine (phenazone)	5	OnL-SPE-I Meth	Ibuprofen	50	OnL-SPE-I Meth	Ethinylestradiol	5	OffL-SPE-I Meth
Propyphenazone	5	OnL-SPE-I Meth	Ibuprofen 1-hydroxy	5	OnL-SPE-I Meth	Estradiol 17 alpha	5	OffL-SPE-I Meth
Dexamethasone	10	OnL-SPE-I Meth	Ibuprofen 2-hydroxy	10 <sup>3</sup>	OnL-SPE-I Meth	Estradiol 17 beta	5	OffL-SPE-I Meth
Naproxen	50	OnL-SPE-I Meth	Piroxicam	5	OnL-SPE-I Meth	Estriol	5	OffL-SPE-I Meth
Prilocaine	1	OnL-SPE-I Meth	Ketorolac (Macril)	50	OnL-SPE-I Meth	Dienestrol	5	OffL-SPE-I Meth
Mepivacaine	10	OnL-SPE-I Meth	Hydrocortisone	20	OnL-SPE-I Meth	Diethylstilbestrol	5	OffL-SPE-I Meth
Bupivacaine	1	OnL-SPE-I Meth	Fenofibric acid	5	OnL-SPE-I Meth			
Atenolol	5	OnL-SPE-I Meth	Clofibric acid	10	OnL-SPE-I Meth			

**D-I EDTA** = Direct Injection and EDTA / **OnL-SPE-I Meth** = On-line SPE injection with methanol / **OffL-SPE-I Meth** = Off-line SPE injection with methanol

**Table 4.** Logarithm of octanol-water partition coefficient ( $\log K_{ow}$ ), organic carbon-based sorption coefficient ( $K_{oc}$ ) and molecular weight (M) of main pharmaceutical products encountered at the Têt River according to their behaviour during the 2015 heavy rain event (see Fig. 3). Data are extracted from PubChem (<https://pubchem.ncbi.nlm.nih.gov>).

Behavior	Rapid decrease	Maintained levels during first flush				Peak at first flush	
<i>Compound</i>	<i>Irbesartan</i>	<i>Carbamazepine</i>	<i>Nicotine</i>	<i>Tramadol</i>	<i>Diclofenac</i>	<i>Ibuprofen</i>	<i>Fenofibric acid</i>
$\log(K_{ow})$	5.31	2.45	1.17	3.01	4.51	3.97	5.19
$K_{oc}$	1 300 000	510	100	616	245	3 400	3 800
M (g/mol)	428.53	236.27	162.24	263.38	296.15	206.28	360.83



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**Supplementary Material**

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