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SORPTION OF ACTIVE PHARMACEUTICAL INGREDIENTS IN UNTREATED WASTEWATER EFFLUENT AND EFFECT OF DILUTION IN FRESHWATER: IMPLICATIONS FOR AN "IMPACT ZONE" ENVIRONMENTAL RISK ASSESSMENT APPROACH

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Abstract

Evidence of ecotoxicological effects of active pharmaceuticals ingredients (APIs) has increased research into their environmental fate. In low and low-middle income countries (LLMICs) the main source of APIs to surface waters is from discharge of untreated wastewater. Consequently, concentrations of APIs can be relatively high in the "impact zone" downstream of a discharge point. Little is known about the fate of APIs in these impact zones. In this laboratory scale investigation, the effect of successive dilution of synthetic untreated wastewater (dilution factor 1 to 10) on the distribution of APIs was studied. The sorption was consistent with the chemical properties of each compound: charge, lipophilicity, and structure. Dilution increased desorption of the basic and neutral APIs (up to 27.7%) and correlated with their lipophilicity (R^2>0.980); the positive charge was of secondary importance. Anions did not significantly desorb (< 10% loss). Increased concentrations of dissolved organic matter at dilutions of 8 and 10 times untreated wastewater coincided with lower API concentrations in solution. The data showed a clear trend in the desorption process of APIs that may lead to higher exposure risk than anticipated. Therefore, it is suggested that these aspects should be accounted for in the development of dedicated environmental risk assessment approach for APIs in riverine impact zones of LLMICs countries.

Key words: pharmaceuticals, wastewater, partitioning, dissolved organic matter, impact zone, dilution

Abbreviations:

APIs, active pharmaceutical ingredients

LLMICs, low and low-middle income countries

DUW, direct discharge of untreated wastewater

DF, dilution factor

CBZ, carbamazepine

ACT, acetaminophen

NVR, nevirapine

DCF, diclofenac

VLS, valsartan

ACE, acebutolol

AMI, amitriptyline

SW, synthetic wastewater

1. Introduction

The increasing consumption and production of active pharmaceutical ingredients (APIs) in low and low-middle income countries (LLMICs) is growing environmental concern owing to the awareness of possible ecotoxicological effects (Kookana et al., 2014). This is related to the diffused practice of direct discharge of untreated wastewater (DUW), the main source of APIs to the environment, which creates a heavily polluted area downstream from the discharge point, named the "impact zone"(A.I.S.E./CESIO, 1995; Finnegan et al., 2009; Kookana et al., 2014; Malik et al., 2015; Nansubuga et al., 2016; Thebo et al., 2017).

Little is known about the environmental fate of APIs in the "impact zone" created by the DUW. Nevertheless, a few available measured environmental concentrations (MECs) of APIs in impact zones of LLMICs show higher concentrations than for high-income countries with developed wastewater treatment infrastructure (Madikizela et al., 2017). For instance, in the Nairobi River basin, Kenya, APIs were detected in concentrations ranging from ng L^{-1} to 160 µg L^{-1} (K'oreje et al., 2016, 2012; Ngumba et al., 2016), in Nigeria, were reported individual concentrations above 50 µg L^{-1} (Olatunde et al., 2014), and again, in South Africa were detected concentrations of atenolol and ibuprofen up to 30 and 85 µg L^{-1} respectively (Agunbiade and Moodley, 2015, 2014; Matongo et al., 2015), and antiretroviral were quantified at concentrations up to hundreds of ng L^{-1} (Wood et al., 2015). Pharmaceutical factories wastewater was deemed as the cause of APIs concentrations up to mg L^{-1} in Pakistan (Ashfaq et al., 2017) and India (Larsson, 2014); and in tropical Asia, sulphonamides antibiotics in surface waters were found to be at higher concentrations than in high-income countries (Shimizu et al., 2013). In one reported case, the environmental risk assessment showed a potential for risk, and pharmaceutical manufactory wastewater contribution was

deemed as important, as also evidenced by other investigations (Ashfaq et al., 2017; Larsson, 2014; Ngumba et al., 2016). Although API manufacturing sites would be expected to be identified as high risk, it should also be noted that in high income countries direct discharge of untreated wastewater from such factories is illegal. The reported data for LLMIC countries therefore highlights the environmental concerns and need for carefully considered risk assessment.

As demonstrated above, globally there are common occurrences of API concentrations in "impact zones" which exceed 0.01 µg L^{-1} for any individual compound. Under the existing risk assessment process, if predicted, such a PEC would trigger Phase II of the environmental risk assessment (ERA) (EMA, 2006), which consists of a two-step tiered protocol to the evaluation of the risk. Tier A is an initial environmental fate and effects analysis that, if resulting in a risk, should be followed by Tier B, an extended environmental fate and effects analysis (EMA, 2006). The latter is a refinement of the predicted environmental concentration (PEC) in the surface water using a distribution coefficient, which considers the moiety adsorbed to sewage sorbents as being retained in the wastewater treatment sludge (OECD, 2000). Equation 1 is used for PEC refinement in tier B of the ERA:

$$PEC_{SURFACE\ WATER} = \frac{Elocal_{water} * F_{stp\ water}}{WASTEW_{inhab} * CAPACITY_{stp} * FACTOR * DILUTION} \quad (1)$$

Where $PEC_{surface\ water}$ is the output of the local surface water concentration (µg l^{-1}); $Elocal_{water}$ is the local emission to wastewater of the relevant residue (µg l^{-1}); $F_{stp\ water}$ is the fraction of emission directed to wastewater (µg l^{-1}); $WASTEW_{inhab}$ is the amount of wastewater per inhabitant per day (l d^{-1}); $CAPACITY_{STP}$ is the capacity of the local wastewater treatment

plant (l); FACTOR accounts for adsorption to suspended matter; and DILUTION is the DF, with a default value of 10 (EMA, 2006).

Where untreated wastewater is discharged there is little or no retention of sludge, the entire crude sewage is input to the "impact zone" scenario. Consequently, the sorbents loaded with APIs are discharged and diluted with the receiving freshwater, and possible redistribution processes might cause imprecise calculation of PECs and the associated risk quotient.

Engineering protocols recommended a ratio of river flow to untreated wastewater flow of 40 (DF) (Keller et al., 2014) to allow dilution and dispersion of pollution. A DF of 10 assuming previous wastewater treatment is used as the default value for environmental risk assessment (EMA, 2006; European Comission Joint Research Centre, 2003).

Although risk assessments are inherently designed to be conservative, data suggests this level of dilution may not always be the case. In at least 14 countries worldwide, the local predicted DF median observations show a value below 10, the majority being in North Africa and the Middle East, with Belgium as the only European country (Keller et al., 2014). The number increases to 53 countries worldwide if data of observations falling in the 5 and 25 percentiles are considered (Keller et al., 2014). The APIs sorption processes to wastewater sorbents control the exposure to biota (Agunbiade and Moodley, 2015; Carmosini and Lee, 2009; Hernandez-Ruiz et al., 2012; Hudson et al., 2007; Lahti and Oikari, 2011; OECD, 2000; Peng et al., 2014; Svahn and Bjorklund, 2015; Wang et al., 2016; Zhou et al., 2007), and since DUW occurs at dilutions that can cause significant desorption of APIs (Hajj-Mohamad et al., 2017; Yang et al., 2011) such exposure might be underestimated with simple dilution calculations.

The aim of this study was to assess the partitioning of APIs to wastewater sorbents and to quantify the potential dilution-induced desorption in receiving freshwaters using a standardised synthetic untreated wastewater diluted across a range of DFs. This approach is aimed to assess the effect of the major constituents present in untreated wastewater, particularly the presence of high concentrations of organic carbon, potentially capable of 'stabilising' APIs in the dissolved phase, on the environmental fate of APIs. Outcomes of the study could then be used to inform the development of an improved exposure assessment approach for a range of contaminants in the impact zone generated by the DUW in freshwaters.

2. Materials and methods

2.1. Active pharmaceutical ingredients

The APIs were selected to reflect consumption patterns of LLMICs where the DUW occurs more commonly. Compound structure and chemical functionality were also fundamental selection criteria due to their fundamental impact on partitioning processes. The selected compounds are the neutral carbamazepine (CBZ), acetaminophen (ACT), and nevirapine (NVR), the acidic diclofenac (DCF) and valsartan (VLS), and the basic acebutolol (ACE), and amitriptyline (AMI) (Table S1 of the Supporting Information). The compounds were obtained at the highest purity available, either from Sigma-Aldrich (acebutolol hydrochloride, amitriptyline hydrochloride, nevirapine, valsartan, acetaminophen) or Fisher Scientific (carbamazepine, diclofenac sodium salt).

2.2. Synthetic wastewater

Wastewater composition is highly variable both within and between wastewater treatment works (WwTW) particularly in LLMIC countries (Tchobanoglous et al., 2003). It is impossible

139 to replicate any given natural matrix within a laboratory setting owing to this inherent
140 variability. The choice of using 'natural' versus synthetic wastewater is an interesting debate
141 with benefits and drawbacks associated with each approach (O'Flaherty and Gray, 2013).
142 The purpose of these experiments was to generate a surrogate untreated wastewater with
143 which to assess the partitioning behaviour of the tested APIs. Consequently, to ensure a
144 consistent, reproducible and stable starting matrix for testing a synthetic wastewater (SW)
145 formulation was used (Boeije et al., 1999). The keys aspects of the starting 'crude' sewage
146 matrix were appropriate suspended solids and organic carbon levels and characteristics. The
147 use of lyophilized primary settled sludge collected from a local WwTW as one of the main
148 'ingredients' provided these bulk characteristics as confirmed by 3-D fluorimetry and Fourier
149 Transfom Infra-Red analysis, which were shown to be stable for at least 24 hours once made
150 up. (see section S1 of the supporting information). The original constituents were further
151 concentrated (x 3) to simulate a high strength wastewater as a worst-case scenario
152 (Tchobanoglous et al., 2003) (S1.2, Table S2). The SW ingredients were mixed with a
153 polycarbonate stirrer bar in a 2 L volumetric flask. The pH was adjusted to 7.5 with 10 mM
154 phosphate buffer (monosodium phosphate, monohydrate, 0.026%; Disodium phosphate,
155 heptahydrate, 0.22%). Sodium azide (NaN_3) was added at 0.02% to prevent bacterial growth
156 (Yamamoto et al., 2009). The formulation involved the addition of dry sewage sludge, which
157 was collected and lyophilized (Kerr et al., 2000; Stevens-Garmon et al., 2011). Briefly, high
158 purity water was added to an aliquot of the sample and shaken for 5 minutes. The
159 suspension was then centrifuged at 4000 rpm for 15 minutes and the supernatant
160 discarded; this process was repeated three times. The resulting solids were placed in sealed
161 glass beakers and frozen at -20 ˚C for at least 24 h. Subsequently, the samples were freeze
162 dried overnight. In order to further reduce the potential for microbiological activity, the

163 samples were heated in an oven at 103 ˚C overnight. The procedure was repeated for each
164 SW synthesis.

165 The SW was characterized for composition and tested for reproducibility and stability. A
166 sacrificial sampling system was designed and run for 24 hours at sampling intervals of 0, 0.5,
167 1, 2, 4, 8, 12, and 24 hours. The SW was characterised using excitation-emission
168 fluorescence spectrophotometry (F-4500 fluorescence spectrophotometer, Hitachi),
169 Dissolved Organic Carbon (DOC) analyses (Shimadzu), and Fourier Transmission Infrared
170 (FTIR) spectrometry (Vertex 70, Bruker) (S1.3).

171 2.3. Analytical methodology

172 Suspended solids removal from the wastewater was obtained by 0.7 µm GF/F filters
173 (Whatman). A solid phase extraction (SPE) method for the selected APIs and SW matrix was
174 used with the aim of removing the analytes from their complex matrix, improving the
175 chromatographic separation and mass spectrometric detection and quantification of the
176 APIs. The protocol followed a previously validated and published method for the multi-
177 residue analysis of pharmaceuticals in wastewater (Vergeynst et al., 2015). The SPE
178 cartridges, OASIS HLB cartridges (Waters) (200 mg polymeric sorbent; 6 mL barrel volume),
179 were activated with methanol (Thermo Fisher Scientific, Optima LC/MS) and ultra-high
180 purity water (UHP) obtained with a MilliQ system (>18.2 $M\Omega cm^{-1}$, Merck Millipore) then
181 loaded with 5 mL of the pre-filtered sample and washed with 1 mL of UHP. Subsequently,
182 the compounds were eluted with 5 mL of methanol amended with formic acid (2%). The
183 eluent was collected in 5 mL HPLC grade vials and evaporated under a gentle nitrogen
184 stream until dryness. Reconstitution was performed with 1:10 methanol/water. All

glassware and plastic ware was acid cleaned prior to use (2% v/v Decon, ≥24 h; 10% v/v HCl, ≥24 h; final rinse with UHP).

The chromatographic separation was obtained with a reversed phase column (XBridge BEH C18 2.5 µm 2.1x50 mm Column XP, Waters) operating at the temperature of 50 °C (Dionex Ultimate 3000, Thermo Scientific). As aqueous eluent was used UHP with 0.1% formic acid LC/MS grade as additive (Fisher scientific). Methanol was used as the organic eluent. The flow rate was set at 500 µL min^{-1}. The elution consisted of a flow gradient of the duration of 5.5 minutes from 100% aqueous to 100% methanol and an aqueous equilibration time of 2.5 minutes.

High-resolution mass spectrometry was performed by means of an orbitrap-based system (Thermo Scientific). The ionisation source was a Heated Electro-Spray Ionisation (HESI) set as follow: Sheath gas 53 Arb (nitrogen); Auxiliary gas 14 Arb (nitrogen); Sweep gas 3 Arb (nitrogen); Vaporiser temperature 300 °C; Polarity Positive and/or negative ion; Spray voltage (+) 3500/ (-) 2500 V; Capillary temperature 270°C; S-lens RF level 50. The mass spectrometer detector settings were as follow: Resolution 17,500 m/z 200; Positive polarity; Scan range full scan m/z 100 -1000; AGC target 1e6 (automatic gain control); Micro scans 1; Maximum ion time was set as automatic. solution. Mass calibration was achieved in positive mode with a mixture of caffeine, MRFA, Ultramark 1621 and n-butylamine in acetonitrile/methanol/acetic solution (Pierce LTQ Velos ESI, Thermo Fisher Scientific).

2.4. Experimental approach

Triplicate SW incubations (500 mL) were spiked with APIs each at a concentration of 100 µg L^{-1} as deemed representative for a possible impact zone concentration. This concentration was chosen for the following reasons (i) it represents levels that can be observed in impact

zones (ii) levels were not so high as to bias any physico-chemical effects which might occur in the impact zone and (iii) concentrations were of sufficiently high to allow accurate and precise determination using the applied analytical technique in the dissolved phase after equilibration (particularly for the strongly adsorbing APIs). Samples were continually stirred and progressively diluted using UHP (MilliQ, deionised water resistivity of at least 18.2 MΩ•cm at 25 degrees Celsius). A pH of 7.5 was chosen to be representative of the environmental and wastewater matrix. Sample blanks and controls were included (Figure 1). The flasks were wrapped in aluminium foil to avoid exposure to light. The dilution distribution dynamics were tested over a range of ten dilution factors (DF): 1, 1.2, 1.4, 1.6, 1.8, 2, 2.2, 4, 8, 10. The DFs were based on the progressive achievement of DF 10, which is the environmental risk assessment default assumption (EMA, 2006; Keller et al., 2014). After each dilution, the sample was left for 24 hours to reach equilibrium before sampling, which was a conservative time estimate (Conrad et al., 2006; Yang et al., 2011).

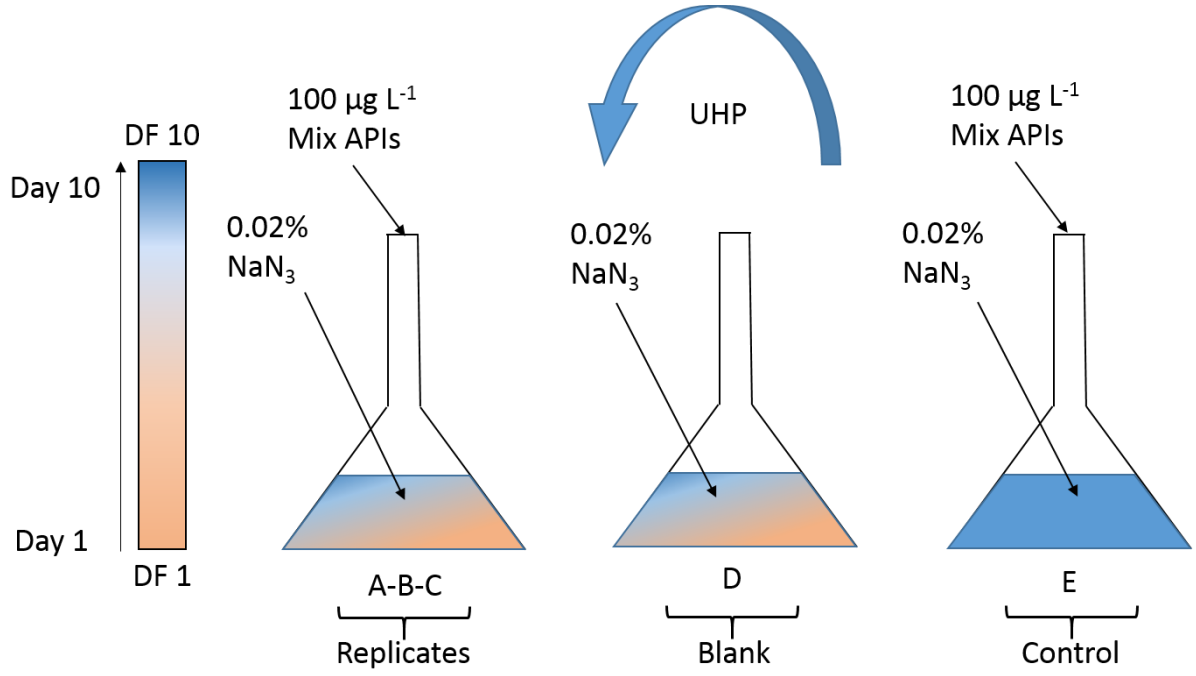

Figure 1. Experimental design of the dilution experiment. A-B-C were sample replicates; D was the blank and E was the control where APIs were added to buffered and

sterilized (NaN_3) ultra-high pure water (UHP). Each batch was progressively diluted with UHP from the dilution factor (DF) 1 to 10 (1, 1.2, 1.4, 1.6, 1.8, 2, 4, 6, 8, 10) along a period of 10 days.

2.5. Calculations

2.5.1. Determination of K_d values

The environmental fate of a contaminant is largely determined by its sorption behaviour. The extent of sorption is expressed as the distribution coefficient, K_d, normally determined by the particulate : dissolved ratio at equilibrium (Franco and Trapp, 2008). In this study the concentration in solids refers to sorption to the bulk sorbents of untreated wastewater, including colloids and DOM, and therefore hereafter named as concentration in sorbents (C_s) whilst the concentration in water (C_w) to the freely available fraction.

Therefore, the $K_{d\ exp.}$ is obtained from the ratio of the compound concentration in the sorbent phase (C_s) and in the aqueous phase (C_w) (Equation 2):

$$\boldsymbol{K_d = \frac{C_s}{C_w}} \qquad \textbf{2}$$

The distribution coefficient was calculated at each DF. The modelled distribution coefficient values ($K_{d\ Mod.}$) were also calculated for comparison to the experimental ones. The pH dependent octanol-water distribution coefficient (D_{ow}), which accounts for compound dissociation, dependent on the pK_a, was calculated for each compound functionality, according to Equations 3-5 (neutral, acidic and basic, respectively):

$$\boldsymbol{\log D_{owN} = logK_{ow}} \qquad \textbf{3}$$

$$\boldsymbol{logD_{owA} = logK_{ow} + log\frac{1}{1+10^{pH-pKa}}} \qquad \textbf{4}$$

$$logD_{owB} = logK_{ow} + log\frac{1}{1+10^{pKa-pH}} \quad (5)$$

Where log D_{ow} is the distribution coefficient octanol-water (log K_{ow}) adjusted to the dissociation of the compound at a given pH; pKa is the dissociation constant of the compound (Lin et al., 2010).

Log D_{ow} was related to K_d using Equation 6 (Lin et al., 2010):

$$\log K_{d\ Mod.} = 0.74 \times \log D_{ow} + 0.15 \quad (6)$$

2.5.2. Variation from theoretical concentration (% VTC)

In order to evaluate the desorption extent for each API, the theoretical concentration was calculated at each DF, including undiluted sample (DF1), and subtracted from experimental data. The results were recalculated as the percentage of variation from the theoretical concentration (%VTC) for normalisation, as shown in Equation 7:

$$\%VTC = (C_{exp} - C_{th}/C_{DF1}) \times 100 \quad (7)$$

Where C_{exp} is the API experimental concentration in water, C_{th} is the API theoretical concentration in water and C_{DF1} was the API concentration in water at DF 1.

3. Results and discussion

3.1. Sorption

The API distribution in undiluted samples (DF 1) is presented in Figure 2 as a percentage of the compound remaining in solution and ordered per log K_{ow}.

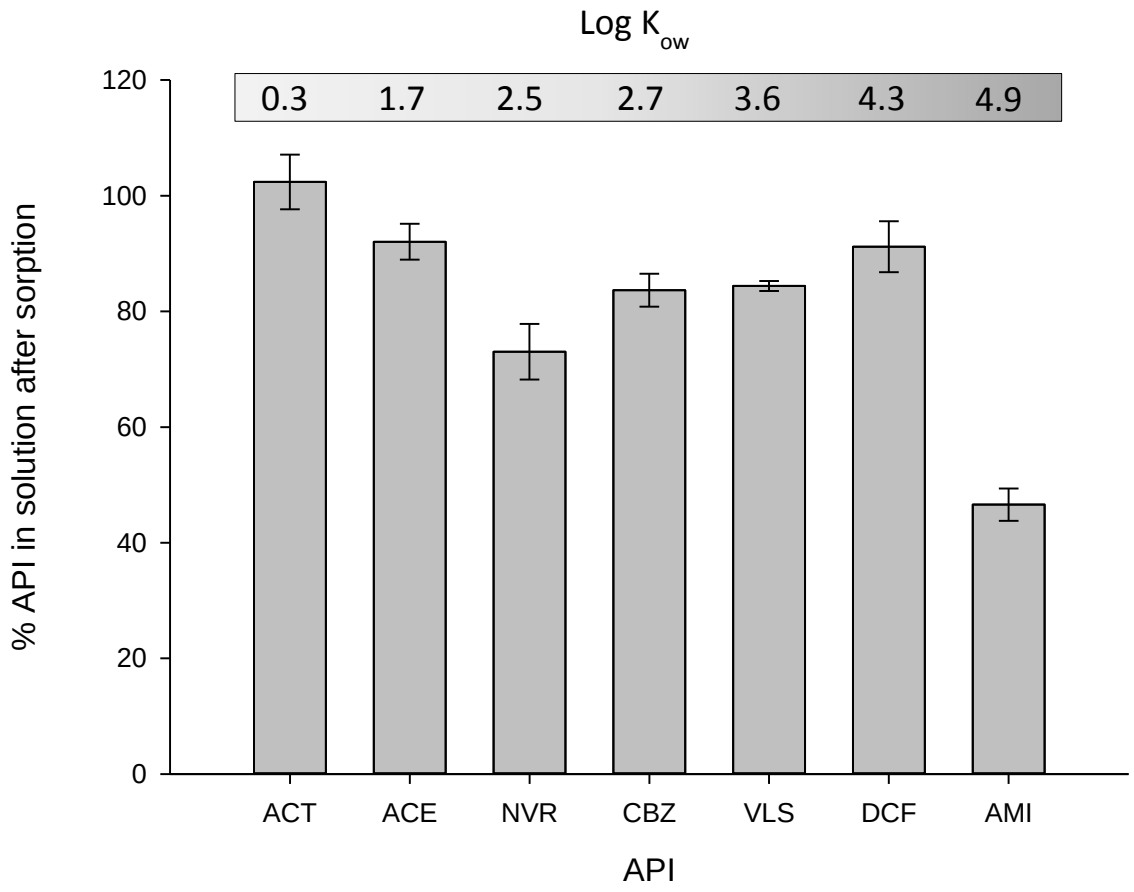

Figure 2. Percentage (%) of APIs in solution after spiking at no dilution (DF 1); the compounds are ordered per increase of API log K_{ow}, as indicated in the top bar. The error bars show the standard deviation (ACT, acetaminophen; ACE, acebutolol; NVR, nevirapine; CBZ, carbamazepine; VSL, valsartan; DCF, diclofenac; AMI, amitriptyline).

These data were used as the initial concentration for the calculation of the theoretical concentration after dilution and the log Kd (Table 1).

Table 1 Measured concentration in undiluted solution (DF1) and experimental solid-water distribution coefficient values.

DF 1	ACT	ACE	NVR	CBZ	VLS	DCF	AMI
µg L^{-1}	102.39	92.05	73.05	83.68	84.42	91.20	46.58
Log K_d [L kg^{-1}]	-1.70	2.27	2.90	2.62	2.60	2.32	3.39

* ACT, acetaminophen; ACE, acebutolol; NVR, nevirapine; CBZ, carbamazepine; VSL, valsartan; DCF, diclofenac; AMI, amitriptyline.

At the experimental pH of 7.5, the acidic and basic APIs are calculated to be fully ionised, and the compounds defined as neutral, ACT (pKa 9.38), NVR (pKa 2.8) and CBZ (pKa 13.2), may be considered fully unionised. The measured sorption behaviour was consistent with the chemical properties of each compound: charge, lipophilicity, and structure, and in accord with previous studies (Jelic et al., 2011; Silva et al., 2011; Verlicchi et al., 2012)

The low log K_{ow} (0.3) of the neutral ACT predicts little sorption, which agrees with previously published studies (Li et al., 2015; Lin et al., 2010; Martínez-Hernández et al., 2014; OECD, 1997). The neutral CBZ and NVR, log K_{ow} of 2.7 and 2.5 respectively, show a similar sorption trend. Sorption was greatest for AMI, consistent with its high lipophilicity (log K_{ow} 4.9) and the influence of the positive charge. In fact, the lipophilic interactions are reported to be most important, whilst the charge on the ionised functional group exercises a secondary control on the distribution processes (Franco and Trapp, 2008; Githinji et al., 2011; Martínez-Hernández et al., 2014; Silva et al., 2011). The low sorption of ACE was supported by its log K_{ow} (1.7), which confirmed the secondary impact of the positive charge in determining the sorption behaviour. DCF and VLS, however, adsorbed less strongly than expected per their relatively high log K_{ow} (3.6 and 4.3, respectively). This was likely due to

287 the degree of repulsion of the negative charge on both the API and sorbent competing with
288 lipophilic attraction (Delle Site, 2001; Paul et al., 2014).

289 The log K_d obtained at DF1 were compared with values available in the literature (Table 2)
290 (Al-Khazrajy and Boxall, 2016; Bai et al., 2008; Hernandez-Ruiz et al., 2012; Lahti and Oikari,
291 2011; Li et al., 2015; Lin et al., 2010; Loffler et al., 2005; Maoz and Chefetz, 2010; Martínez-
292 Hernández et al., 2014; Maskaoui et al., 2007; Maskaoui and Zhou, 2010; Stein et al., 2008;
293 Svahn and Bjorklund, 2015; Yamamoto et al., 2009; Zhou and Broodbank, 2014). The data
294 show the importance of the sorbent quality (i.e. protein-like or humic-like organic matter) in
295 determining the extent of API sorption. Wastewater is mainly composed of proteinaceous
296 material which binds organic contaminants more weakly than humic-like substances typical
297 of freshwater (Hernandez-Ruiz et al., 2012; Peng et al., 2014; Wang et al., 2016). The
298 characterization of the synthetic wastewater used during this study confirmed the
299 predominance of proteinaceous components (Figure S1) and the $K_{d\,exp.}$ were consistent with
300 its comparative binding strength. In fact, the log K_d of -1.70 L kg^{-1} for ACT was in the range of
301 values obtained for suspended solids (SS) (-2.2 and 0.5) in a simulated sewage system (Hajj-
302 Mohamad et al., 2017). Also, the log K_d for CBZ (2.62 L kg^{-1}) obtained in this study
303 corresponded to the value reported by Maoz and Chefetz (Maoz and Chefetz, 2010) for
304 DOM extracted from bulk sewage sludge (2.64 L kg^{-1}), and in the range obtained by Lahti
305 and Oikari (Lahti and Oikari, 2011) for sediments from wastewater effluent (2.00-3.42 L kg-
306 1) (Table S3). CBZ sorption to humic-like substances revealed a much larger log K_d in
307 contrast of up to 6.66 L kg^{-1} (Table S3). The proteinaceous composition of the SW could
308 explain the lack of ACE sorption despite the positive charge, consistent with the range (log
309 K_d of 0.5 - 1.0 L kg^{-1}) obtained by Lahti and Oikari (Lahti and Oikari, 2011) for particulate
310 matter derived from wastewater treatment works effluent, considerably less than 3.28 L kg-

311 [1], obtained by Lin et al. for freshwaters, typically characterized by the presence of humic-like
312 substances (Lin et al., 2010). However, the repulsion of negative charges on the dissociated
313 acidic compounds is more important in sorption processes than the sorbent quality. This
314 was shown by the log $K_{d\ exp.}$ 2.13 L kg^{-1} for DCF obtained for synthetic humic-like suspended
315 solids by Ra et al. (Ra et al., 2008) that was close to the value of 2.32 L kg^{1} obtained in this
316 study (Table 1).

317 3.2. Trend of dissolved concentration of APIs as a function of
318 dilution

319 The variation in concentration of the dissolved APIs with dilution is shown in Figure 3.
320 Desorption is expressed as the percentage variation from the theoretical concentration
321 (%VTC) against DF. The extent of the deviation, as a dilution effect, varied between
322 compounds, determined by the relative influence of compound functionality and
323 lipophilicity.

324 Maximum deviation was measured at low DF, namely DF 2, whilst at higher DF the
325 concentrations of APIs are similar to the theoretical values. The highest %VTC occurred for
326 AMI (27.7%), followed by CBZ (12.4%), NVR (11.8%), ACE (7.7%), DCF (4.2%), ACT (1.3%), and
327 VSL (-3.2%).

328 Figure 3 shows the behaviour of the compounds separated by functionality. The compound
329 ACT showed no variation from the theoretical concentration at each dilution factor (Figure
330 3A), which was expected as sorption was insignificant (Figure 3). ACT (pK_a 9.38) was neutral
331 at the experimental pH so functionality would not have influenced sorption. The low log K_{ow}
332 (0.3 L Kg^{-1}) indicates negligible lipophilicity, consistent with the low retention shown by the

wastewater sorbents. As such, ACT behaved conservatively at each DF. The neutral compounds NVR and CBZ show a similar trend of deviation from predicted concentration (+10 %VTC at DF2). The two APIs were both neutral at the experimental pH and their log K_{ow} values are similar (2.50 and 2.67 L Kg^{-1}, respectively), which explains the similar trend, and highlights the role of lipophilicity in controlling the sorption of APIs to and from the wastewater sorbents. CBZ and NVR have similar molecular structures that could be the cause of the notable persistence of the former (Andreozzi et al., 2004), and, if true also for the latter, would help explain the ubiquitous presence of NVR in impact zones (K'oreje et al., 2016, 2012; Ngumba et al., 2016).

Figure 3B shows the trend in the deviation from the theoretical concentration for the basic compounds AMI and ACE. AMI shows the largest %VTC (27.7%) amongst the compounds investigated, which is concomitant with the largest log K_{ow} value (4.9). ACE is a cation at the experimental pH, but the lipophilicity (log K_{ow} 1.7) appeared to be the only physico-chemical parameter affecting desorption.

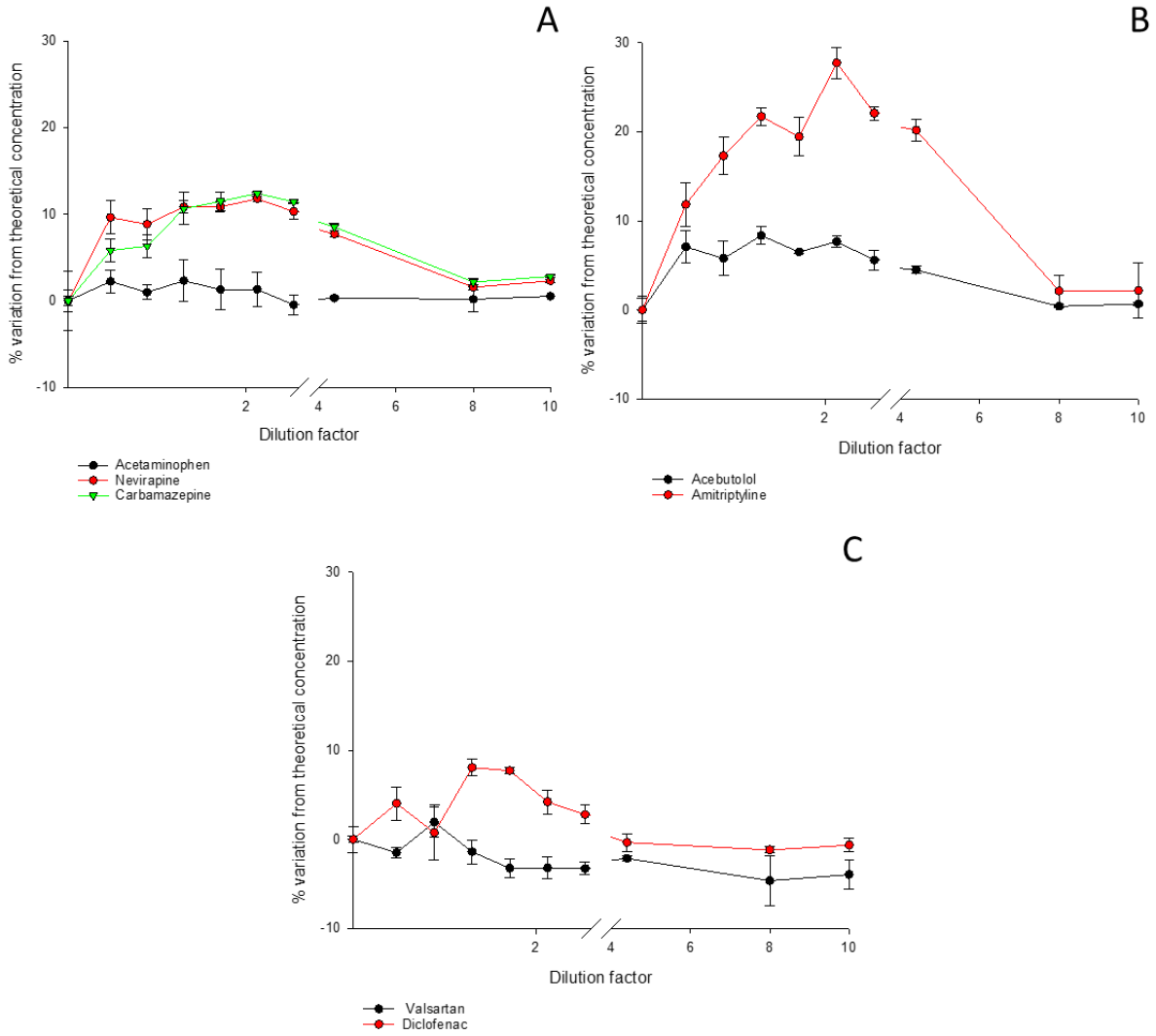

Figure 3 Percentage of variation from theoretical concentration of A: neutral compounds acetaminophen (ACT), Nevirapine (NVR), and carbamazepine (CBZ); B: basic compounds Acebutolol (ACE) and Amitriptyline (AMI); C: acidic compounds Valsartan (VLS) and Diclofenac (DCF); at DF from 1 to 10.

Figure 3C shows the behaviour of the acidic compounds VLS and DCF. As previously discussed, these acidic compounds showed little sorption, despite the large log K_{ow}, likely due to repulsion between the negative charge on the compound and the negative net charge of the organic matter sorbents (Refaey et al., 2017). Also, little desorption was measured for DCF (10%VTC) and none for VLS. The former behaviour was likely determined by strong binding of electrical forces involving charge transfer (~40 kJ mol^{-1}), which regards

the moiety of negative charged compounds that once adsorbed would be unlikely reversible (Martínez-Hernández et al., 2014).

Lipophilicity was the main parameter determining the behaviour of the neutral and cationic APIs, whilst the negative charge on the anionic APIs strongly interfered with the sorption/desorption processes. This trend is shown in Figure 4A, which depicts the relationships between log K_{ow} and the %VTC of neutral and cationic APIs, on the right of the black line, and acidic compounds, on the left. Figure 4B shows the correlation of the %VTC and the log K_{ow} of the neutral and positively charged compounds with the coefficient of determination (R^2) greater than 0.950 in 7 of the 9 DFs.

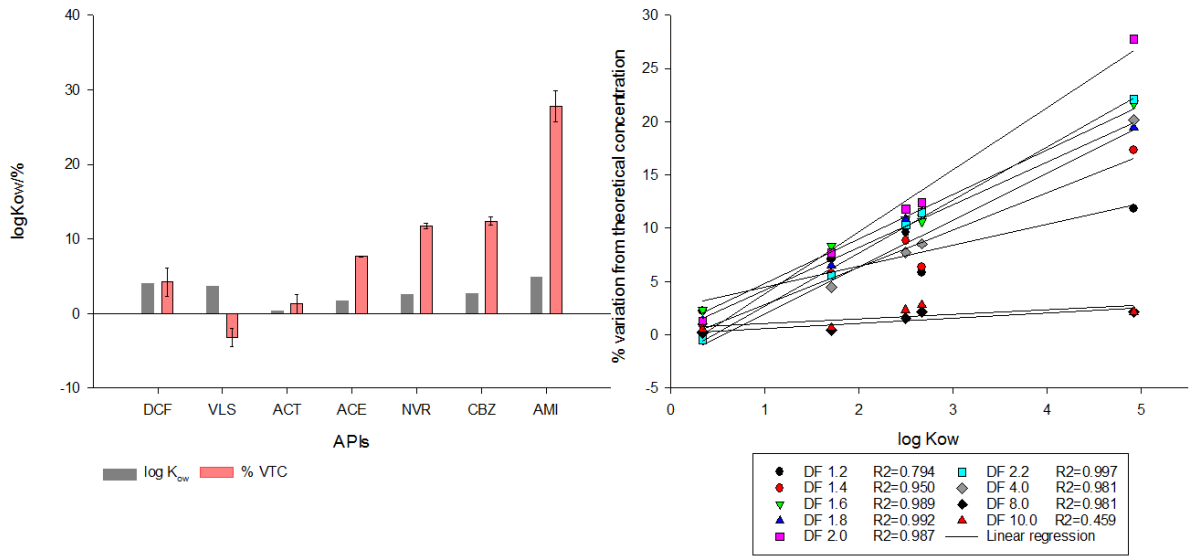

Figure 4 **[A] The relationships between the log K_{ow} of neutral and positively charged APIs on the right of the black line at the percentage of variation from theoretical concentration (%VTC) of 2, and the lack of relationship of the acidic compounds, on left side. [B] The correlation of the neutral and positively charged compounds versus dilution.**

3.3. Modelled versus experimental K_d

The log K_d values for the APIs were obtained from experimental data (log $K_{d\ exp.}$) and a theoretical model (log $K_{d\ mod.}$) (Lin et al., 2010). Additionally, literature solid-water

distribution coefficients (log $K_{d\ lit.}$) were collected (Table S3), and the upper and lower values added to Table 2 for comparison.

Although the log $K_{d\ mod.}$ at DF 1 did not exactly match the experimental values, the data were within the range of literature values, which demonstrated the validity of the model (Table 2). The calculated log K_d for AMI was closest to the experimental value (DF 1), but did not correspond to the literature range of values. However, the log $K_{d\ lit.}$ values for AMI originated from a single study and related to distribution to sediments, whilst the ranges for other compounds related to more relevant sorbents, namely DOM, colloids and suspended solids. As previously discussed, the sorbent type and quality strongly affect distribution processes and, therefore, the K_d values.

Table 2 Modelled (Log $K_{d\ mod.}$), literature values (log K_d lit.), and experimental (Log $K_{d\ exp.}$) distribution coefficient values for the APIs investigated in this study, including DFs (Al-Khazrajy and Boxall, 2016; Bai et al., 2008; Hernandez-Ruiz et al., 2012; Lahti and Oikari, 2011; Li et al., 2015; Lin et al., 2010; Loffler et al., 2005; Maoz and Chefetz, 2010; Martínez-Hernández et al., 2014; Maskaoui et al., 2007; Maskaoui and Zhou, 2010; Stein et al., 2008; Svahn and Bjorklund, 2015; Yamamoto et al., 2009; Zhou and Broodbank, 2014).

Log K_d [L/kg]	DF	ACT	ACE	NVR	CBZ	VLS	DCF	AMI
Log $K_{d\ mod.}$	/	0.40	1.42	2.00	2.13	2.85	3.15	3.79
Log $K_{d\ lit.}$	/	-0.3 - 2.4	0.5 - 3.3	n. a.	-1.5 - 6.7	n. a.	0.9 - 6.9	0.9 - 2.4
Log $K_{d\ exp.}$	**1.0**	-1.70	2.27	2.90	2.62	2.60	2.32	3.39
	1.2	-2.12	0.48	2.78	2.49	2.74	2.08	3.37
	1.4	-2.06	0.94	2.82	2.47	2.68	2.42	3.35
	1.6	-2.32	2.21	2.76	1.77	2.88	2.06	3.32
	1.8	-2.27	2.09	2.75	1.78	3.02	2.21	3.36
	2.0	-2.34	2.44	2.65	2.33	3.08	1.61	3.21
	2.2	-1.80	2.24	2.73	2.40	3.14	2.19	3.32
	4.4	-2.54	2.94	2.32	3.10	3.47	3.04	3.12
	8.0	-2.80	2.96	3.57	2.51	4.18	3.56	4.16
	10.0	-3.19	2.61	3.39	3.16	4.32	3.57	4.22

n. a.: not available

A general increase of log K_d occurred at DF 8 and 10 for all APIs, especially NVR, CBZ, VLS and AMI, where this was up to one order of magnitude (Table 2). These increases were related with increased concentration of dissolved organic carbon (DOC) at the DF of 8 and 10, as

depicted by the plot of theoretical and experimental DOC in Figure 5. As the DOC concentration is a representative measure of the concentration of DOM, it follows that the dissolution of organic matter from particulate organic matter (POM) increments the cation exchange capacity because of the increase in specific surface area, and therefore sorption. Therefore, the decrease of API concentration at the DF of 8 and 10 is likely due to an interplay of dilution and additional sorption to the proportionally increased DOM, with respect to the expected concentration from the theoretical calculation.

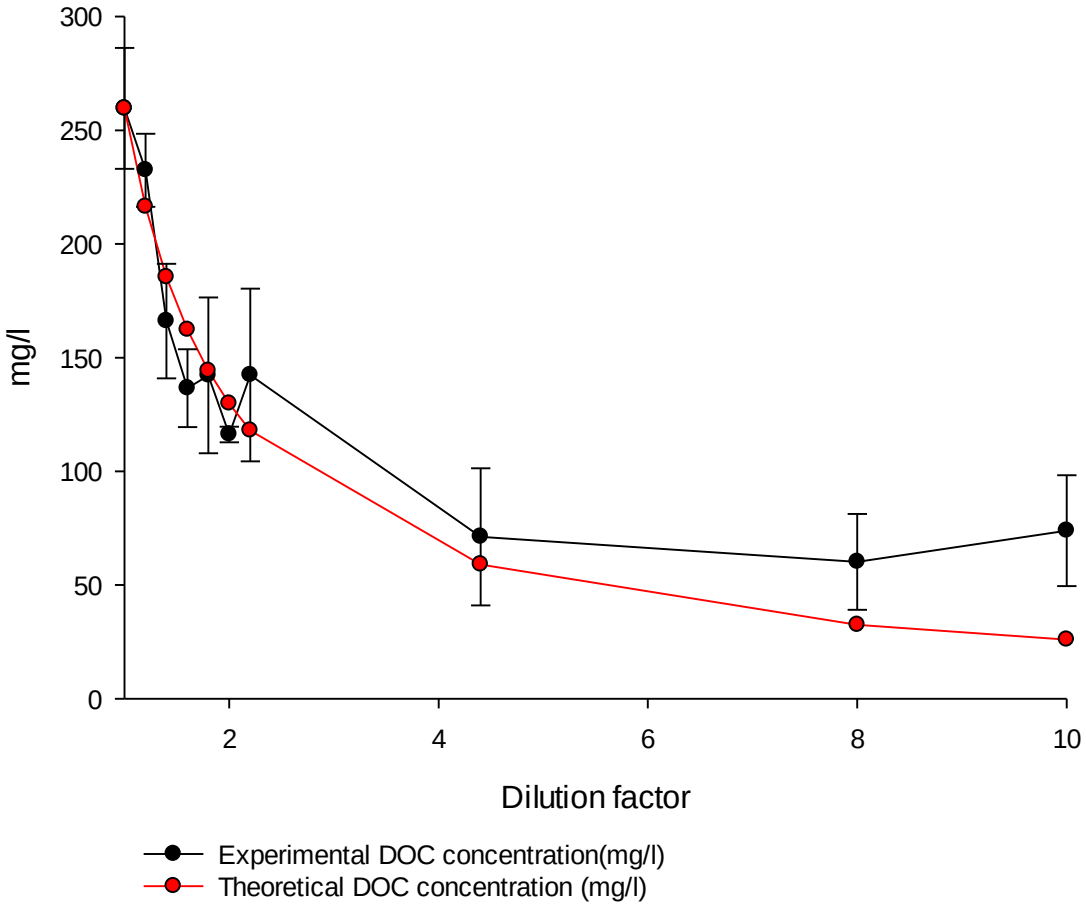

Figure 5 **Theoretical and experimental dissolved organic carbon (DOC) concentrations recorded at each DF; and the increase from theoretical concentration at DF 8 and 10.**

3.4. Implication of API desorption within the impact zone for ERA

ERA guidelines do not include a protocol for evaluating ecological risk posed by the direct discharge of API-containing untreated wastewater (EMA, 2006). Although from a human health and environment point of view such practices should not happen, the fact is that across LLMIC it is a widespread occurrence. Phase 1 of the ERA guideline is aimed at estimating exposure within the aquatic environment only. It does not consider the route of administration, API form, metabolism and excretion. If the PEC is calculated above 0.01 μg l^{-1}, then a phase 2 analysis, which includes the generation of environmental fate and effect data, should be performed. However, in the phase 2 tier B environmental fate analysis, the PEC calculation considers the distribution of APIs to the sewage sludge accordingly to the experimental log K_{oc}, defined as the log K_d value normalized to organic content in sewage sludge as from the OECD 106 protocol (OECD, 2000).

Equation 1 may not be applicable to discharges of poorly or untreated wastewater where wastewater treatment is limited or does not occur. In fact, as from the obtained evidence, highly lipophilic neutral or positively charged APIs desorb more readily with dilution (Figure 4), and omitting desorption could lead to potential underestimation of APIs PEC. Municipal and industrial wastewater are considered the primary source of APIs to the environment, while poor or absent wastewater treatment is widespread globally (Malik et al., 2015). This study has identified clear trends in API environmental cycling during wastewater dilution

429 which are not addressed in current APIs environmental risk assessment legislation, and
430 which could have consequences for the estimation of precise environmental concentrations.

431 4. Conclusions

432 Inadequate wastewater treatment and consequent direct discharge of untreated
433 wastewater to surface waters is a global problem. This study presents data on the sorption
434 of APIs to untreated wastewater sorbents, and their deviation from theoretical
435 concentrations during dilution in freshwaters, for the evaluation of exposure
436 concentrations, using APIs representative of LMICs.

437 The measured sorption behaviour was consistent with the chemical properties of each
438 compound: charge, lipophilicity, and structure. ACT was not adsorbed because of its low
439 lipophilicity and lack of charge, while the behaviour of NVR and CBZ was similar, consistent
440 with the proximity of their log K_{ow} values and chemical structure. The behaviour of the basic
441 compounds, AMI and ACE, indicated that primary control of sorption was lipophilicity with a
442 secondary role for the positively-charged functional group. In contrast, sorption of the acidic
443 compounds, DCF and VLS, was low due to repulsion between the negatively-charged
444 compound and the similar net charge on the sorbent surface sites. The measured log K_d
445 values were consistent with reported values for the types of sorbent studied.

446 Dilution caused significant positive deviation from theoretical concentrations of the neutral
447 and basic APIs at low dilution factors, and showed a high correlation to the lipophilicity, with

448 the positive charge playing a secondary role. The negatively-charged compounds did not
449 show significant desorption (i.e. 0 % loss for VLS and < 10 % for DCF). This behaviour was
450 attributed to irreversible binding of the negatively-charged functional group to positively-
451 charged sites on the sorbent. In addition to dilution, the concomitant increase in DOM
452 concentration at the higher DF (i.e. 8 and 10) appeared to result in further sorption of APIs.

453 As a conclusive reflection, the possibility of de-conjugation of conjugates as metabolites
454 could be summed up to the mechanistic desorption magnitude described in the results.

455 This study has identified clear trends in API environmental cycling during wastewater
456 dilution which are not addressed in current APIs environmental risk assessment legislation,
457 and which could have consequences for the estimation of precise environmental
458 concentrations.

459

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6. Supporting information

Active pharmaceutical ingredients selected for this study. List of the ingredients of the synthetic wastewater (SW) and the concentrations augmented three times. Synthetic crude wastewater formulation and characterization. Partition coefficient for DOM, colloids, suspended solids (SS) and sediments (Log KDOM) for carbamazepine (CBZ), diclofenac (DCF), acebutolol (ACE), acetaminophen (ACT), amitriptyline (AMI), available in the published literature, and sources of the sorbent.

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