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Abstract

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

Keywords: pharmaceutically active compounds, water quality, multicontamination phenomena, coastal rivers, 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, 17α-ethinylestradiol, 17β-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 (Coynel 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 PACs compared to other pollutants is therefore fundamental to assess their environmental risk (Boxall et al. 2012), particularly during first flush multicontamination phenomena. Moreover, few environmental studies detail the fate and the way pharmaceuticals are transported along well-characterized river watersheds during different seasons (Pal et al. 2010), particularly in conjunction with other micropollutants (Biales et al. 2015; Fairbairn et al. 2016; Garrido et al. 2016) and during storm events and floods (Pailler et al. 2009). The lack of information regarding their sources, seasonal occurrence and potential environmental risk might be the reason why medical and veterinary drugs are not yet properly regulated and thoroughly included in monitoring lists of priority pollutants.

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

2. Material and Methods

2.1 Sampling

2.1.1 Stations

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

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

2.1.2 Campaigns

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

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

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

2.1.3 Heavy rains and flood sampling strategy

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

2.2 Medical, veterinary and emerging drugs analyses

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

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

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

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

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

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

2.3. Rare Earth Element (REE) analyses

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

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

3. Results

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

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

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

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

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

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

sampling time.

In order to consider the influence of the river flow, we calculated instantaneous mass fluxes at both stations, R2 (Fig. 4a) and R0 (Fig. 4b). Considering seasonal variations, most PACs fluxes were higher in winter than in summer at both R2 and R0 stations, although some were 0 g/L for both seasons. Exceptions to this rule were nicotine at R2, and acebutolol at R0 with the opposite behavior. During the autumnal heavy rain event at R2 station, cotinine and bisoprolol fluxes were always 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 the event (Fig. 4a). Tramadol and irbesartan fluxes were also near 0 g/h throughout the rain event with the exception of peaks of 1.8 and 4.1 g/h, respectively, but at different times. While tramadol peaked at 18 h, irbesatan did so at 23 h. Nicotine had two high peak fluxes, one of 14.8 g/h at 18 h, 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 decrease to 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 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. All these four molecules decreased sharply after 22 h but never reached 0 g/h with the exception of diclofenac. All other molecules that peaked at 22 h showed a rapid decrease to 0 g/h after 22 h. Finally, ibuprofen, sotalol, clarithromycin, atenolol, acebutolol, diltiazem, clarithromycin, erythromycin and trimethoprim had their peak fluxes at 18 h followed by a sharp decrease immediately after, and remained at near 0 g/h during the rest of the rain event.

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

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

4. Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. Conclusions and Perspectives

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

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

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

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