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## **Active Pharmaceutical Ingredients Entering the Aquatic Environment From Wastewater Treatment Works: A Cause for Concern?**

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### **Abstract**

This work reports on the variation in wastewater treatment works (WwTW) influent concentrations of a wide variety of active pharmaceutical ingredients (APIs), their removal efficiency, effluent concentrations and potential risks to the aquatic environment. The research is based on data generated from two large UK-wide WwTW monitoring programmes. Taking account of removal of parent compound from the aqueous phase during treatment in combination with estimates of dilution available it is possible to prioritise the APIs of greatest risk of exceeding estimates of predicted no effect concentrations (PNEC) in receiving waters for all WwTW in the UK. The majority of substances studied were removed to a high degree, although with significant variation, both within and between WwTW. Poorer removal (between influent and effluent) was observed for ethinyloestradiol, diclofenac, propranolol, the macrolide antibiotics, fluoxetine, tamoxifen and carbamazepine. All except the last two of these substances were present in effluents at concentrations higher than their respective estimated PNEC (based on measurement of effluents from 45 WwTW on 20 occasions). Based on available dilution data as many as 890 WwTW in the UK (approximately 13% of all WwTW) may cause exceedances of estimated riverine PNECs after mixing of their effluents with receiving waters. The overall degree of risk is driven by the toxicity value selected, which in itself is controlled by the availability of reliable and relevant ecotoxicological data and

37 consequently the safety factors applied. The dataset and discussion, provides information to assist in  
38 the future management of these types of chemicals.

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40 **Key words: pharmaceuticals, API, wastewater, effluent, fate, risk assessment**

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## 45 **1. INTRODUCTION**

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47 The use and environmental prevalence of pharmaceuticals increases on an annual basis due to a  
48 variety of reasons including the widening array of medical treatments available, greater availability of  
49 medicines across the world, affordability, population growth, population ageing (in some countries)  
50 and changing perspectives towards, for example, pain (Jelic et al., 2011). Active Pharmaceutical  
51 Ingredients (API) are detected throughout the environment in water, soil, sediment, sludge as well as  
52 in drinking waters in some countries (Kasprzyk-Hordern et al., 2008; Zorita et al., 2009; Wahlberg et al.,  
53 2011; Jones et al., 2014; Lees et al., 2016). Although the mere presence of pharmaceutical is not  
54 always associated with harm to the environment or human health, concerns are rising associated with  
55 antimicrobial resistance and chronic impacts on biodiversity including endocrine disrupting effects on  
56 fish (Levado et al., 2004; Jobling et al., 2005; Tyler et al., 2008). The main source of occurrence of  
57 APIs in the river environment is from human use of pharmaceuticals, via the continuous discharge of  
58 effluent from the Wastewater Treatment Works (WwTW) (Gardner et al., 2012; Melvin et al., 2016).  
59 Hence, investigating the occurrence, fate and risk of APIs is currently of great interest to regulators  
60 and the water industry alike, with a focus to better understand the loadings entering WwTW and the  
61 observed within and between works variation in removal efficiencies and concentrations often  
62 observed for APIs (Gardner, 2013).

63

64 The range of concentrations found for pharmaceuticals studied in the UK is similar to that observed in  
65 continental Europe as well as in the USA (Kolpin et al., 2002; Ashton et al., 2004; Hope et al., 2012;  
66 Bradley et al., 2016; Burns et al., 2017). Table 1 provides examples of other reported data for APIs  
67 determined as part of this research, rather than a complete list of all APIs detected in effluent and  
68 receiving waters. Other studies have also shown that there is a clear association between the number  
69 of pharmaceuticals used in a society and the levels of API found in receiving water bodies ranging  
70 from API concentration of typically less than 100 ng/l in the surface and groundwater and below 50  
71 ng/l in treated drinking water (WHO, 2011; Furlong et al., 2017) to higher levels reported adjacent to  
72 production facilities (Phillips et al., 2010). Predicted no effect concentrations (PNECs) have been  
73 reported for some APIs below 1 ng/l and APIs such as diclofenac (CAS 15307-79-6), 17-beta-

74 estradiol (E2) (CAS 50-28-2) and 17-alpha-ethinylestradiol (EE2) (CAS 57-63-6) are on the European  
75 Water Framework Directive (WFD) 'watch list' (EU, 2013). This requires member states to gather  
76 monitoring data in order to assess risk to the environment, leading to significant sources of APIs  
77 needing to be quantified and factors controlling the discharge of APIs carefully considered along with  
78 impacts on receiving water ecology, including effects of mixtures (Bound and Voulvoulis, 2006).  
79

80 **Table 1. Average aquatic concentrations for APIs of interest to this research found in river**  
 81 **water, as well as usage, excretion and removal in WwTW.**

82

API	Therapeutic Class	Upstream (µg/l)	Influent (µg/l)	Effluent (µg/l)	WwTW removal (%)	Down stream (µg/l)	UK consumption (ton/year), 2009 and 2011	Excreted unchanged compound (%)
<b>Aspirin (acetylsalicylic acid)</b>	Anti-inflammatory/analgesics	NA	NA	NA	NA	<0.0005 <sup>b</sup>	130 <sup>d</sup>	<1 <sup>b</sup>
<b>Atenolol</b>	Beta blocker	NA	NA	NA	NA	0-0.56 <sup>b</sup>	28 <sup>e</sup>	90 <sup>f</sup>
<b>Azithromycin</b>	Antibiotic	NA	0.163 <sup>l</sup>	0.030 <sup>l</sup>	90 <sup>l</sup>	NA	NA	NA
<b>Carbamazepine</b>	Antiepileptic	NA	2.593 <sup>b</sup>	3.117 <sup>b</sup>	ND <sup>b</sup>	0.0005-0.356 <sup>b</sup>	48 <sup>e</sup>	3 <sup>b</sup>
<b>Ciprofloxacin</b>	Antibiotic	NA	1.090 <sup>l</sup>	0.052 <sup>l</sup>	97 <sup>l</sup>	NA	NA	NA
<b>Clarithromycin</b>	Antibiotic	NA	0.524 <sup>l</sup>	0.092 <sup>l</sup>	91 <sup>l</sup>	NA	NA	NA
<b>Diclofenac</b>	Anti-inflammatory	<0.020 <sup>a</sup>	0.107-0.981 <sup>c</sup>	0.599 <sup>a</sup>	70-92 <sup>c</sup>	0.154 <sup>a</sup>	28 <sup>e</sup>	15 <sup>f</sup>
<b>Erythromycin</b>	Antibiotic	<0.010 <sup>a</sup>	2.0 <sup>k</sup>	0.109 <sup>a</sup>	25-91 <sup>l</sup>	0.159 <sup>a</sup>	3 <sup>d</sup>	25 <sup>f</sup>
<b>Oestrogen (E1)</b>	Natural hormone	NA	0.042 <sup>g</sup>	0.011-0.025 <sup>g</sup>	58-96 <sup>g</sup>	NA	NA	NA
<b>Oestradiol (E2)</b>	Contraceptive	NA	0.016 <sup>g</sup>	0.0013-0.0039 <sup>g</sup>	89-96 <sup>g</sup>	NA	NA	NA
<b>Ethinylestradiol (EE2)</b>	Contraceptive	NA	0.0017 <sup>g</sup>	0.00033-0.00078 <sup>g</sup>	53-71 <sup>g</sup>	NA	NA	NA
<b>Fluoxetine</b>	Psychiatric drugs	NA	0.070 <sup>k</sup>	0.023 <sup>j</sup>	33-100 <sup>h</sup>	NA	6.4 <sup>m</sup>	NA
<b>Ibuprofen</b>	Analgesic	0.432 <sup>a</sup>	14.0 <sup>k</sup>	4.201 <sup>a</sup>	90-100 <sup>l</sup>	1.105 <sup>a</sup>	258 <sup>e</sup>	10 <sup>f</sup>
<b>Oxytetracycline</b>	Antibiotic	NA	1.09 <sup>l</sup>	0.029 <sup>l</sup>	99 <sup>l</sup>	NA	NA	NA
<b>Ofloxacin</b>	Antibiotic	NA	0.081 <sup>l</sup>	0.023 <sup>l</sup>	89 <sup>l</sup>	NA	NA	NA
<b>Propranolol</b>	Antihypertensive	0.010 <sup>a</sup>	0.542 <sup>b</sup>	0.093 <sup>a</sup> 0.388 <sup>b</sup>	28 <sup>b</sup>	0.041 <sup>a</sup>	15 <sup>e</sup>	<0.5 <sup>b</sup>
<b>Tamoxifen</b>	Anti-cancer	<0.010 <sup>a</sup>	0.0002-0.015 <sup>c</sup>	<0.010 <sup>a</sup>	32-45 <sup>c</sup>	<0.010 <sup>a</sup>	NA	NA

83

84 ND = not detected; NA = not available. <sup>a</sup>Ashton et al., 2006; <sup>b</sup>[Kasprzyk-Hordern et al., 2008](#); <sup>c</sup>Zhou et al., 2009;  
 85 <sup>d</sup>2006 sales data for Wales; [Kasprzyk-Hordern et al., 2008](#); <sup>e</sup>IMS figure on active ingredient sales; <sup>f</sup>WHO, 2011;  
 86 <sup>g</sup>Heffley et al., 2014; <sup>h</sup>Clara et al., 2005; <sup>i</sup>Li et al., 2014; <sup>j</sup>Gardner et al., 2012; <sup>k</sup>Gardner et al., 2013; <sup>l</sup>Singer et  
 87 al., 2014; <sup>m</sup>Boxall et al., 2014

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89 Many countries have therefore started monitoring programs to investigate the exposure of APIs in  
 90 order to gain a better understanding of their sources, fate and risk (Falås et al., 2012). The Chemical  
 91 Investigation Program (CIP) in the UK is a large ongoing investment being undertaken by the water  
 92 industry to assist the UK in meeting its obligations under the WFD to monitor concentrations of  
 93 priority chemicals including APIs in WwTW influent, intermediate processes and effluent as well as  
 94 assessing their risk to receiving waters (Gardner et al., 2013). The first phase of the CIP (named CIP1  
 95 here) was a project that ran from 2012-2015 with one of its aims to investigate the fate of trace  
 96 substances (including 11 APIs) in influent, effluent and intermediate WwTW processes of 25 WwTW.  
 97 Some of results from this program have been reported previously (Gardner et al., 2012, Gardner et al.;  
 98 2013, Jones et al.; 2013 and Comber et al., 2014). The £140 million investment in the second phase of  
 99 the CIP (labelled CIP2 in this work) program builds on the outputs from CIP1 but extends the range  
 100 of WwTW monitored and the number of determinands in order to in some cases measure (for WFD  
 101 priority substances and priority hazardous substances) and in some cases predict (for emerging

102 chemicals such as APIs) the impact on receiving waters. The CIP2 determinands include 19 APIs and  
103 4 metabolites at currently 45 WwTW on 20 occasions. In total, over 60 000 samples are to be taken,  
104 with over 2 million determinations. This study reports on the findings for APIs from the CIP1 and  
105 CIP2 programmes.

106

107 WwTWs are primarily designed to serve the purpose of removing pathogens, suspended solids and  
108 gross organic and inorganic matter, rather than the removal of the increasing numbers of modern  
109 chemicals generally present in the  $\mu\text{g/l}$  range or less (Melvin, 2016). It has also been observed that  
110 there is a wide variation in removal rates for different substances, both within and between WwTWs.  
111 This difference in removal rate creates large uncertainty factors for the prediction and modeling of  
112 effluent concentrations and therefore creates a challenge in conducting meaningful risk assessments.  
113 There are currently no statutory consents applied to APIs in WwTW effluent, however, there is an  
114 urgent need to better understand the risk posed by APIs in effluents to receiving waters in order to  
115 inform future investment and to design and implement better risk assessment (Gardner, 2013). The  
116 presence of APIs is not measured on a routine basis for most WwTWs owing to cost and lack of  
117 legislative drivers. Consequently, there are a number of previous studies modelling the impact of APIs  
118 based on consumption, WwTW removal and dilution but the cost of analysis generally prevents the  
119 actual measurement of APIs in effluent (Johnson et al., 2013a,b; 2015).

120

121 This study utilizes CIP 1 (11 APIs, from 25 WwTW sampled on up to 15 occasions) and the more  
122 recent CIP2 program (19 parent APIs and 4 metabolites, from WwTW sampled on 20 occasions).  
123 Although the APIs studied represent only a fraction of the total APIs in use, financial and practical  
124 constraints associated with sampling, preservation, analysis and replication meant the number of  
125 determinands needed to be controlled. However, APIs were prioritised on potential risk to the aquatic  
126 environment and all of the main classes of API have been represented (Table A1). Concentrations in  
127 the WwTW effluent have been compared with derived PNECs in receiving waters in order to generate  
128 a priority list of APIs of potential concern.

129

## 130 **2. MATERIALS AND METHODS**

### 131 **2.1 Selection of Pharmaceuticals**

132 The selection of chemicals for CIP1 is discussed elsewhere (Gardner et al., 2012). The list of  
133 candidate APIs for inclusion in CIP2 was based primarily on a prioritization study undertaken by  
134 UKWIR in 2014 (UKWIR, 2014). Unlike many previous prioritisations, which focused on usage and  
135 concentrations detected in surface waters/effluents, problem sites or substances, this study adopted a  
136 risk assessment approach by comparing the estimated environmental concentrations of nearly 150  
137 pharmaceuticals (screened on usage and perceived hazard from a list of thousands of candidate

138 substances) with data for their respective effect concentrations on a variety of receptor organisms in  
139 the aquatic environment.

140

141 For the purposes of CIP2, this list was further refined by selection of substances that were considered  
142 to have the greatest potential as candidate WFD priority substances. The criteria for this selection  
143 were a) that the risk characterisation ratio (predicted concentration divided by the highest probable no  
144 effect concentration (PEC/PNEC) ranked higher than 1 in the overall 2014 UKWIR prioritisation and  
145 b) that the data supporting the derivation of a PNEC were relatively reliable and complied with the  
146 WFD approach to PNEC derivation (EU 2011). In effect, this meant that PNECs were derived using  
147 experimental rather than modelled effects, long-term effects in organisms from different trophic levels  
148 were available (though short term exposure was also considered) and assessment factors were applied  
149 according to WFD guidance (EU 2011).

150

151 The APIs prioritised were then further reviewed for their relevance to wastewater treatment, and the  
152 likelihood that the substance might be present in sewage effluents and hence discharged to surface  
153 waters (rather than being partitioned to sewage sludge). This resulted in the list of substances  
154 tabulated in Table A1 of the Electronic Supplementary Information (ESI). For the purposes of  
155 estimating risks, the PNEC values derived in the UKWIR prioritization (UKWIR 2014) were then re-  
156 examined and (where available) they were substituted with the latest estimates derived by the EU  
157 Joint Research Centre (JRC, 2015), by the pharmaceutical industry (Astra Zeneca, 2016; NSF, 2016)  
158 or published in the open literature (Murray-Smith et al., 2012). Where no PNEC was available from  
159 these sources, the ecotoxicology data applied in deriving the PNECs reported by UKWIR (UKWIR  
160 2014) were used to deterministically estimate PNECs, according to WFD guidance (EU 2011) (Table  
161 2 and ESI Table A1). It is recognized that as new ecotoxicity data becomes available, substance  
162 PNECs are subject to update, and the estimates of PNECs applied in the present study may not, in  
163 every case, reflect the most up to date applied or proposed PNEC for regulatory purposes (e.g. under  
164 the WFD or European Medicines Agency (EMA) Environmental Risk Assessments. However, the  
165 estimated PNECs reported here were applied in the CIP for the purposes of selection for monitoring,  
166 preliminary risk assessment and prioritization, and so remain relevant in this context, and it is beyond  
167 the objectives of the present study to derive new PNECs for each of the APIs monitored.

168

## 169 **2.2 Sampling programme**

170

171 WwTWs were selected for the CIP program on the basis of broadly representing the distribution of  
172 UK WwTWs (A1, ESI), predominantly activated sludge plants (ASP) and trickling biofilters (TF) but  
173 also Membrane bioreactors (MBR) and oxidation ditches (OD) (Table A2 of ESI).

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Data used for this research were (Table A2 of ESI):

- **CIP1 program:** 25 WwTW data for primary, secondary and tertiary process for 11 APIs. Sampling for this element of the programme was conducted over a two-year period between 2011 and 2013. In this part of the programme two samples (spaced more than 4h apart to provide a degree of replication) were taken on between 10 and 15 occasions.
- **CIP2 program:** 19 APIs and 4 metabolites were sampled on 20 occasions at 45 WwTWs in the influent and effluent (not intermediate process stages, unlike CIP1) over a two-year period between 2015 and 2017.

Samples were collected on a stratified/random spot sampling basis (i.e. grab samples taken at discrete times rather than multiple integrated sampling), with sampling occasion spaced at approximately monthly intervals. A minimum of 15% of samples was taken at non-working hours (evenings and weekends) to ensure a wide a range possible of sampling intervals.

### 2.3 Sampling and analysis

The samples were collected in stainless steel samplers, stored in glass container and transported at 4° C to the analysis laboratories. The samples were stored a maximum of 5 days prior to analysis. This period was shown to be appropriate as not leading to more than a 20% change in determinand concentration; as confirmed before the start of the CIP sampling programme by undertaking tests of sample stability. Samples for the determination of steroid oestrogens were preserved by adding 30% hydrochloric acid and copper nitrate (Gardner, 2012). All analysis was by laboratories with ISO17025 accreditation. Prior to the programme candidate laboratories were required to undertake tests of analytical performance to demonstrate that they met the stated programme requirements for limit of detection, precision and recovery in relevant sample matrices at relevant concentrations – that is, proof of performance was required, rather than methods being stipulated. Methods used for the determination of pharmaceuticals were all based on variants of High Performance Liquid Chromatograph–Mass Spectrometry (HPLC-MS) or Gas Chromatography-Mass Spectrometry (GC-MS). Quality assurance/quality control (QA/QC) procedures, including the use of field blanks, were observed and reported for sample collection. Within laboratory QC sample pre-treatment and analysis for both laboratory tests and field sampling. Laboratories also took part in a bespoke proficiency testing scheme for pharmaceuticals. Details of the proficiency testing scheme used to ensure quality assurance is provided in A2 of the ESI. Where reported concentrations were below LOD (for the majority of substances apart from ibuprofen and tamoxifen this applied to fewer than 10% of the approximately 1000 results reported), the result was substituted at half face value - as stipulated in the



210 relevant daughter Directive (EC, 2009) of the WFD. There were significant instances of inter-  
 211 laboratory bias or inter-regional variation, which would otherwise indicate if there was a bias in the  
 212 procedure of sample handling and analysis methodology.

213

214

215 **Table 2. Determinand abbreviations and required limits of detection and total error**

Code	Determinand	Concentration (µg/l)			P% <sup>2</sup>
		PNEC <sup>1</sup>	Required LOD effluent	Required LOD river	
ATNL	Atenolol	148	0.01	0.01	50
ATOV	Atorvastatin	1.7	0.01	0.01	50
ATOV <sub>o</sub>	Ortho-hydroxy-atorvastatin	1.7	0.01	0.01	50
ATOV <sub>p</sub>	Para-hydroxy-atorvastatin	1.7	0.01	0.01	50
AZMY	Azithromycin	0.09	0.005	0.005	50
CBAZ	carbamazepine	2.5	0.1	0.1	50
CBAZe	10,11- epoxy-carbamazepine	2.5	0.1	0.1	50
CIPR	Ciprofloxacin	0.089	0.01	0.01	50
CLMY	Clarithromycin	0.13	0.01	0.01	50
DCF	Diclofenac	0.05	0.01	0.01	50
ERMY	Erythromycin	0.2	0.1	0.1	50
ERMY <sub>n</sub>	Norerythromycin	0.2	0.1	0.1	50
E1	Oestrone	0.003	0.001	0.001	50
E2	17β oestradiol	0.001	0.0003	0.0003	50
EE2	17α ethinyloestradiol	0.0001	0.00003	0.00003	50
FLXT	Fluoxetine	0.047	0.01	0.01	50
IBPF	Ibuprofen	0.01	0.01	0.01	50
METF	Metformin	13.45	0.1	0.1	50
PRPL	Propranolol	0.1	0.01	0.01	50
RNTD	Ranitidine	0.31	0.1	0.1	50
SERT	Sertraline	0.121	0.01	0.01	50
SERT <sub>n</sub>	Norsertaline	0.121	0.01	0.01	50
TMXF	Tamoxifen	0.49	0.005	0.005	50

216 <sup>1</sup> Estimated PNEC (ESI Table 1). <sup>2</sup>The target maximum tolerable error is equal to:

$$217 \left[ (targetLOD)^2 + \left( \frac{A \times P\%}{100} \right)^2 \right]^{\frac{1}{2}}$$

218

219 Where the target maximum LOD and P% are given in the table and A is the determinand concentration in the  
 220 sample. Performance testing should seek to demonstrate that the tolerable total error limit is achieved by  
 221 showing that precision (2 x standard deviation) and bias are respectively no larger than half the target maximum  
 222 total error. Thus, for example, for a total error limit of 100 units, standard deviation should be shown not to be  
 223 larger than 25 and bias should not exceed 50. LOD was defined as 3.3x the standard deviation of blank-  
 224 corrected results of determinations made on a sample containing essentially no determinand (where possible in a  
 225 relevant sample matrix) (Thompson and Ellison, 2013) In many cases, it was not possible to find effluent  
 226 samples free from determinands in which case a synthetic sample was used.)

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## 228 2.4 Data handling and analysis

229 The data handling and the statistical analysis were conducted with either Microsoft Excel (2016) or

230 IBM SPSS Statistics software (version 20).

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In the data handling, the replicates were averaged and this value was then used for further statistical calculations. Mean, median, maximum, minimum and percentiles were calculated from the daily average. Fraction remain was calculated from the influent concentration as a fraction of the various stages of the process. The removal was calculated as percentage from the concentration (C):

$$\text{Removal (\%)} = (C_{\text{influent}} - C_{\text{effluent}}) / C_{\text{influent}}$$

For the purpose of this research the term ‘removal’ relates to the loss of specified compounds from the aqueous phase between influent and effluent (and intervening process steps where quoted). It should be noted that the term removal does not necessarily mean degradation of the API; the loss of the parent compound may be a result of a combination of partitioning to particulates and/or degradation to metabolites.

## **2.5 Risk assessment approach**

### **2.5.1 Face value risk ranking**

A “face value” exceedance is one in which the mean effluent concentration is greater than the relevant estimated PNEC; a “high confidence” exceedance is one for which the lower part of the 90% confidence interval about the mean effluent concentration is greater than the estimated PNEC i.e. there is 95% confidence that the mean is larger than the estimated PNEC.

### **2.5.2 Refined risk assessment based on estimated available dilution**

Previous research has used a combination of modelled average river flows (Comber et al., 2013) and average WwTW discharge volumes to estimate dilution of effluent with receiving water. Effluent flow data was derived from measured values for larger WwTW, but estimated for works serving less than 2000 population equivalent based on water company estimates of connected population and per capita wastewater discharge to sewer (200 l/head/day- including an allowance for runoff) (Comber et al., 2007). A matrix (Table 3) of available dilution was then generated.

261 **Table 3. Estimated dilutions available for UK WwTW**

262

	Dilution ratio band									Total no. works
	0-1	1-2	2-5	5-10	10-15	15-20	20-50	50-100	100+	
Midpoint dilution	1	1.5	3.5	7.5	12.5	17.5	35	75	100	
Combined dist' dil' <sup>1</sup>	0 <sup>2</sup>	4.4	10.6	23.6	36.5	35	70	150	200	
<b>Population served</b>										
<250	86	75	54	54	11	21	86	86	2656	3127
251-500	0	6	0	6	25	0	50	81	605	774
501-2000	0	5	20	20	51	46	351	285	544	1322
2001-10000	17	25	151	160	130	84	202	93	130	993
10001-50000	82	67	160	103	24	30	48	15	18	548
50001-200000	54	29	27	12	5	12	20	5	0	164
200001-1m	74	0	11	0	0	0	0	0	0	85
>1m	4	4	0	0	0	0	0	0	0	7
<b>Total</b>	<b>316</b>	<b>211</b>	<b>423</b>	<b>355</b>	<b>246</b>	<b>194</b>	<b>756</b>	<b>564</b>	<b>3954</b>	<b>7020</b>
<b>%</b>	<b>5</b>	<b>3</b>	<b>6</b>	<b>5</b>	<b>4</b>	<b>3</b>	<b>11</b>	<b>8</b>	<b>56</b>	

263 <sup>1</sup> Values used to calculate PECs in river using a Combined Distribution simulation (see A3 and Table  
 264 A3). <sup>2</sup> A worst case scenario of zero dilution.

265

266 The next step was to generate a cumulative percentile distribution of effluent concentration data (in  
 267 10%ile intervals between 10 and 100%). This was achieved by averaging the effluent concentrations  
 268 for each of the 45 WwTW sampled as part of the CIP2 survey. Step three was to divide each  
 269 percentile concentration by the dilution available (using the value from the combined distribution  
 270 estimate – See A3 of the ESI) to generate a PEC. The PEC can then be compared with estimated API  
 271 PNECs to determine the number of WwTW at risk of exceeding the PNEC for any given each dilution  
 272 band and percentile effluent concentration. An example of the risk assessment is provided in Table  
 273 A4 of the ESI.

274

### 275 **3. RESULTS and DISCUSSION**

276

#### 277 **3.1 Removal efficiency for APIs**

278

279 The CIP1 study generated removal data for APIs across all stages of treatment, influent, after primary  
 280 settlement, secondary biological treatment and where applied, post tertiary treatment. To gain a better  
 281 understand of the fate of the 11 pharmaceuticals through the treatment train, the fraction of API  
 282 remaining in the effluent after treatment was calculated across all 25 WwTW in the CIP1 program  
 283 (Table 4).

284

285 Each cycle of sampling was treated as an isolated entity (averaging the samples within the same day),  
 286 thus simplify the ability to compare APIs removal across the diverse range of works. As seen from the

287 data in Table 4, most APIs are removed in the secondary biological treatment process and very little  
 288 through further tertiary treatment. This corresponds well with previously published data (Stockholm  
 289 Vatten, 2010). The absolute effluent concentrations (Table 4) also correspond well with those reported  
 290 elsewhere for predominantly UK effluents (Table 1).

291

292 **Table 4. CIP1 data for API fraction remaining throughout the process stages in the WwTW, as**  
 293 **well as the absolute effluent concentration**  
 294

Fraction of API remaining in effluent after treatment												
API	Primary Process			Secondary Process			Tertiary Process			Effluent Concentration (µg/l)		
	Median	5-%ile	95-%ile	Median	5-%ile	95-%ile	Median	5-%ile	95-%ile	Median	5-%ile	95-%ile
Diclofenac (DCF)	0.76	0.40	1.6	0.52	0.18	1.2	0.44	0.16	1.0	0.20	0.084	0.51
Erythromycin (ERMY)	0.79	0.26	1.7	0.52	0.11	1.2	0.44	0.08	1.1	0.43	0.052	2.0
Ethinylestradiol (EE2)	0.96	0.36	2.4	0.54	0.13	1.9	0.49	0.10	3.5	0.0003	0.0001	0.0020
Oestrone (E1)	1.0	0.59	2.1	0.28	0.02	2.4	0.10	0.01	1.2	0.0048	0.0007	0.058
Oestradiol (E2)	0.97	0.44	1.6	0.11	0.01	0.8	0.05	0.01	0.80	0.0009	0.0001	0.012
Fluoxetine (FLXT)	0.79	0.38	1.5	0.48	0.08	1.2	0.46	0.09	1.1	0.032	0.0050	0.066
Ibuprofen (IBPF)	0.83	0.39	1.3	0.04	0.00	0.2	0.01	0.00	0.21	0.19	0.0050	2.9
Ofloxacin (OFLX)	0.88	0.12	2.2	0.45	0.08	1.4	0.34	0.05	1.0	0.016	0.0050	0.14
Oxytetracycline (OXTCY)	0.66	0.13	1.6	0.16	0.00	0.6	0.13	0.01	0.54	0.21	0.019	1.1
Propranolol (PRPL)	0.91	0.52	1.4	0.68	0.14	1.2	0.65	0.16	1.2	0.14	0.042	0.32
Salicylic acid (SLCYA)	0.85	0.28	1.6	0.01	0.00	1.1	0.01	0.00	0.33	0.18	0.017	3.8

295

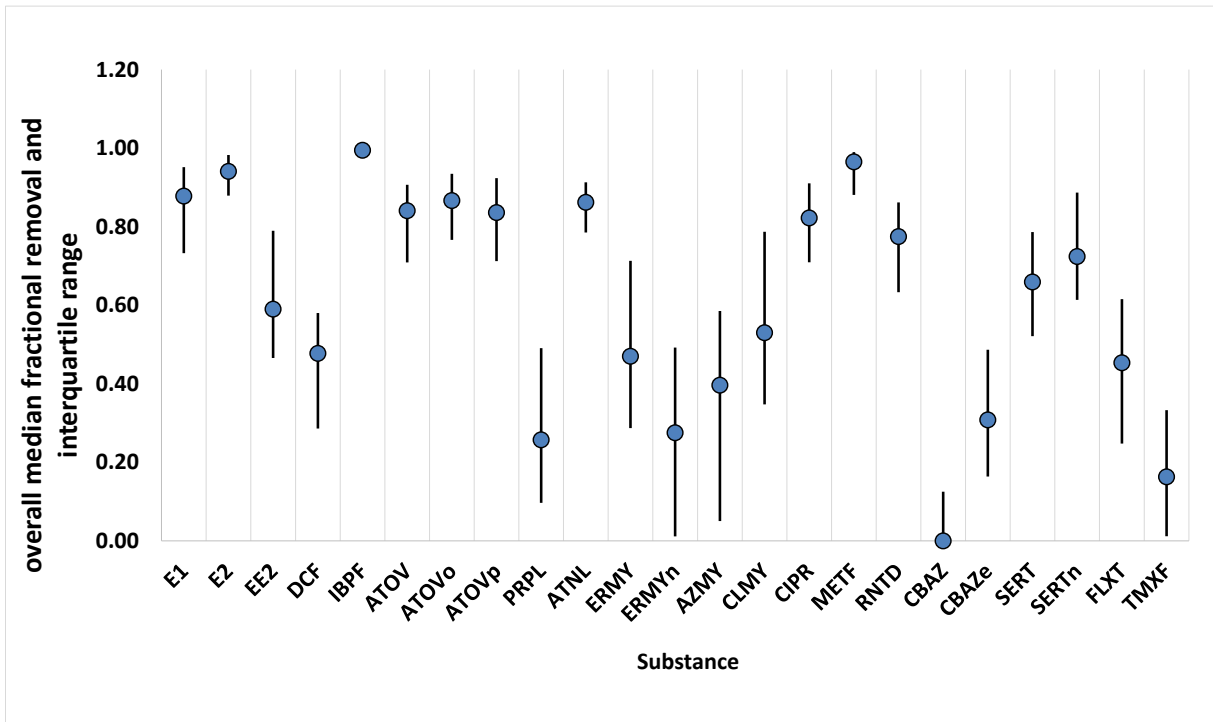
296

297 ERMY, DCF, FLXT and OXTCY were all shown to have similar removal efficiencies throughout the  
 298 primary and secondary treatment processes based on the CIP1 dataset. The primary process relies  
 299 mostly on removal of APIs through adsorption onto sludge (Stockholm Vatten, 2010) as retention  
 300 times are relatively low and so this fits well to the data found for OXTCY, as it is previously known  
 301 to adsorb strongly onto solids (Verlicchi, 2012) and found at higher concentration (4 mg/kg) in sludge  
 302 compared with other APIs such as DCF, ERMY and FLXT (0.07, 0.05 and 0.12 mg/kg, respectively)  
 303 (Jones et al., 2014). PRPL had overall poor removal of 35% and 26% (0.65 and 0.74 fraction  
 304 remaining) between influent and effluent for CIP1 and CIP2 respectively (Table 4 and 5), which also  
 305 corresponded well with previously published data of 28% removal efficacy (0.72 fraction remaining)  
 306 in WwTW (Kasprzyk-Hordern et al., 2008).

307

308 In the CIP2 data set (Table 5) there was high total removal (based on comparison of influent and  
 309 effluent API concentrations) of IBPF, METF, E2, ATNL, ATOV<sub>p</sub>, E1, ATOV, CIPR, ATOV<sub>o</sub>, which  
 310 all had fraction remaining ratios of 0.2 or lower (i.e. better than 80% removal efficiency) (Figure 1,

311 and Table A5). This suggested either rapid biodegradation of the parent compound and/or adsorption  
 312 to sludge. None of the substances are considered sufficiently volatile to suggest any significant loss to  
 313 the atmosphere. The intermediate set of APIs consisting of SERTn, RNTD, CLMY, EE2, FLXT, DCF  
 314 and ERMV, which all had fraction remaining below 0.6 (i.e. greater than 40% removal efficiency).  
 315 PRPL, CBAZe, ERMVn, AZMY and CBAZ all showed poor removal through the WwTW process  
 316 (Figure 1 and Table A5).



317  
 318 **Figure 1. Fractional removal for APIs in CIP2**

319  
 320

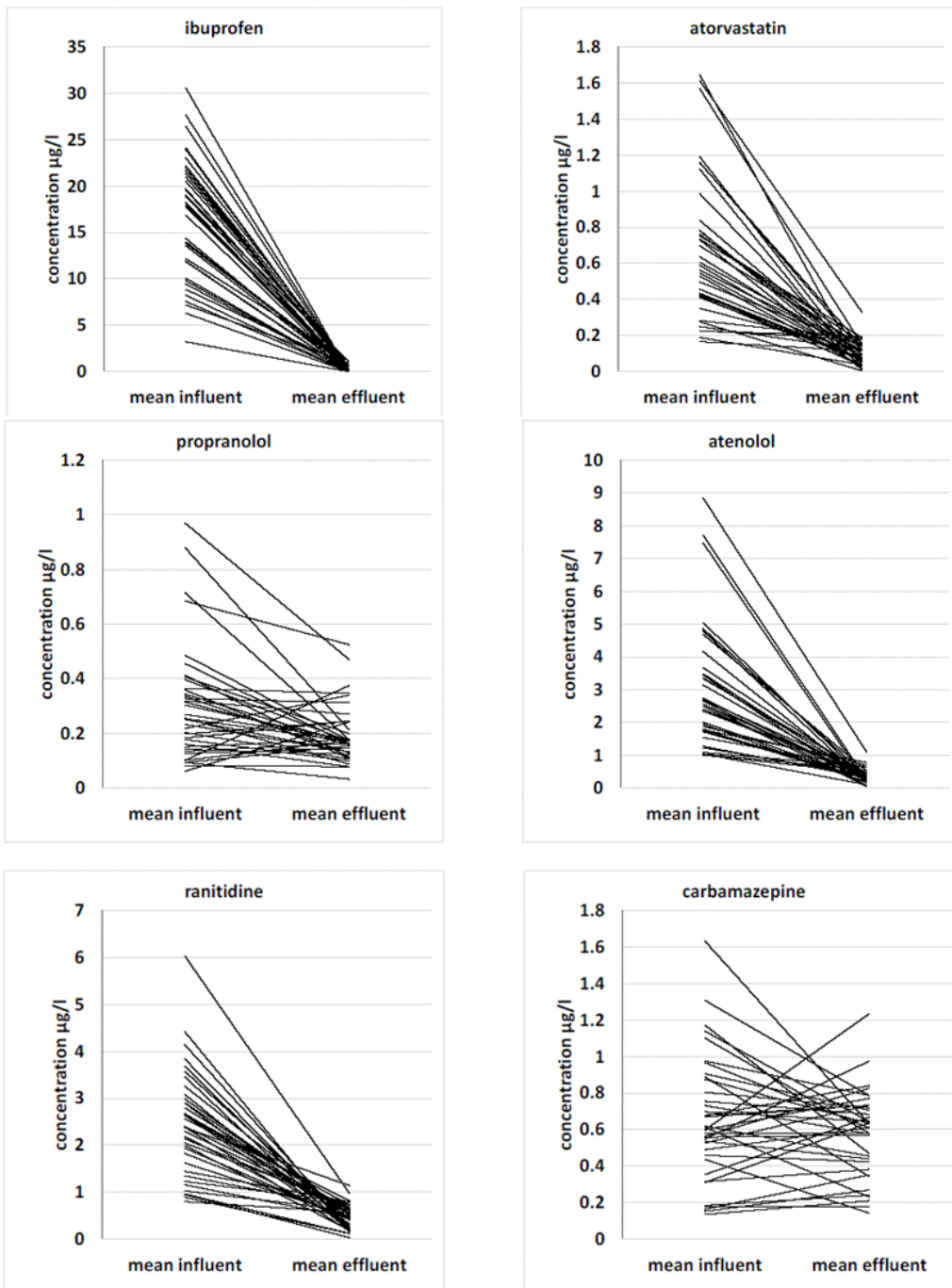
321  
322

**Table 5. Summary concentration values for CIP2 APIs (45 WwTW sampled on 20 occasions)**

Substance	Influents (µg/l)			Effluents (µg/l)		
	Median of WwTW average values	25%ile	75%ile	Median of WwTW average values	25%ile	75%ile
E1	0.038	0.030	0.049	0.004	0.002	0.014
E2	0.014	0.011	0.019	0.001	0.0003	0.002
EE2	0.00051	0.00041	0.00097	0.00020	0.00014	0.00040
DCF	0.54	0.40	0.76	0.29	0.20	0.41
IBPF	18.13	12.08	21.32	0.11	0.02	0.56
ATOV	0.61	0.41	1.01	0.10	0.06	0.16
ATOV <sub>o</sub>	1.33	0.81	1.76	0.17	0.08	0.29
ATOV <sub>p</sub>	1.33	0.82	2.03	0.21	0.12	0.35
PRPL	0.260	0.171	0.354	0.174	0.119	0.245
ATNL	2.600	1.872	3.297	0.323	0.210	0.463
ERMY	0.733	0.551	1.161	0.350	0.190	0.558
ERMY <sub>n</sub>	0.060	0.050	0.091	0.050	0.027	0.050
AZMY	0.351	0.171	0.748	0.202	0.095	0.425
CLMY	0.953	0.684	1.564	0.400	0.265	0.711
CIPR	0.861	0.385	1.510	0.147	0.067	0.276
METF	129	104	208	4.8	1.7	15
RNTD	2.35	1.68	3.06	0.529	0.286	0.730
CBAZ	0.60	0.43	0.84	0.641	0.477	0.756
CBAZ <sub>e</sub>	0.18	0.11	0.42	0.117	0.072	0.292
SERT	0.18	0.12	0.27	0.063	0.037	0.081
SERT <sub>n</sub>	0.12	0.10	0.21	0.033	0.016	0.045
FLXT	0.10	0.07	0.15	0.051	0.036	0.079
TMXF	0.0034	0.0026	0.0047	0.0025	0.0025	0.0028
TXP	0.0050	0.0028	0.0052	0.0050	0.0026	0.0050
BZT	2.16	1.60	3.97	1.38	1.08	2.62
TZT	1.59	1.19	2.60	1.27	0.88	1.96

323  
324  
325  
326  
327

Figure 2 below represents mean concentrations in the influent and effluent for selected APIs with the others shown in Figure A2 and demonstrates the degree of variability for APIs between WwTW.



329

330

331

332 **Figure 2. Graphic representation of mean concentrations of APIs in influent and effluent of**  
 333 **individual CIP2 WwTWs**

334

335 In some cases there appears to be an increase in API concentrations in the effluent compared with the  
 336 influent (Figure 2 and A2 of ESI). There are three main reasons for this:

- 337 1) The hydraulic retention time (HRT) within a WwTW means that samples of influent and  
 338 effluent collected at the same time (a practical requirement of the work) may not reflect actual  
 339 removal efficiency owing to within works management practices, e.g. batch flow, sludge

340 return pumping, taking place at the time of sampling. Given HRTs vary vastly between works  
341 and types of works it was not practical to calculate nor practically sample WwTW based on  
342 their HRTs.

343 2) The APIs were detected at ng/l levels in a highly complex matrix (particularly the influent)  
344 therefore analytical errors may lead to apparent increase in concentrations during treatment  
345 (Jelic et al., 2011).

346 3) In some cases this is a real effect, for example E1 is a degradation product of E2 (Heffley et  
347 al., 2014) and so if the rate of loss of E1 during treatment is less than that of E2, then an  
348 apparent increase in E1 will occur.

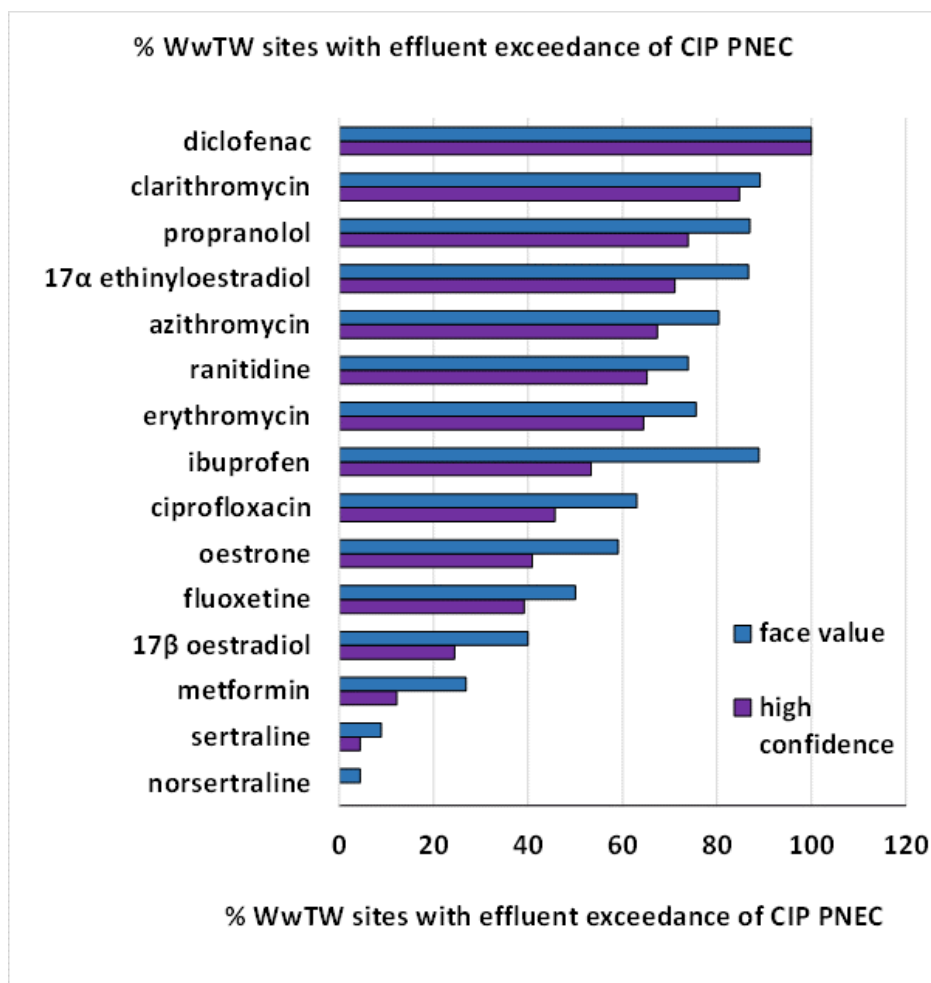
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### 350 **3.2 What is the environmental risk of the APIs being discharged in WwTW effluent?**

351 The median and interquartile concentration values of pharmaceuticals in influents and effluents are  
352 summarised in Table 5. Figure 3 shows a summary risk ranking of the CIP pharmaceutical group of  
353 substances in relation to the estimated predicted no-effect concentrations applied in CIP (CIP  
354 PNECs). A “face value” exceedance is one in which the mean effluent concentration is greater than  
355 the relevant estimated PNEC; a “high confidence” exceedance is one for which the lower part of the  
356 90% confidence interval about the mean effluent concentration is greater than the estimated PNEC i.e.  
357 there is 95% confidence that the mean is larger than the estimated PNEC. Substances not shown do  
358 not figure as noteworthy exceedances.

359





360

361 **Figure 3. Risk ranking of CIP2 APIs**

362

363 Figure 3 above illustrates the severity of potential non-compliances for pharmaceuticals as the ratio of  
 364 the observed concentrations in effluents to the relevant estimated PNEC. This ratio represents the  
 365 dilution that would be required to achieve compliance, assuming zero upstream concentrations. An  
 366 important proportion of UK wastewater treatment discharges are not subject to very much greater than  
 367 a twofold dilution so the potential for downstream non-compliance with PNEC values does exist on  
 368 the basis of a single effluent discharge alone. Table 3 shows that over 500 WwTW has estimated  
 369 dilutions of less than 2, 8% of all the WwTW in the UK. Added to this concern must be a  
 370 consideration of the pharmaceutical concentrations already present in a receiving watercourse  
 371 upstream of the discharge. Whilst the CIP2 programme did not include the determination of  
 372 pharmaceuticals in upstream river samples such analysis was undertaken for a range of Priority  
 373 Substances, including trace organic compounds that like pharmaceuticals, are primarily discharged as  
 374 a result of domestic inputs to wastewater. The evidence obtained from these investigations is that the  
 375 burden of upstream contamination is far from irrelevant and that discharges in the higher parts of a  
 376 river catchment, for example from septic tanks and small WwTW, can raise concentrations to values

377 that subsequent discharges lower in the catchment only serve to maintain (Phillips et al., 2015). This  
378 is an aspect that deserves careful future examination in the context of pharmaceuticals.

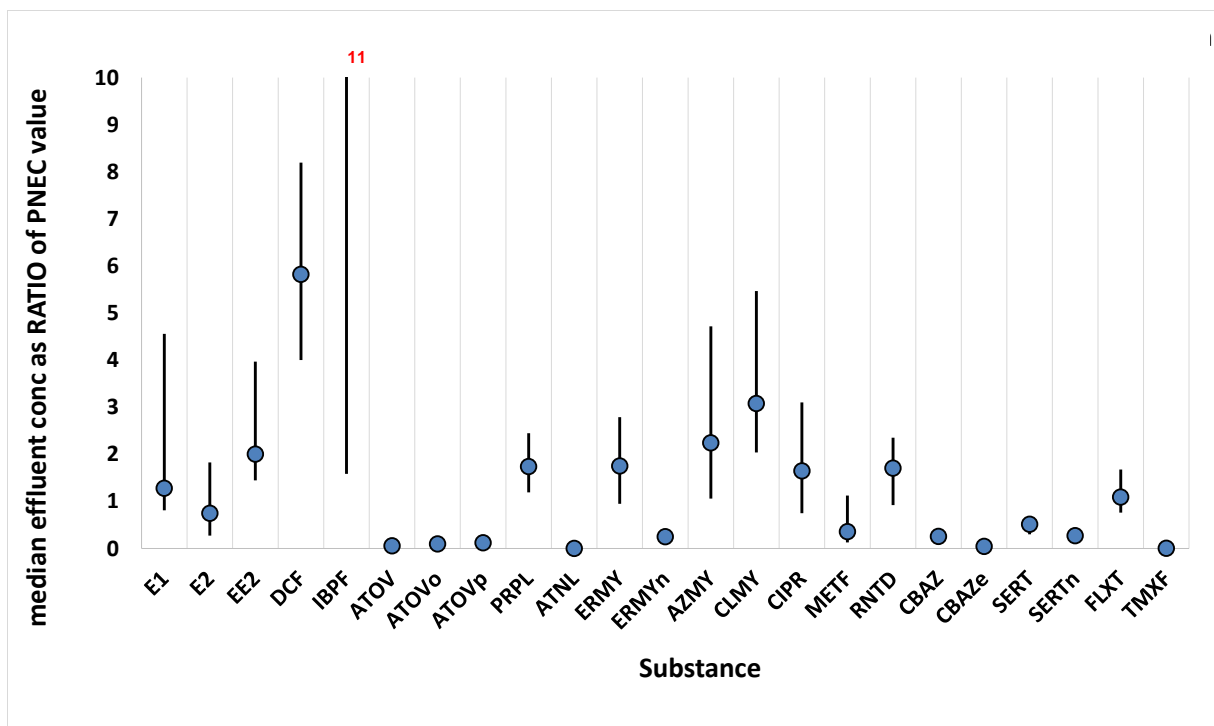
379

380 Figure 4 shows that several pharmaceuticals have been shown to be present in effluents at  
381 concentrations close to, or in many cases in excess of, values that might form the basis of future  
382 regulatory limit values.

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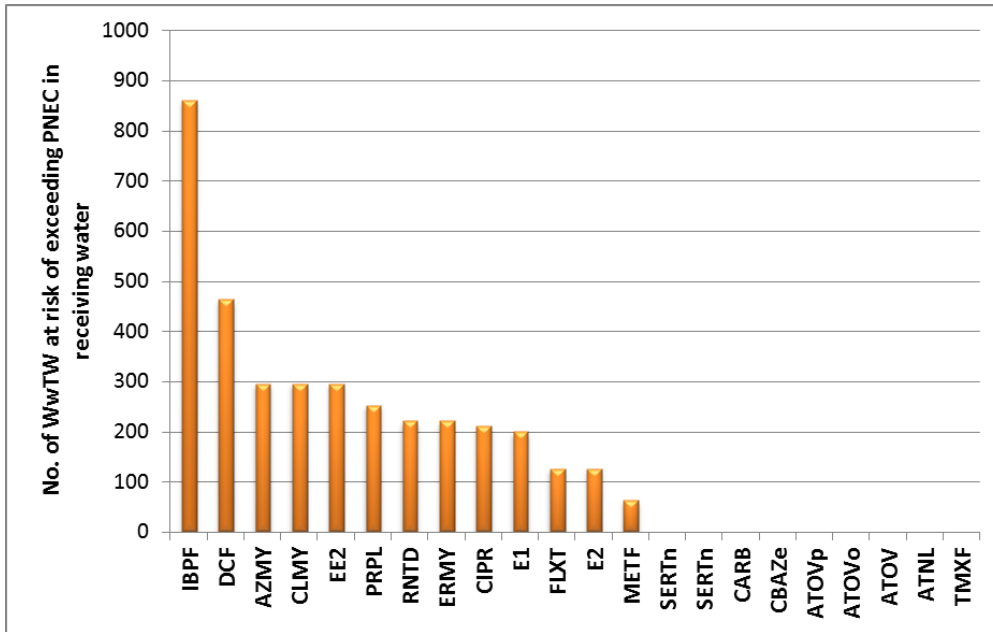
387 **Figure 4. Required within river dilution of WwTW effluent for API concentrations to be**  
388 **less than their estimated PNEC.**

389 **Note median effluent concentration for ibuprofen (IBPF) as a ratio of estimated PNEC is 11.**

390

391 Applying a more realistic risk assessment using estimates of available dilution for UK WwTW  
392 effluents discharged to receiving waters, combined with the measured API concentrations from the  
393 CIP2 dataset generates a similar priority ranking list in terms of the number of WwTW potentially  
394 exceeding downstream estimated PNECs after the effluent has mixed with receiving water (Figure 5).  
395 For IBPF this equates to 890 WwTW or 13% of all WwTW in the UK. This estimate is also based on  
396 the assumption that there are no significant inputs of API upstream of the WwTW in question.

397



398

399 **Figure 5. Number of WwTW at risk of exceeding estimated PNEC downstream of receiving**  
 400 **water**

401

402 DCF, AZMY, CLMY, EE2, PRPL, CIPR, RNTD and E1 are all predicted to exceed downstream  
 403 PNECs in over 200 WwTW. Required mean removal efficiency for any tertiary treatment would  
 404 range from 35% to 61% depending on the API (Table A6 of ESI). Whether the same tertiary treatment  
 405 technology could be applied to all of the APIs largely depends on their physico-chemical  
 406 characteristics. The use of granulated activated carbon (GAC) would require an API to have a  
 407 reasonable affinity for carbon (i.e. a relatively high octanol:water coefficient - logKow) which may  
 408 not always be the case for APIs with a high degree of polarity, particularly those that are charged at  
 409 typical effluent pH (pH 7.5) which would include DCF, IBPF, ATOV and to a degree CIPR (pKa =  
 410 6.09). Furthermore, as can be seen from Figures 1 and 2, there are considerable variations in the  
 411 removal rates between WwTW and so it may be expected to observe a similarly wide variation in  
 412 removal rates and/or final effluent API concentration, if additional tertiary treatment were to be  
 413 applied. This would obviously lead to a degree of uncertainty regarding possible compliance with any  
 414 given in river PNEC or water quality standard.

415

416 Figures 1 and 2 show that WwTW in general, have a high (but variable) removal rate for most  
 417 substances with only E2, EE2 propranolol, the macrolide antibiotics, carbamazepine fluoxetine and  
 418 tamoxifen exhibiting poor removal. It is clear (and unsurprising) that more complex factors, such as  
 419 the contaminant load on the WwTW, residence time in the works, overall strength of the influent,  
 420 questions of operation and maintenance as well as the presence of absence of tertiary treatment “add-  
 421 ons”, combine at each location to result in the observed treatment performance (Zorita et al., 2009;  
 422 Le-Minh et al., 2010; Deegan et al., 2011). In the wider context, the persistence of pharmaceuticals in  
 423 surface waters will be determined by the degree of upstream contamination from other (in this case,

424 presumably WwTW) inputs higher in the river catchment. As has been seen in elements of the CIP2  
425 programme dealing with Priority Substances, upstream contamination and lack of headroom for  
426 downstream discharges can often be more important than the local impact of a given WwTW. The  
427 likely importance of upstream inputs for pharmaceuticals is unclear. Whilst upstream inputs are  
428 inevitable in all sites except those at the top of catchments (where there may still be influences from  
429 septic tanks) the effect of such inputs is not known, but if smaller WwTW are less efficient than the  
430 predominantly larger works selected for the CIP programmes, then the risk to surface waters of  
431 exceeding estimated PNECs for APIs may be significant. Persistence and the degree and rate of  
432 breakdown in the environment are critical in this context. To fulfil their purpose pharmaceuticals need  
433 to be absorbed by the patient, to remain for sufficient time to have the desired effect and then be  
434 excreted. This means that in terms of their structure and hence fate and behaviour, pharmaceuticals  
435 tend to occupy a middle ground between substances on the one hand that are non-polar, hydrophobic,  
436 insoluble, and persistent and those that are highly polar, soluble, mobile and relatively readily  
437 biodegradable. This suggests that some degree of degradation in-river might mean that input of  
438 pharmaceuticals upstream may not be as great a risk as it is for other persistent, highly mobile priority  
439 substances such as some metals, persistent pesticides and industrial compounds.

440

441 It should, however, be noted that this assessment is based on the mixing of single APIs in effluent and  
442 receiving water under average flow conditions for a fraction of the APIs currently available and used.  
443 During summer months river flows are significantly lower than average values, yet effluent flows will  
444 remain relatively stable (accepting rain events contributing to flow in combined sewerage systems)  
445 leading to generally lower dilution available and therefore higher concentrations of effluent derived  
446 contaminants in receiving waters. Seasonal pattern of use for some APIs, antihistamines in summer,  
447 flu vaccines in winter etc, would also lead to a variable distribution of APIs in WwTW effluent and  
448 hence variable risk to receiving waters. The potential risk of mixtures is complex and requires detailed  
449 knowledge of ecotoxicology for the APIs of interest. Such assessments along with determining  
450 temporal variations in risk, require more a significantly detailed dataset (not necessarily currently  
451 available) and as such is beyond the scope of this broader risk assessment.

452

453 Whilst the objective of this research has not been to estimate costs for compliance, drawing on  
454 previous estimates of costs for API treatment based on fitting sand filters and granulated carbon  
455 sorption technology, the whole life cost (based on 2007 data) for achieving downstream compliance  
456 with the estimated IBPF PNEC would approximately £9bn (Comber et al., 2007). So for illustrative  
457 purposes it is evident that achieving compliance for all API estimated PNECs would be a substantial  
458 investment by the water industry. These estimates are only based on mixing downstream of receiving  
459 water and effluent and do not take account of any biodegradation or sorption to particulates leading to

460 reduced exposure which would need to be considered as part of a more detailed risk assessment prior  
461 to considering any remedial action regarding removal of APIs from WwTW effluent.

462

463 Much in relation to future compliance (and therefore cost to the water companies) will depend on the  
464 derivation method and data used to set water quality standards. The outputs of the CIPs in this case  
465 constitute a valuable risk assessment of the likely impact of whatever regulations might be introduced  
466 in the future. Of the pharmaceuticals / likely future Priority Substances, the so-called WFD watch list  
467 substance diclofenac, the steroids as well as possibly ibuprofen appear to be at risk of causing  
468 widespread exceedances of estimated PNECs in UK rivers. With respect to these substances, options  
469 of regulated use and control of patient behaviour relating to disposal of unused medicines might be  
470 enough to make a substantial difference. However, wastewater treatment solutions might turn out to  
471 be essential for the steroids, at least in the case of EE2.

472

#### 473 **4. CONCLUSIONS**

474 As has been observed for the CIP1 program there are a high variability in the removal of APIs  
475 observed between and within the individual plants. This variation may be due to many factors such as  
476 process technology as well as regional variation. Rates of removal in wastewater treatment have also  
477 been determined. The majority of substances studied are removed to a high degree, but with a wide  
478 variation in performance. Those that are less substantially reduced in concentration are  
479 ethinyloestradiol, diclofenac, propranolol, the macrolide antibiotics, fluoxetine, tamoxifen and  
480 carbamazepine. All except the last two of these substances are present in effluents at concentration  
481 higher than their estimated respective PNECs.

482

483 If the PNECs applied in the present study were all implemented as regulatory quality standards under  
484 the WFD, the risk assessment undertaken suggests that over a 10 times dilution would be required, to  
485 ensure that some APIs (ibuprofen in this case) meet their downstream quality standards, assuming no  
486 upstream contribution to background concentrations. This could entail treatment at up to 890 WwTW  
487 to meet current PNECs.

488

489 Much in relation to the need for future action by dischargers depends on whether or not these  
490 substances are regulated and the water quality standard chosen, but if the CIP estimated PNECs are a  
491 guide to regulatory limits, then there is potential for localised non-compliance in surface waters; at  
492 least in the case of ethinyloestradiol, diclofenac, ibuprofen, propranolol and the macrolide antibiotics.  
493 Further monitoring of pharmaceuticals in surface waters to determine the temporal variations in river  
494 concentrations associated with changing river flows (and hence dilution), the persistence, and the  
495 bioavailability of APIs needs to be considered.

496

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