

2018-05-15

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<http://hdl.handle.net/10026.1/10498>

10.1016/j.scitotenv.2017.12.092

Science of the Total Environment

Elsevier

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1 OPEN ACCESS VERSION PRIOR TO PROOF – MAIN TEXT AVAILABLE FROM
2 SCIENCE OF THE TOTAL ENVIRONMENT - DOI:[10.1016/J.SCITOTENV.2017.12.092](https://doi.org/10.1016/J.SCITOTENV.2017.12.092)

3
4 **SORPTION OF ACTIVE PHARMACEUTICAL INGREDIENTS IN UNTREATED**
5 **WASTEWATER EFFLUENT AND EFFECT OF DILUTION IN FRESHWATER:**
6 **IMPLICATIONS FOR AN “IMPACT ZONE” ENVIRONMENTAL RISK**
7 **ASSESSMENT APPROACH**

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15 **Abstract**

16 Evidence of ecotoxicological effects of active pharmaceutical ingredients (APIs) has
17 increased research into their environmental fate. In low and low-middle income countries
18 (LLMICs) the main source of APIs to surface waters is from discharge of untreated
19 wastewater. Consequently, concentrations of APIs can be relatively high in the “impact zone”
20 downstream of a discharge point. Little is known about the fate of APIs in these impact
21 zones. In this laboratory scale investigation, the effect of successive dilution of synthetic
22 untreated wastewater (dilution factor 1 to 10) on the distribution of APIs was studied. The
23 sorption was consistent with the chemical properties of each compound: charge,
24 lipophilicity, and structure. Dilution increased desorption of the basic and neutral APIs (up to
25 27.7%) and correlated with their lipophilicity ($R^2 > 0.980$); the positive charge was of
26 secondary importance. Anions did not significantly desorb (< 10% loss). Increased
27 concentrations of dissolved organic matter at dilutions of 8 and 10 times untreated
28 wastewater coincided with lower API concentrations in solution. The data showed a clear
29 trend in the desorption process of APIs that may lead to higher exposure risk than
30 anticipated. Therefore, it is suggested that these aspects should be accounted for in the
31 development of dedicated environmental risk assessment approach for APIs in riverine
32 impact zones of LLMICs countries.

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

35 **Abbreviations:**

36 APIs, active pharmaceutical ingredients

37 LLMICs, low and low-middle income countries

38 DUW, direct discharge of untreated wastewater

39 DF, dilution factor

40 CBZ, carbamazepine

41 ACT, acetaminophen

42 NVR, nevirapine

43 DCF, diclofenac

44 VLS, valsartan

45 ACE, acebutolol

46 AMI, amitriptyline

47 SW, synthetic wastewater

48

49 **1. Introduction**

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

57 Little is known about the environmental fate of APIs in the “impact zone” created by the
58 DUW. Nevertheless, a few available measured environmental concentrations (MECs) of APIs
59 in impact zones of LLMICs show higher concentrations than for high-income countries with
60 developed wastewater treatment infrastructure (Madikizela et al., 2017). For instance, in the
61 Nairobi River basin, Kenya, APIs were detected in concentrations ranging from ng L^{-1} to 160
62 $\mu\text{g L}^{-1}$ (K’oreje et al., 2016, 2012; Ngumba et al., 2016), in Nigeria, were reported individual
63 concentrations above $50 \mu\text{g L}^{-1}$ (Olatunde et al., 2014), and again, in South Africa were
64 detected concentrations of atenolol and ibuprofen up to 30 and $85 \mu\text{g L}^{-1}$ respectively
65 (Agunbiade and Moodley, 2015, 2014; Matongo et al., 2015), and antiretroviral were
66 quantified at concentrations up to hundreds of ng L^{-1} (Wood et al., 2015). Pharmaceutical
67 factories wastewater was deemed as the cause of APIs concentrations up to mg L^{-1} in
68 Pakistan (Ashfaq et al., 2017) and India (Larsson, 2014); and in tropical Asia, sulphonamides
69 antibiotics in surface waters were found to be at higher concentrations than in high-income
70 countries (Shimizu et al., 2013). In one reported case, the environmental risk assessment
71 showed a potential for risk, and pharmaceutical manufactory wastewater contribution was

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

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

$$PEC_{SURFACE\ WATER} = \frac{E_{local\ water} * F_{stp\ water}}{WASTEW_{inhab} * CAPACITY_{STP} * FACTOR * DILUTION} \quad 1$$

88

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

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

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

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

104 Although risk assessments are inherently designed to be conservative, data suggests this
105 level of dilution may not always be the case. In at least 14 countries worldwide, the local
106 predicted DF median observations show a value below 10, the majority being in North Africa
107 and the Middle East, with Belgium as the only European country (Keller et al., 2014). The
108 number increases to 53 countries worldwide if data of observations falling in the 5 and 25
109 percentiles are considered (Keller et al., 2014). The APIs sorption processes to wastewater
110 sorbents control the exposure to biota (Agunbiade and Moodley, 2015; Carmosini and Lee,
111 2009; Hernandez-Ruiz et al., 2012; Hudson et al., 2007; Lahti and Oikari, 2011; OECD, 2000;
112 Peng et al., 2014; Svahn and Bjorklund, 2015; Wang et al., 2016; Zhou et al., 2007), and since
113 DUW occurs at dilutions that can cause significant desorption of APIs (Hajj-Mohamad et al.,
114 2017; Yang et al., 2011) such exposure might be underestimated with simple dilution
115 calculations.

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

125 **2. Materials and methods**

126 **2.1. Active pharmaceutical ingredients**

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

136 **2.2. Synthetic wastewater**

137 Wastewater composition is highly variable both within and between wastewater treatment
138 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 Transform 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 $-20\text{ }^\circ\text{C}$ 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 ($>18.2 \text{ M}\Omega\text{cm}^{-1}$, 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

185 glassware and plastic ware was acid cleaned prior to use (2% v/v Decon, ≥ 24 h; 10% v/v HCl,
186 ≥ 24 h; final rinse with UHP).

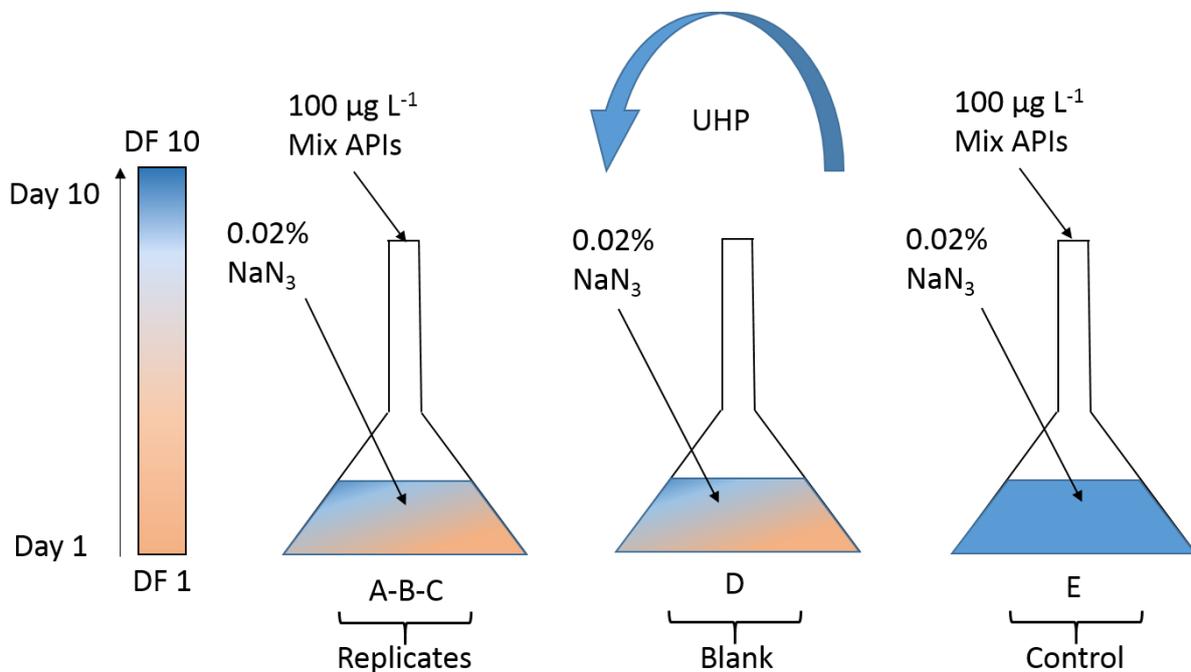
187 The chromatographic separation was obtained with a reversed phase column (XBridge BEH
188 C18 2.5 μm 2.1x50 mm Column XP, Waters) operating at the temperature of 50 $^{\circ}\text{C}$ (Dionex
189 Ultimate 3000, Thermo Scientific). As aqueous eluent was used UHP with 0.1% formic acid
190 LC/MS grade as additive (Fisher scientific). Methanol was used as the organic eluent. The
191 flow rate was set at 500 $\mu\text{L min}^{-1}$. The elution consisted of a flow gradient of the duration of
192 5.5 minutes from 100% aqueous to 100% methanol and an aqueous equilibration time of 2.5
193 minutes.

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

204 2.4. Experimental approach

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

208 zones (ii) levels were not so high as to bias any physico-chemical effects which might occur in
 209 the impact zone and (iii) concentrations were of sufficiently high to allow accurate and
 210 precise determination using the applied analytical technique in the dissolved phase after
 211 equilibration (particularly for the strongly adsorbing APIs). Samples were continually stirred
 212 and progressively diluted using UHP (MilliQ, deionised water resistivity of at least 18.2
 213 $M\Omega\cdot cm$ at 25 degrees Celsius). A pH of 7.5 was chosen to be representative of the
 214 environmental and wastewater matrix. Sample blanks and controls were included (Figure 1).
 215 The flasks were wrapped in aluminium foil to avoid exposure to light. The dilution
 216 distribution dynamics were tested over a range of ten dilution factors (DF): 1, 1.2, 1.4, 1.6,
 217 1.8, 2, 2.2, 4, 8, 10. The DFs were based on the progressive achievement of DF 10, which is
 218 the environmental risk assessment default assumption (EMA, 2006; Keller et al., 2014). After
 219 each dilution, the sample was left for 24 hours to reach equilibrium before sampling, which
 220 was a conservative time estimate (Conrad et al., 2006; Yang et al., 2011).



221

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

224 sterilized (NaN₃) ultra-high pure water (UHP). Each batch was progressively
225 diluted with UHP from the dilution factor (DF) 1 to 10 (1, 1.2, 1.4, 1.6, 1.8, 2, 4, 6,
226 8, 10) along a period of 10 days.

227 2.5. Calculations

228 2.5.1. Determination of K_d values

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

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

$$K_d = \frac{C_s}{C_w} \quad 2$$

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

$$\log D_{owN} = \log K_{ow} \quad 3$$

$$\log D_{owA} = \log K_{ow} + \log \frac{1}{1 + 10^{pH-pK_a}} \quad 4$$

$$\log D_{owB} = \log K_{ow} + \log \frac{1}{1 + 10^{pKa-pH}} \quad 5$$

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

245 $\log D_{ow}$ was related to K_d using Equation 6 (Lin et al., 2010):

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

246

247 *2.5.2. Variation from theoretical concentration (% VTC)*

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

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

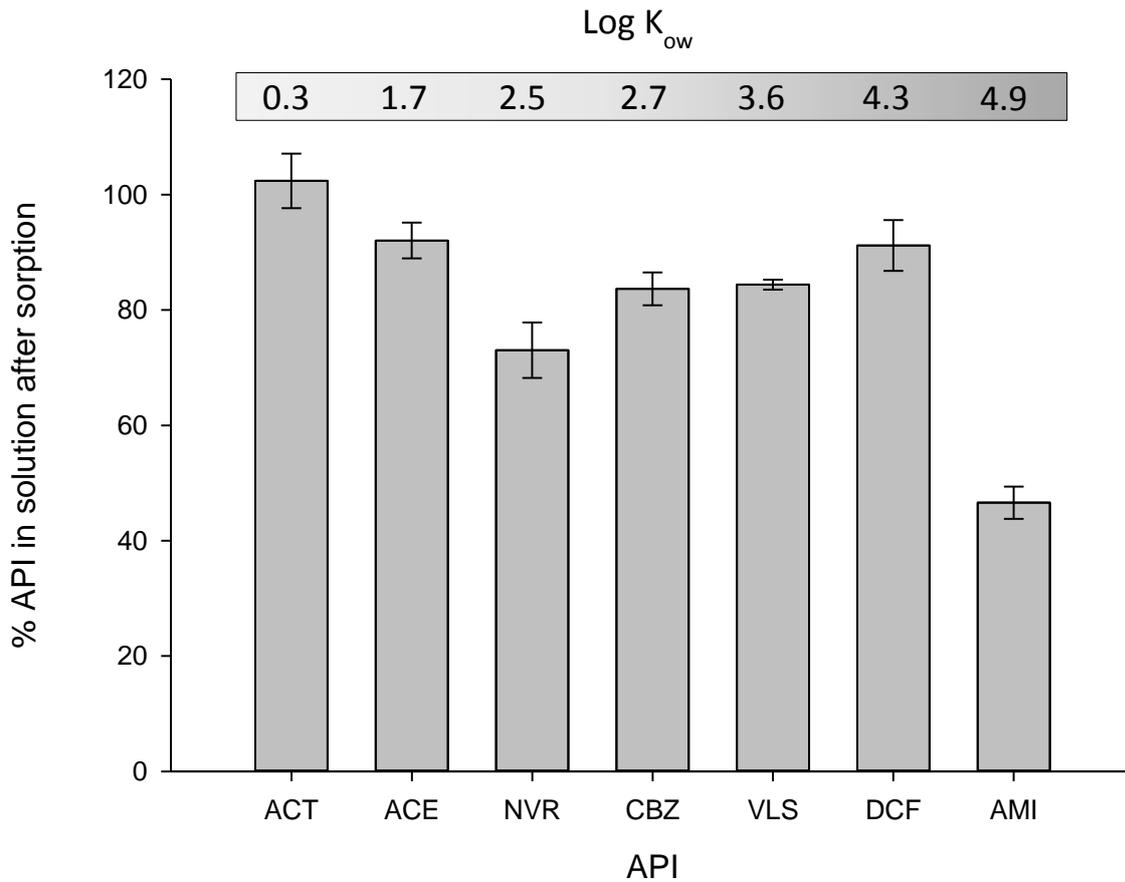
252 Where C_{exp} is the API experimental concentration in water, C_{th} is the API theoretical
 253 concentration in water and C_{DF1} was the API concentration in water at DF 1.

254

255 **3. Results and discussion**

256 **3.1. Sorption**

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



259

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

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

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

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

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

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

276 The low $\log K_{ow}$ (0.3) of the neutral ACT predicts little sorption, which agrees with previously
 277 published studies (Li et al., 2015; Lin et al., 2010; Martínez-Hernández et al., 2014; OECD,
 278 1997). The neutral CBZ and NVR, $\log K_{ow}$ of 2.7 and 2.5 respectively, show a similar sorption
 279 trend. Sorption was greatest for AMI, consistent with its high lipophilicity ($\log K_{ow}$ 4.9) and
 280 the influence of the positive charge. In fact, the lipophilic interactions are reported to be
 281 most important, whilst the charge on the ionised functional group exercises a secondary
 282 control on the distribution processes (Franco and Trapp, 2008; Githinji et al., 2011;
 283 Martínez-Hernández et al., 2014; Silva et al., 2011). The low sorption of ACE was supported
 284 by its $\log K_{ow}$ (1.7), which confirmed the secondary impact of the positive charge in
 285 determining the sorption behaviour. DCF and VLS, however, adsorbed less strongly than
 286 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 $K_{d \text{ exp.}}$ 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^{-1})
306 (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 $0.5 - 1.0 \text{ L kg}^{-1}$) 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^{-1}

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 $\log K_{d \text{ exp.}} = 2.13 \text{ L kg}^{-1}$ 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

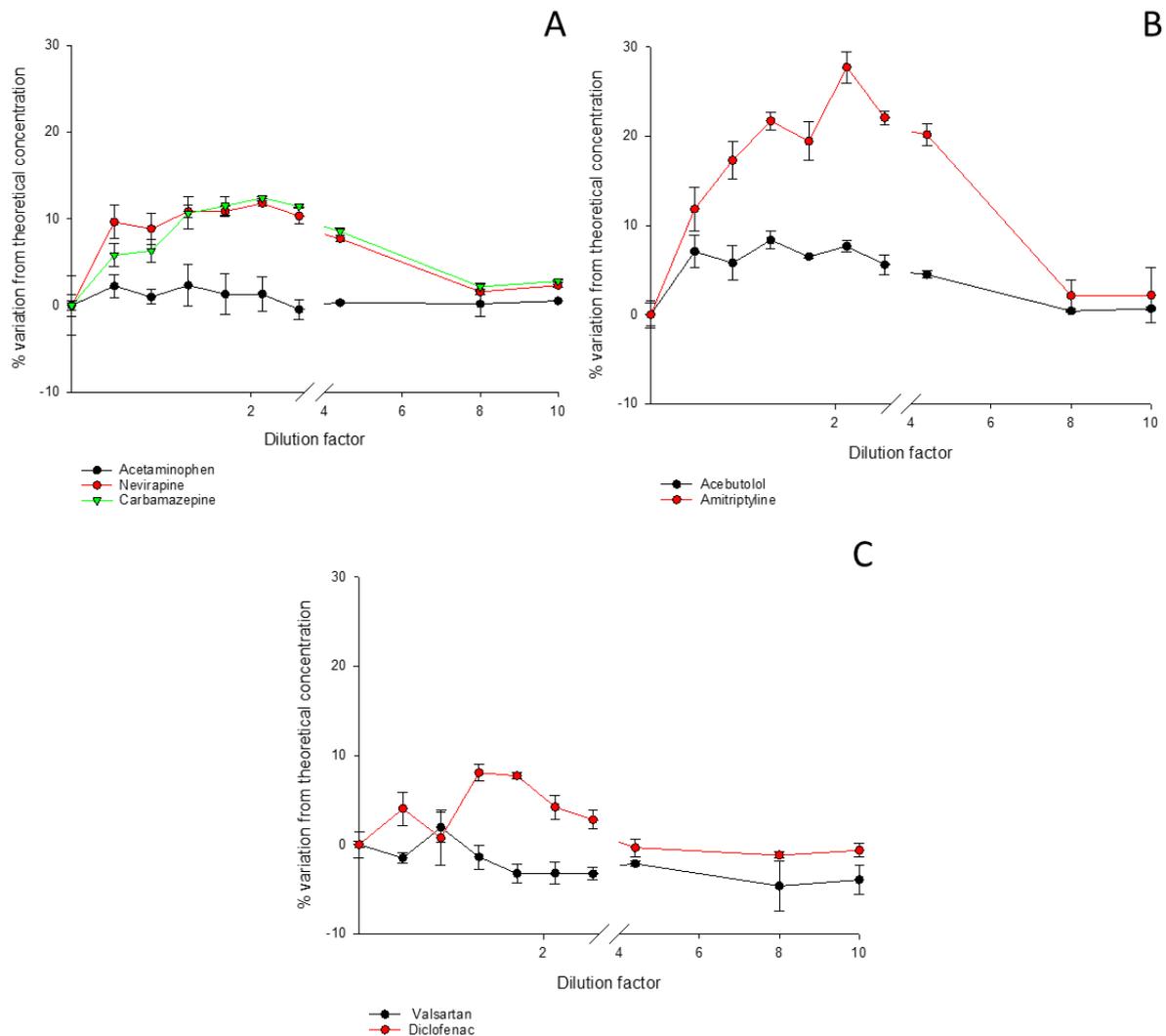
319 The variation in concentration of the dissolved APIs with dilution is shown in Figure 3.
320 Desorption is expressed as the percentage variation from the theoretical concentration
321 (%VTC) against DF. The extent of the deviation, as a dilution effect, varied between
322 compounds, determined by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

333 wastewater sorbents. As such, ACT behaved conservatively at each DF. The neutral
334 compounds NVR and CBZ show a similar trend of deviation from predicted concentration
335 (+10 %VTC at DF2). The two APIs were both neutral at the experimental pH and their log K_{ow}
336 values are similar (2.50 and 2.67 L Kg⁻¹, respectively), which explains the similar trend, and
337 highlights the role of lipophilicity in controlling the sorption of APIs to and from the
338 wastewater sorbents. CBZ and NVR have similar molecular structures that could be the
339 cause of the notable persistence of the former (Andreozzi et al., 2004), and, if true also for
340 the latter, would help explain the ubiquitous presence of NVR in impact zones (K'oreje et al.,
341 2016, 2012; Ngumba et al., 2016).

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



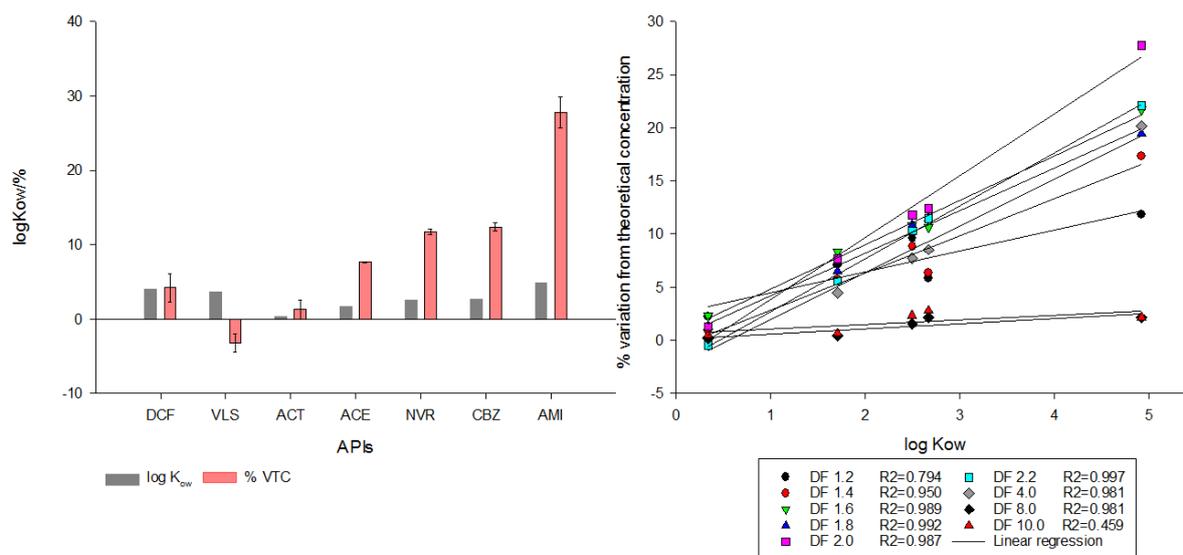
347

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

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

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

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



367
368 **Figure 4** [A] The relationships between the $\log K_{ow}$ of neutral and positively charged
369 APIs on the right of the black line at the percentage of variation from
370 theoretical concentration (%VTC) of 2, and the lack of relationship of the acidic
371 compounds, on left side. [B] The correlation of the neutral and positively
372 charged compounds versus dilution.

373 3.3. Modelled versus experimental K_d

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

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

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

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

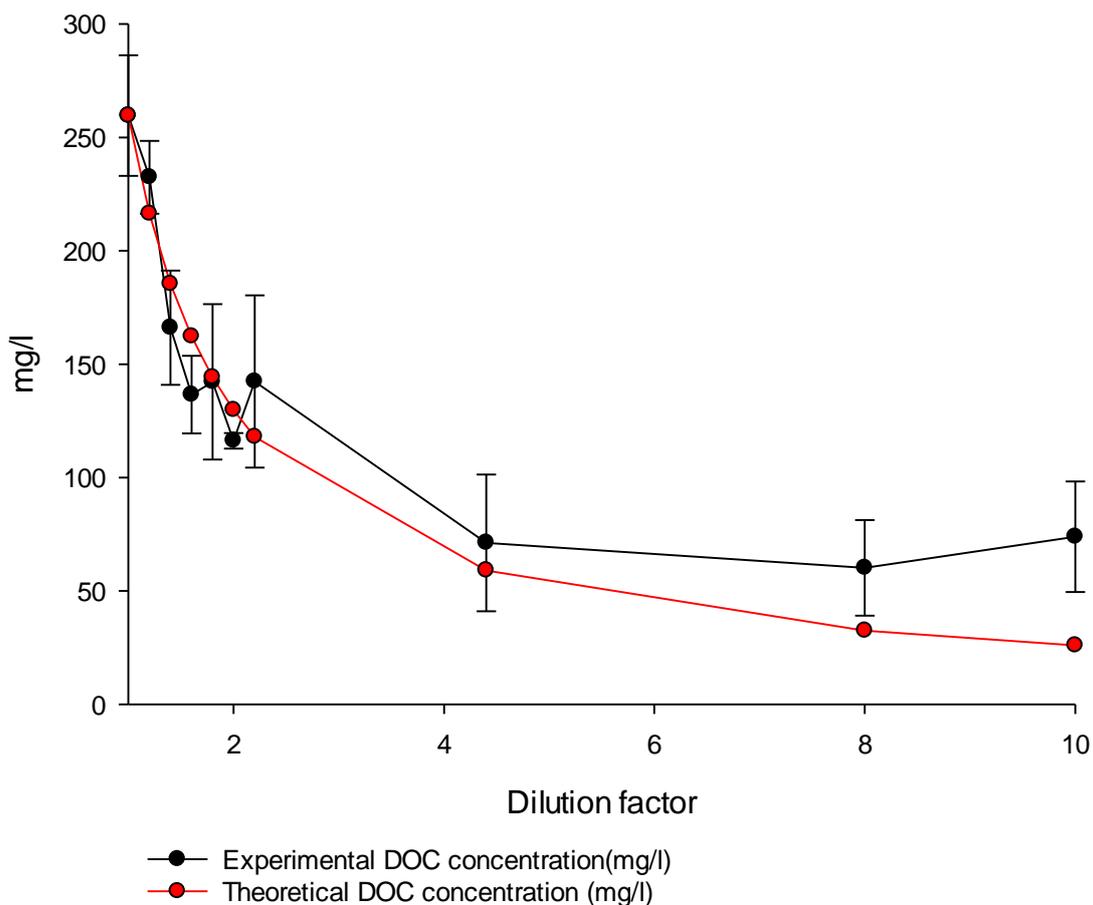
Log $K_{d \text{ [L/kg]}}$	DF	ACT	ACE	NVR	CBZ	VLS	DCF	AMI
Log $K_{d \text{ mod.}}$	/	0.40	1.42	2.00	2.13	2.85	3.15	3.79
Log $K_{d \text{ lit.}}$	/	-0.3 - 2.4	0.5 - 3.3	n. a.	-1.5 - 6.7	n. a.	0.9 - 6.9	0.9 - 2.4
Log $K_{d \text{ exp.}}$	1.0	-1.70	2.27	2.90	2.62	2.60	2.32	3.39
	1.2	-2.12	0.48	2.78	2.49	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

393 n. a.: not available

394 A general increase of $\log K_{d \text{ mod.}}$ occurred at DF 8 and 10 for all APIs, especially NVR, CBZ, VLS and
 395 AMI, where this was up to one order of magnitude (Table 2). These increases were related
 396 with increased concentration of dissolved organic carbon (DOC) at the DF of 8 and 10, as

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

404



405

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

409

410 3.4. Implication of API desorption within the impact zone for ERA

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

422 Equation 1 may not be applicable to discharges of poorly or untreated wastewater where
423 wastewater treatment is limited or does not occur. In fact, as from the obtained evidence,
424 highly lipophilic neutral or positively charged APIs desorb more readily with dilution (Figure
425 4), and omitting desorption could lead to potential underestimation of APIs PEC. Municipal
426 and industrial wastewater are considered the primary source of APIs to the environment,
427 while poor or absent wastewater treatment is widespread globally (Malik et al., 2015). This
428 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

460 **5. Funding**

461 This work was supported by AstraZeneca UK, Global Safety, Health and Environment,
462 Macclesfield, UK and Biogeochemistry Research Centre, School of Geography, Earth and
463 Environmental Sciences, University of Plymouth, Plymouth, PL4 8AA, UK

464 **6. Supporting information**

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

471

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