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1 ARE EXPOSURE PREDICTIONS, USED FOR THE PRIORITISATION OF  
2 PHARMACEUTICALS IN THE ENVIRONMENT, FIT FOR PURPOSE?

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22 **Abstract:** Prioritisation methodologies are often used for identifying those pharmaceuticals  
23 that pose the greatest risk to the natural environment and to focus laboratory testing or  
24 environmental monitoring towards pharmaceuticals of greatest concern. Risk-based  
25 prioritisation approaches, employing models to derive exposure concentrations, are  
26 commonly used but the reliability of these models is unclear. The present study evaluated  
27 the accuracy of exposure models commonly used for pharmaceutical prioritisation. Targeted  
28 monitoring was conducted for 95 pharmaceuticals in the Rivers Foss and Ouse in the City of  
29 York, UK. Predicted environmental concentration (PEC) ranges were estimated based on  
30 localised prescription, hydrological data, reported metabolism and wastewater treatment  
31 plant (WwTP) removal rates, and were compared to measured environmental  
32 concentrations (MECs). For the River Foss, PECs, obtained using highest metabolism and  
33 lowest WwTP removal, were similar to MECs. In contrast, this trend was not observed for  
34 the River Ouse, possibly due to pharmaceutical inputs beyond our modelling.  
35 Pharmaceuticals were ranked by risk based on either MECs or PECs. With two exceptions  
36 (dextromethorphan and diphenhydramine), risk ranking based on both MECs and PECs  
37 produced similar results in the River Foss. Overall, these findings indicate that PECs may well  
38 be appropriate for prioritisation of pharmaceuticals in the environment when robust and  
39 local data on the system of interest are available and reflective of most source inputs to the  
40 system.

41 **Keywords:** Pharmaceuticals, Prioritisation, Risk ranking, Exposure, Hazard/risk assessment

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## INTRODUCTION

47 There is increasing concern over the presence and potential effects of pharmaceuticals in  
48 the natural environment. The ubiquitous presence of pharmaceuticals in aquatic systems is  
49 well-established [1,2]. Pharmaceuticals are designed to induce a biological response at  
50 nanomolar concentrations, raising questions regarding the risk for unintended sub-lethal  
51 chronic effects in exposed non-target organisms [3]. Of the approximately 1500  
52 pharmaceuticals currently in use in the UK alone, acute ecotoxicity data are available for  
53 only a small proportion of these and chronic data are even more scarce [4]. Additionally,  
54 little is known about the environmental fate of most pharmaceuticals [5]. Few have  
55 undergone extensive fate testing such as quantifying half-lives in environmental matrices,  
56 partitioning to sludge, soils, or sediment and uptake into terrestrial and aquatic organisms.  
57 Therefore substantial knowledge gaps exist that need to be filled before we can fully  
58 understand the effects of pharmaceuticals in the natural environment. To fill these gaps  
59 experimentally, however, would require substantial effort in terms of time and cost.

60 Prioritisation methodologies provide a useful tool for identifying which of the thousands  
61 of pharmaceuticals in use have the greatest potential to cause unintended effects in non-  
62 target organisms and which therefore should be experimentally tested in terms of their fate  
63 and effects [6]. Several prioritisation approaches have been proposed for pharmaceuticals.  
64 For example, hazard-based approaches have involved the prediction of persistence,  
65 bioaccumulation, and toxicity of a pharmaceutical and these have then been used to  
66 develop an overall hazard score. Compounds with the highest scores are considered to have  
67 the highest priority [7]. Risk-based approaches have involved the estimation or  
68 measurement of pharmaceutical concentrations in environmental media and the

69 comparison of these concentrations with an effect endpoint, for example predicted no-  
70 effect concentrations derived from acute or chronic ecotoxicity data [8–10] or predictions  
71 [11], plasma therapeutic concentrations [12], acceptable daily intakes for humans [13] or a  
72 combination of these [4]. Risk-based methods have been identified as preferable due to the  
73 consideration of effects and environmental occurrence, ruling out the possibility of  
74 prioritising compounds that have little chance of accumulating in the environment at  
75 ecologically relevant concentrations [6,13].

76 All risk-based approaches require an assessment of the concentration of pharmaceuticals  
77 in the environment. Real environmental data are desirable, however, monitoring data are  
78 generally lacking for a wide range of pharmaceuticals. Moreover, when monitoring data are  
79 available, the relevance of the data is often questionable due to sampling designs that do  
80 not consider seasonal biases, hydrologic conditions or spatiotemporal fluctuations [14]. As a  
81 result, comparing absolute measured concentrations of pharmaceuticals for prioritisation  
82 has been questioned [15]. Furthermore, sufficiently sensitive analytical methods, suitable  
83 for complex environmental matrices, or isotopically labelled standards necessary for  
84 accurate quantitation are not yet available for the majority of pharmaceuticals in use,  
85 making determination of pharmaceuticals in environmental matrices challenging [9,11].

86 Consequently, many risk-based prioritisation methods have employed exposure  
87 prediction models or algorithms to derive predicted environmental concentrations (PECs) in  
88 order to prioritise pharmaceuticals that have no monitoring data and/or to provide  
89 conservative estimates of environmental concentrations [16]. PECs are typically derived  
90 based on data on pharmaceutical usage, degree of metabolism in humans, removal in  
91 wastewater treatment plants (WwTP) and environmental dilution. The method most

92 commonly used is based on the approach recommended in the European Medicines Agency  
93 (EMA) guidelines for assessment of the risk of human pharmaceuticals in the environment  
94 [6,9,11,17–23]. Default parameters (e.g. for dilution of wastewater) proposed by the EMA  
95 guidance are regularly used in these prioritisation exercises, regardless of their suitability  
96 [6,10,19,20]. The use of site-specific data when performing these calculations for  
97 prioritisation is a rarity [21].

98 The impact of using PECs for prioritisation has not been explored, although several  
99 authors have explored how well PECs compare to measured environmental concentrations  
100 (MECs) [1,2,16,24–29]. These comparisons have provided varied results, with some studies  
101 showing that PECs adequately represent MECs [24–28], while others suggest the differences  
102 are too great to be useful, or that PECs generally under represent MECs [1,16,29]; in  
103 addition, these comparative studies concentrate on pharmaceuticals that have been  
104 identified as being of concern, or of high usage and generally focus on fewer than 10  
105 compounds [28], limiting the relevance of their conclusions across the broader spectrum of  
106 physico-chemically diverse pharmaceuticals known to be present in the environment  
107 globally.

108 Usually the determination of PEC relevancy is reliant on determining a PEC/MEC ratio.  
109 The acceptability of the PEC depends on how close this ratio is to 1 [29], however the  
110 acceptable range varies between studies [28]. This poses a problem when trying to assess  
111 the relevance of results across studies because the derivation of these ranges is subjective  
112 and dependent on the motive of the study (e.g. prioritisation or risk assessment).

113 In the present study, we evaluate PEC models for use in prioritisation by comparing  
114 modelled and monitoring data from a comprehensive set of 95 pharmaceuticals derived

115 from a wide range of therapeutic classes with different modes of action, an extensive range  
116 of chemical and physical properties, high and low usage, as well as select pharmaceuticals  
117 not thought to be prescribed in the UK. The city of York (population of 227 000) was chosen  
118 as the study system due to the availability of local prescription data, a well-defined and  
119 accessible hydrological system (i.e. two rivers that pass through the city), and numerous  
120 access points to the rivers via bridges, which enables a detailed characterisation of  
121 pharmaceutical concentrations throughout the city. The prioritisation approach used to  
122 compare PECs and MECs was based on the Fish Plasma Model (FPM) [12]. Studies of this  
123 nature that assess a large range of compounds (95), are an important check on ensuring  
124 that priority compounds identified, using common modelling approaches, are comparable  
125 to those using environmental data representative of key seasonal, locational, water  
126 treatment and hydrological differences.

127

## METHODS

### *Study site and sampling*

129 We collected and analysed river water samples from eight sites along the Rivers Ouse  
130 and Foss in the City of York in the UK where flow conditions were below the long term mean  
131 flow and near the Q50 (i.e where flow is equal or exceeded 50% of the time) in February  
132 2015 ([Figure 1](#))[30]. Site locations were chosen based on ease of access and their position in  
133 relation to WwTP outfalls discharging into these river systems (Supplemental Data, Table  
134 S1). Two WwTPs serve the city of York that impact the sampling network. There is a third  
135 WwTP; however, it is downstream of the city and sampling points (not included in Figure 1).  
136 The first of these two WwTPs (WwTP A) serves a population of 27 900, employs  
137 conventional activated sludge (CAS) as secondary treatment and nitrifying filters as a  
138 tertiary treatment option, and the second (WwTP B) serves a population of 18 600 and uses

139 trickling filter technology as secondary treatment paired with biological aerated filtration for  
140 tertiary treatment.

141 At each site, three 1-L samples were collected at points distributed equidistant across the  
142 width of the river channel and homogenised into a single 1 L composite sample. Three 10-  
143 mL aliquots were taken from the composite sample and filtered through 0.7  $\mu\text{m}$  glass  
144 microfiber (GF/F) disposable filters (Whatman Inc.). To ensure that filtration and field  
145 handling of samples did not result in cross-contamination, high-performance liquid  
146 chromatography (HPLC)-grade water was also filtered and prepared in the field identically to  
147 river samples (i.e. a field blank) three times during the sampling. Samples were frozen  
148 directly in the field using dry ice and transported to the U.S. Geological Survey (USGS)  
149 National Water Quality Laboratory in Denver Colorado, USA. They arrived four days later  
150 and were immediately thawed and analysed.

#### 151 *Analytical Methods*

152 Samples were analysed using a direct injection (100  $\mu\text{L}$ ) high-performance liquid  
153 chromatography/tandem mass spectrometry with an electrospray ionization source (LC-ESI-  
154 MS/MS) method for the determination of 110 pharmaceuticals, pharmaceutical degradates,  
155 and wastewater indicator compounds [31]. Of the 110 compounds, 95 pharmaceuticals  
156 were targeted in the present study with method detection limits (MDL) as defined by the  
157 US Environmental Protection Agency (USEPA) [32] down to 0.45 ng/L (Table 1).  
158 Instrumentation included an Agilent 6410 triple quadrupole MS/MS system coupled with an  
159 Agilent 1200 Series HPLC. Mobile phases were HPLC-grade water modified with 1M formic  
160 acid and 1M ammonium formate (A) and 100% HPLC grade methanol (B). Chromatography  
161 gradient and conditions are detailed in Supplemental Data, Table S2. Quantification and



162 identification was achieved by external calibration with known standards for each of the  
163 pharmaceuticals and completed using Agilent Mass Hunter software in accordance with the  
164 USGS methodology described in Furlong et al. [31]. The MS/MS was operated in multiple  
165 reaction monitoring (MRM) mode, where two MRM transitions and correct retention times  
166 were required for ion qualification, while quantification was based on the major transition  
167 (Supplemental Data, Table S3). Additionally, ion ratios between the major and secondary  
168 transitions were required to fall within a compound-specific range determined from the  
169 corresponding analytical standard [31]. Concentrations reported in the present study are  
170 the median of three aliquots taken from each site.

171 *Statistical analysis and quality control.* The limit of quantification (LOQ) was established  
172 as 2 to 5 times the MDL where the probability of incorrectly reporting the presence of an  
173 analyte is less than 1% when concentrations are equal to or greater than the LOQ [33].  
174 Concentrations greater than the LOQ were fully quantitative while concentrations detected  
175 between the LOQ and MDL were considered semi-quantitative estimates. To enable the  
176 consideration of as many pharmaceuticals as possible, both quantitative and semi-  
177 quantitative data were used in subsequent data analyses.

178 Quality control samples were analysed to (1) assess matrix recovery efficiency and  
179 identify the presence of matrix interferences that could induce ion suppression or  
180 enhancement [34], and (2) identify any blank contamination from sampling and analysis. For  
181 recovery assessment, an environmental sample was amended with the pharmaceuticals of  
182 interest (matrix spike) to a concentration of 400 ng/L. The aforementioned field blank  
183 samples were analysed to identify any potential contributions of pharmaceuticals during  
184 sample collection, laboratory processing and analysis. In addition to the field blank and

185 matrix spike samples, analogous laboratory spike and blank samples, using high purity HPLC-  
186 grade water, also were analysed with each batch of environmental samples.

187

### 188 *PEC Modelling*

189 The calculation of PECs for the 95 pharmaceuticals was based on Equation 1.

$$190 \text{ PEC} = \frac{\text{consumption} * F_{\text{excreta}} * (1 - \text{WwTP removal})}{\text{inhabitants} * \text{WW}_{\text{inhab}} * \text{dilution}} \quad (1)$$

191 Where the numerator represents the river input rate (ng per day): consumption =  
192 amount used per day (ng/day);  $F_{\text{excreta}}$  is the fraction of pharmaceutical excreted unchanged  
193 by patients; and WwTP removal is the fraction of a pharmaceutical removed by water  
194 treatment. The denominator is the river flushing rate where: inhabitants = population  
195 served by the WwTP;  $\text{WW}_{\text{inhab}}$  = amount of wastewater generated (L/day·person), which has  
196 a default value of 200; dilution was based on site-specific conditions in each river.

197 Pharmaceutical usage was generated from localised prescription data released monthly  
198 by the National Health Service for January 2015 [35]. Relevant medical practices were  
199 selected by postal code (Supplemental Data, Table S4). The  $F_{\text{excreta}}$  term was obtained from  
200 either the peer-reviewed literature or online databases such as Drugbank, MedSafe and  
201 RXmed, as well as publicly available pharmaceutical data sheets released by government  
202 organisations such as MedSafe New Zealand or the Food and Drug Agency (Supplemental  
203 Data, Table S5). When a pharmaceutical was metabolised to conjugated metabolites (e.g.  
204 glucuronide or sulfato-conjugates), the portion released as a conjugate was added to the  
205 unchanged parent excretion estimate. These metabolites can undergo reactions during  
206 water treatment such as cleavage and thus be converted back into their parent compounds,

207 increasing the parent pharmaceutical load in wastewater effluent [36]. Estimates of  
208 unchanged pharmaceutical excretion varied across sources; this led to a range of possible  
209 unchanged excretion estimates, which were used to calculate a PEC range. For ophthalmic  
210 and topical preparations, metabolism was assumed to be zero and therefore the  $F_{\text{excreta}}$  was  
211 set to 1 [19].

212 Wastewater treatment removal was considered in two ways due to the limited  
213 availability of removal estimates for all pharmaceuticals in the present study [37]. Firstly,  
214 removal values from the literature were collected and, similarly to  $F_{\text{excreta}}$  estimates, varied  
215 substantially (Supplemental Data, Table S5). The range of possible WwTP removal estimates  
216 were used to calculate a possible PEC range. Secondly, data gaps were filled using the  
217 USEPA's EPISuite software STPWIN program [38], similarly to a recent prioritisation exercise  
218 in Asia [20].

### 219 *Evaluation of PECs*

220 Separate PEC ranges were calculated for pharmaceuticals for both the River Foss and  
221 River Ouse. The PEC range incorporated a river-specific dilution factor reflecting hydrological  
222 conditions on the day of sampling. The lowest  $F_{\text{excreta}}$  and highest WwTP removal values  
223 found in the literature were paired to give a minimum PEC, while the maximum was derived  
224 using the highest  $F_{\text{excreta}}$  and lowest WwTP removal found in the literature. A PEC (worst  
225 case) was also calculated which only considered site-specific dilution (ie.  $F_{\text{excreta}} = 1$ , WwTP  
226 removal = 0).

### 227 *Prioritisation Approach*

228 The fish plasma model (FPM) approach [12,39], which has been used in previous  
229 prioritisation exercises [6], was selected as the method used for prioritisation.

230 Bioconcentration factors (BCFs) for neutral and ionisable compounds were estimated  
231 according to the approach of Fu et al. [40] (Supplemental Data, Equations S1-S5) and used  
232 to determine fish plasma concentrations (FPCs) based on either PECs or MECs . FPCs were  
233 then compared to human plasma therapeutic concentrations (indicated by  $C_{max}$ ) using  
234 Equation 2 to determine the risk quotient (RQ). The  $K_{ow}$  and  $C_{max}$  for all compounds were  
235 collected from the MaPPFAST database compiled by Berninger et al. [41].

$$236 \quad RQ = \frac{PEC * BCF}{C_{max}} \quad (2)$$

237 RQs are ranked from highest to lowest risk, where a larger RQ indicates a greater  
238 potential risk. Using this approach, we obtained two ranking lists, one based on FPCs  
239 obtained from PECs, the other using FPCs obtained from MECs.

## 240 **RESULTS AND DISCUSSION**

### 241 *Pharmaceutical Occurrence*

242 No pharmaceuticals were detected in the field blanks collected indicating that sample  
243 collection, handling, and analysis did not result in measurable contamination of the water  
244 samples (i.e. protocols did not generate false positives for the present study). Calculated  
245 recoveries from quality control matrix spike samples generally fell within 60-120% and were  
246 considered acceptable [42]. Recoveries failing to meet these criteria are identified and  
247 subsequently interpreted with caution. Reported values were not corrected for percentage  
248 of analyte recovered in environmental matrix spikes [43]. The median matrix recovery was  
249 88% while the 25 and 75 percentiles were 81 and 160% respectively; this distribution  
250 suggests that some matrix enhancement of compound recoveries is occurring.

251 Of the 95 pharmaceuticals surveyed, 25 compounds were detected and quantified  
252 (Figure 2) in the eight water samples collected from the York network. A further 19  
253 pharmaceuticals were detected, however only qualitative or semi-quantitative assessment  
254 was appropriate due to either quantification limits (11) or unacceptable matrix  
255 interferences (7) (Table 1). Of the 25 pharmaceuticals quantified, 10 have not been  
256 previously identified in the UK aquatic environment to the authors' knowledge: acyclovir,  
257 diphenhydramine, glyburide, hydrocodone, lidocaine, methocarbamol, oseltamivir,  
258 sitagliptin, triamterene and loratadine. The remaining 15 pharmaceuticals detected were  
259 consistent with the ranges reported previously in the literature (Table 1). Ten  
260 pharmaceuticals included in the analysis are not prescribed in the UK and were not detected  
261 in any samples. Median and maximum detected concentrations, along with detection  
262 frequency and matrix recoveries for all target analytes are reported in Table 1.

263 The concentrations and number of detections between the Rivers Ouse and Foss varied  
264 (Fig. 2) with concentrations of six pharmaceuticals in the River Foss being significantly higher  
265 than in the Ouse (Student's T-test,  $p < 0.05$ ). A greater number of and more consistent  
266 detections occurred in the River Foss, (Fig. 2) which has both a lower dilution factor and the  
267 corresponding WwTP (WwTP B) provides less sophisticated water treatment (trickling filter)  
268 compared to the treatment used by WwTP A discharging to the River Ouse (conventional  
269 activated sludge).

#### 270 *Evaluation of Modelled Concentrations with Monitoring Data*

271 The EMEA PEC model describes an annual average concentration for the region the  
272 consumption data cover; in general, usage data from the whole of a country is averaged to  
273 give a single PEC [4]. Evaluating this approach with localised, temporally limited samples

274 would introduce a source of potential error as it has been shown that seasonal usage is  
275 important for some pharmaceuticals and that demographics in a specific area may differ  
276 substantially from the national average [25,26]. To reduce these potential biases, local  
277 usage data, corresponding to time of sampling, was used. In addition, site-specific dilution  
278 factors were incorporated to avoid the use of EMEA [23] default dilution factors (i.e. 10).  
279 The  $WW_{inhab}$  term could not be refined to actual discharge because both WwTPs are highly  
280 variable and discharge measurements were not available for the sampling dates. This  
281 permits a focus on other factors that could be affecting the suitability of PECs such as WwTP  
282 removal and metabolism.

### 283 *Overall PEC Performance*

284 Many pharmaceuticals targeted were not detected in the monitoring campaign, however  
285 based on their PECs, this was not unexpected. To assess the overall performance of the  
286 PECs, a semi-quantitative approach was taken. Each of the 77 pharmaceuticals for which a  
287 PEC could be calculated were sorted into one of four possible categories (**Figure 3**).  
288 Pharmaceuticals that were expected to be detected in the monitoring campaign (i.e. PEC  
289 greater than the corresponding analytical MDL) were sorted into either detected or not  
290 detected categories. Similarly, pharmaceuticals not expected to be detected (i.e. PEC less  
291 than the respective analytical MDL) were sorted into detected and not detected categories.  
292 Overall in the semi-quantitative analysis, the PECs in the two rivers performed well with 79%  
293 and 86% of predictions correctly confirmed in the River Foss and Ouse, respectively, by the  
294 monitoring data.

295 The large difference in dilution between the two rivers, factors of 17.8 and 540 for the  
296 Foss and Ouse respectively, led to larger PECs in the River Foss and therefore a higher

297 number of expected detections. A larger proportion of expected detections were not  
298 identified in our monitoring campaign in the Foss in comparison to the Ouse; it could be that  
299 pharmaceuticals were missed by our sampling effort, however our results indicate that  
300 pharmaceutical concentrations are stable throughout the River Foss over an 8-hour period  
301 (Figure 2), which diminishes the likelihood of missing a detection. Conversely, the  
302 metabolism or WwTP removal selected from the literature may have produced PECs larger  
303 than real-world concentrations. The number of unexpected but detected pharmaceuticals is  
304 greater in the River Ouse, despite corrections for upstream contributions detected at site 4,  
305 (Figure 2). The River Ouse could be subject to a greater number of sources not reflected in  
306 our usage estimate in contrast to the more rural River Foss. Sources of pharmaceuticals  
307 beyond the scope of localised prescription data exist within the city include, for example, a  
308 substantial tourism industry and two post-secondary institutions. Recent studies have  
309 demonstrated the impact of post-secondary institutions [44] and music festivals [45] on  
310 MECs, and it is likely that MECs in the Ouse are influenced by demographic factors not  
311 inclusive of localised prescription-based usage estimates.

### 312 *Impact of Metabolism and WwTP Removal Uncertainty on PECs*

313 *Underestimated PECs:* A breakdown of how each pharmaceutical PEC performed in  
314 comparison to the MEC is shown for the River Foss (Figure 4) and the River Ouse (Figure 5).  
315 While the overall semi-quantitative performance of PECs in the River Ouse was slightly  
316 better than the Foss, these results were not repeated when quantitative data were  
317 compared. In the Foss and the Ouse, 38% and 78% respectively, of the MEC ranges were  
318 entirely greater than the corresponding PEC range. This drops to 12% and 44% respectively  
319 when the PEC (worst case) is considered. The PEC (worst case) does not include metabolism  
320 or WwTP removal, only dilution, and when this PEC still falls below the MEC it indicates a

321 problem with the consumption estimate. The analytical matrix spike recoveries indicated  
322 that matrix enhancement is occurring, which could affect the comparisons with PECs. To  
323 investigate, each compound with a MEC range greater than the PEC range was theoretically  
324 corrected based on the compound specific matrix recovery. All of the theoretically corrected  
325 MEC ranges were still greater than the corresponding PEC ranges in the River Ouse and Foss  
326 with one exception, erythromycin, where the MEC range corresponded with the top of the  
327 PEC range in the River Foss. Therefore we do not expect our results to be significantly  
328 altered by the distribution in matrix recoveries.

329 In the River Foss, three pharmaceuticals (dextromethorphan, diphenhydramine and  
330 pseudoephedrine) had greater MECs than PEC (worst case) estimates and are all available  
331 over-the-counter (OTC). This consumption pathway was not considered in our consumption  
332 estimate as we were unable to access data on sales of OTC medicines. As a result, PECs for  
333 these pharmaceuticals should be systematically underestimated [2,24,27]. This was not  
334 reflected for all OTC pharmaceuticals, similarly to a recent study in Canada [28]. This  
335 highlights the need for a new approach to incorporate OTC consumption into WwTP  
336 pharmaceutical loadings [4,27]. The results from the River Ouse (Figure 5) are more  
337 complicated, a mixture of both OTC and prescription-only pharmaceuticals had MECs which  
338 were greater than the PEC (worst case) estimates. This supports our semi-quantitative  
339 findings where a problem exists with the consumption estimate and is likely a result of the  
340 specific demographics impacting pharmaceutical loads for the River Ouse.

341 *PEC ranges:* The PEC range is large for many of the pharmaceuticals. For instance the  
342 paracetamol PEC range covers over 4 orders of magnitude (Figure 4). This large uncertainty  
343 is a result of the extensive variability in experimental WwTP removal and  $F_{\text{excreta}}$  estimates



344 obtained from the literature. In both rivers, the majority of PEC ranges vary by at least 2  
345 orders of magnitude, which could be important from both a risk assessment and  
346 prioritisation perspective. The large PEC range does mean that, in general, the MEC range  
347 did correspond with predictions in the River Foss (Figure 4). The MEC range is typically near  
348 the top of the PEC range, where the smallest WwTP removal was paired with the highest  
349 unchanged excretion found in the literature. This finding has two implications: firstly,  
350 choosing the worst-case fate parameters to estimate PECs is likely the best approach to  
351 avoid underestimations of PECs, which is in agreement with PEC approaches in the literature  
352 [46]; secondly, anything short of an exhaustive literature review could lead to  
353 underestimated PECs in the majority of cases shown in Figures 4 & 5. This is because the  
354 PEC ranges determined herein are the result of an exhaustive literature review; in a larger  
355 scale prioritisation exercise the time resources required to thoroughly check each  
356 compound would be impractical and the process itself highly subjective. This could lead  
357 authors to different conclusions about the resulting risks and priority compounds as it is a  
358 single value computed for the PEC, not a range, which is a substantial flaw not often  
359 considered when the fate data used in a PEC are collected in this manner.

360 Our results indicate that consideration of metabolism and WwTP removal is essential  
361 when calculating PECs because PEC (worst case) is a large overestimate of actual  
362 concentrations in the majority of cases (Figure 4), also shown by others [6,10,22]. In the  
363 River Foss, prescription pharmaceuticals are described well using the PEC approach. This is  
364 in sharp contrast in the River Ouse, where multiple consumption sources are likely affecting  
365 concentrations of the pharmaceuticals in the environment, making it impossible to evaluate  
366 the effect of the fate parameters with the current dataset. Further monitoring that  
367 incorporates sampling WwTP influents and effluents to compute actual removals will be

368 critical to assessing PECs relative to MECs. In addition, the uncertainty in measured  
369 concentrations can be limited by incorporating time-averaged composite samples  
370 representative of the average conditions [14]. Further work which includes a seasonal  
371 monitoring campaign is suggested to quantify the seasonal variability and magnitude of  
372 influence that tourism and post-secondary institutions have on MECs in addition to serving  
373 as a check of the findings from the present initial scoping study.

374

375

#### 376 *Implications for prioritisation*

377 Risk ranking order is important as it dictates which pharmaceuticals are of highest risk  
378 and thus, most likely to receive further costly investigations into effects and occurrence [4].  
379 Therefore we evaluated the similarities and differences between risk rankings obtained  
380 based on MECs and rankings based on PECs for the River Foss (Figure 6A) and River Ouse  
381 (Figure 6B). In the River Foss, while there was some variability in the ranking position of  
382 individual compounds, generally, the rankings based on MECs and PECs followed a similar  
383 trend. Compounds identified as highest risk based on MECs also were identified as highest  
384 risk based on PECs and those ranked as lower risk based on MECs also ranked as lower risk  
385 using PECs (Figure 6A). The exceptions were dextromethorphan and diphenhydramine  
386 where the rank position was much higher based on MECs than based on PECs. This degree  
387 of similarity was not observed in the River Ouse (Figure 6B). Eight of the MEC ranks are  
388 higher risk than their PEC rank counterparts, which visually, is a more variable but gentler  
389 rise (Figure 6B). This indicates that the degree in which PECs were underestimated in the  
390 River Ouse affects prioritisation ranking order trends.

391

## CONCLUSIONS

392 We have presented real-world monitoring data for a comprehensive set of 95  
393 pharmaceuticals in two rivers that run through the city of York, UK. During a snapshot  
394 sampling where flow conditions were below the long-term mean and near the Q50 in  
395 February 2015, 25 pharmaceuticals were quantified (i.e. detected), 10 of which had not  
396 been previously measured in the UK aquatic environment. Site-specific PEC ranges varied up  
397 to four orders of magnitude due to the variability in metabolism and WwTP removal values  
398 found in the literature. The largest unchanged excretion paired with the lowest WwTP  
399 removal approach provided the greatest comparability to measured concentrations. Some  
400 of the observed differences between MECs and PECs might be explained by complex social  
401 demographics, such as tourism or post-secondary institutions, which are suspected of  
402 influencing wastewater loading estimates. When PECs and MECs were used to prioritise the  
403 detected pharmaceuticals based on risk, generally the two approaches provided similar  
404 ranking outcomes for well-defined systems such as the River Foss, but were less comparable  
405 in the more complicated system, the River Ouse. The findings for the Foss, in particular,  
406 provide some confidence in the use of PECs in prioritisation exercises for pharmaceuticals.

407

## SUPPLEMENTAL DATA

408 Table S1 National grid references of sampling site locations

409 Tables S2-S3 Analytical operating conditions.

410 Tables S4-S5 PEC parameters.

411 Equations S1-S5 Bioconcentration factor equations.

412

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420

421 *Data availability*—Data, associated metadata, and calculation tools are available by  
422 contacting the corresponding author (alistair.boxall@york.ac.uk).

423

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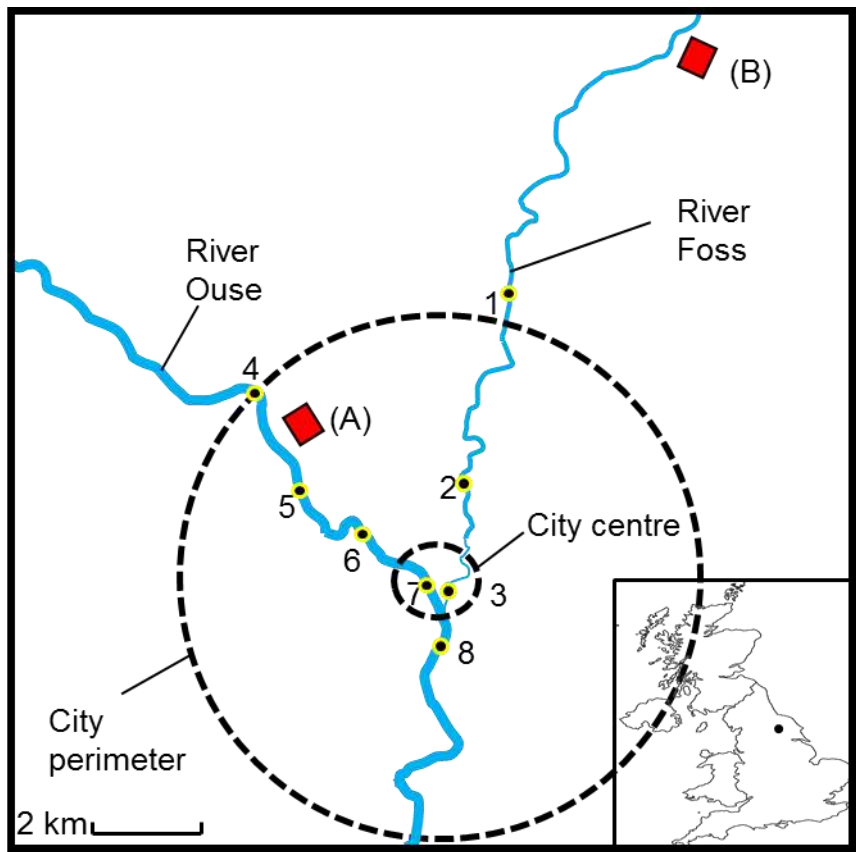
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601



602

603 Figure 1. Locations of the 8 sampling sites around the city of York, UK. A and B represent the WWTPs  
 604 that service the city. Grab samples were collected in February 2015.

605

606 Table 1. Occurrence data for the 8 water samples collected during February 2015 from the sampling network with matrix recovery and method detection  
607 limits for each of the 95 pharmaceuticals, pharmaceutical degradates and wastewater indicators targeted.

Pharmaceutical	Source or use	MDL (ng/L)	Detection Frequency %	Max (ng/L)	Median (ng/L)	Matrix recovery % (median)	Detected in the UK (ng/L)
10-Hydroxy-amitriptyline	Degradate of amitriptyline	1.7	0	ND	ND	110	
Abacavir	Antiviral	4.1	0	ND	ND	73	
Acyclovir <sup>a</sup>	Antiviral	4.4	13	7.9	7.9	60	
Albuterol <sup>a</sup>	β2-adrenergic receptor	1.2	0	ND	ND	180	38 – 470 <sup>2 e</sup>
Alprazolam	Benzodiazepine	4.3	0	ND	ND	75	
Amitriptyline	Antidepressant	19	25	<MDL	<MDL	250	1.0 – 72 <sup>f,g</sup>
Amphetamine	Psychostimulant	4.1	0	ND	ND	76	1.1 -4 <sup>f</sup>
Antipyrine <sup>b</sup>	Analgesic	58	20	<MDL	<MDL	87	
Atenolol	Beta blocker	2.7	13	25	25	97	<1 – 530 <sup>e</sup>
Benzotropine <sup>b,c</sup>	Anticholinergic	7.9	0	ND	ND	300	
Bupropion	Antidepressant	3.6	0	ND	ND	86	
Carbamazepine	Anticonvulsant	0.84	38	27	22	80	<0.5 – 52 <sup>e,h</sup>
Carisoprodol	Muscle relaxant	2.5	0	ND	ND	81	
Chlorpheniramine <sup>a,c</sup>	Antihistamine	0.94	13	2.4	2.4	220	
Cimetidine <sup>c</sup>	H2-receptor antagonist	5.6	38	<MDL	<MDL	100	<0.5 – 202 <sup>e</sup>
Citalopram <sup>c</sup>	Antidepressant	1.3	50	37	14	170	53 <sup>i</sup>
Clonidine	Antihypertensive	30	0	ND	ND	87	
Dehydronifedipine	Nifedepine metabolite	4.9	0	ND	ND	78	
Desmethyl-diltiazem <sup>c</sup>	Degradate of diltiazem	2.5	25	48	44	210	
Desvenlafaxine	Antidepressant, venlafaxine metabolite	3.8	88	85	16	87	7.3 – 290 <sup>i,j</sup>

Pharmaceutical	Source or use	MDL (ng/L)	Detection Frequency %	Max (ng/L)	Median (ng/L)	Matrix recovery % (median)	Detected in the UK (ng/L)
Dextromethorphan <sup>a,c</sup>	Cough suppressant	1.6	25	6.7	6.0	140	
Diazepam	Benzodiazepine	0.45	63	1.3	1.0	81	0.6– 1.1 <sup>f,g</sup>
Diltiazem <sup>c</sup>	Calcium channel blocker	5.1	63	44	9.1	180	<1 – 49 <sup>e</sup>
Diphenhydramine <sup>a</sup>	Antihistamine	2.9	25	6.0	5.6	100	
Erythromycin <sup>c</sup>	Macrolide antibiotic	27	25	180	170	250	<0.5 – 1000 <sup>k,l</sup>
Ezetimibe <sup>c</sup>	Cholesterol-reducing agent	13	25	<MDL	<MDL	160	
Fadrozole <sup>b</sup>	Aromatase inhibitor	1.5	0	ND	ND	92	
Fenofibrate	H2-receptor antagonist	1.3	0	ND	ND	100	
Fexofenadine	Antihistamine	4.0	100	130	18	90	64 <sup>j</sup>
Fluconazole <sup>a</sup>	Antifungal	36	0	ND	ND	76	
Fluoxetine <sup>c</sup>	Antidepressant	5.4	0	ND	ND	360	6.2 – 34 <sup>f,m</sup>
Fluticasone <sup>c</sup>	Synthetic corticosteroid	0.92	63	<MDL	<MDL	86	
Glipizide	Antidiabetic	17	0	ND	ND	82	
Glyburide	Antidiabetic	0.79	88	3.1	<MDL	81	
Hydrocodone	Opioid, codeine metabolite	2.1	25	39	34	110	
Hydrocortisone	Natural glucocorticoid hormone	29	0	ND	ND	77	
Hydroxyzine	Glucocorticoid hormone	1.5	0	ND	ND	110	
Iminostilbene	Carbamazepine degradate	73	0	ND	ND	98	
Ketoconazole <sup>c</sup>	Antifungal	56	0	ND	ND	430	
Lamivudine <sup>c</sup>	Antiretroviral	3.2	0	ND	ND	160	
Lidocaine <sup>a</sup>	Topical anesthetic	3.1	75	9.6	8.9	84	
Loperamide <sup>c</sup>	Antidiarrheal	5.7	0	ND	ND	420	
Loratadine <sup>a</sup>	Antihistamine	1.4	88	8.5	1.5	120	
Pharmaceutical	Source or use	MDL (ng/L)	Detection	Max	Median	Matrix	Detected in

			Frequency %	(ng/L)	(ng/L)	recovery % (median)	the UK (ng/L)
Lorazepam	Benzodiazepine (anxiolytic)	58	0	ND	ND	84	
Meprobamate	Anxiolytic	17	0	ND	ND	74	
Metaxalone <sup>b</sup>	Muscle relaxant	7.8	0	ND	ND	80	
Metformin	Antidiabetic	6.6	100	1300	630	120	2300 <sup>j</sup>
Methadone <sup>c</sup>	Synthetic opioid	3.8	0	ND	ND	200	10 – 18 <sup>g</sup>
Methocarbamol	Muscle relaxant	4.4	25	10	8.7	81	
Methotrexate	Chemotherapy agent	11	0	ND	ND	76	<6.3 <sup>n</sup>
Metoprolol <sup>c</sup>	Beta-blocker	14	0	ND	ND	86	<0.5 – 12 <sup>e</sup>
Morphine	Analgesic (opioid)	2.8	30	21	19	84	0.6 – 36 <sup>f,g</sup>
Nadolol	Beta-blocker	16	0	ND	ND	85	
Nevirapine <sup>c</sup>	Antiretroviral	3.0	25	<MDL	<MDL	81	
Nizatidine <sup>c</sup>	Acid inhibitor (ulcers)	9.5	0	ND	ND	240	
Noreisterone	Oral contraceptive component	2.2	13	<MDL	<MDL	85	<10 – 17 <sup>s</sup>
Nordiazepam	Benzodiazepine, diazepam metabolite	21	0	ND	ND	82	0.1 – 6.8 <sup>f</sup>
Norverapamil <sup>c</sup>	Verapamil metabolite	1.7	0	ND	ND	400	
Omeprazole <sup>c</sup>	Proton pump inhibitor	2.8	0	ND	ND	260	
Oseltamivir	Antiviral	2.9	38	3.6	<MDL	85	
Oxazepam	Benzodiazepine (anxiolytic)	28	0	ND	ND	81	0.9 – 21 <sup>f</sup>
Oxycodone	Opioid analgesic	5.0	0	ND	ND	90	0.4 – 7.1 <sup>f,g</sup>
Paracetamol <sup>a</sup>	Analgesic	3.6	63	1000	260	88	52 – 2400 <sup>d,e</sup>
Paroxetine <sup>c</sup>	Antidepressant	4.1	0	ND	ND	300	
Penciclovir <sup>c</sup>	Antiviral	8.1	0	ND	ND	160	
Pharmaceutical	Source or use	MDL (ng/L)	Detection Frequency %	Max (ng/L)	Median (ng/L)	Matrix recovery % (median)	Detected in the UK (ng/L)

Pentoxifylline <sup>c</sup>	Cardiovascular drug	4.7	10	<MDL	<MDL	86	
Phenazopyridine <sup>b</sup>	Urinary tract analgesic	2.7	0	ND	ND	84	
Phendimetrazine <sup>b</sup>	Appetite suppressant	16	0	ND	ND	86	
Phenytoin	Antiepileptic	94	0	ND	ND	78	
Piperonyl butoxide <sup>b</sup>	Pesticide, lice treatment	1.5	13	2.8	2.8	87	
Prednisolone	Synthetic corticosteroid, prednisone metabolite	75	0	ND	ND	91	
Prednisone	Synthetic corticosteroid	84	0	ND	ND	120	
Promethazine <sup>a,c</sup>	Antihistamine	10	50	<MDL	<MDL	190	
Propoxyphene	Opioid analgesic	3.4	0	ND	ND	140	9 -680 <sup>k,o</sup>
Propranolol	Beta blocker	13	50	27	18	110	3.9- 220 <sup>k,p</sup>
Pseudoephedrine <sup>a</sup>	Decongestant	5.5	13	8.5	8.0	81	12 – 17 <sup>g</sup>
Quinine <sup>a,c</sup>	Antimalarial, flavouring agent	16	50	41	23	140	
Raloxifene	Selective estrogen receptor modulator	4.9	0	ND	ND	420	
Ranitidine <sup>a</sup>	Acid inhibitor (ulcers)	38	100	180	72	100	<3 – 73 <sup>e,h,q</sup>
Sertraline <sup>c</sup>	Antidepressant	3.3	0	ND	ND	300	
Sitagliptin	Antihyperglycemic	20	25	36	20	81	
Sulfadimethoxine <sup>b</sup>	Sulfonamide antibiotic	33	0	ND	ND	83	
Sulfamethizole <sup>b</sup>	Sulfonamide antibiotic	21	0	ND	ND	82	
Sulfamethoxazole	Sulfonamide antibiotic	13	38	<MDL	<MDL	80	1.8 – 8 <sup>e,j</sup>
Tamoxifen <sup>c</sup>	Cancer treatment	11	0	ND	ND	3300	<10 – 210 <sup>k,o</sup>
Temazepam	Benzodiazepine (hypnotic)	9.2	25	<MDL	<MDL	81	1.4 – 78
Theophylline	Diuretic	8.3	0	ND	ND	75	
Pharmaceutical	Source or use	MDL (ng/L)	Detection Frequency %	Max (ng/L)	Median (ng/L)	Matrix recovery % (median)	Detected in the UK (ng/L)
Thiabendazole <sup>b</sup>	Fungicide	0.82	0	ND	ND	83	



Tiotropium <sup>c</sup>	Bronchodilator	8.6	0	ND	ND	220	
Tramadol	Opioid analgesic	3.0	50	77	49	90	3.0 – 7700 <sup>e,f</sup>
Triamterene	Diuretic	2.6	25	4.2	<MDL	80	
Trimethoprim	Antibiotic	3.8	75	31	22	86	<1.5 – 180 <sup>e,r</sup>
Venlafaxine	Antidepressant	0.90	38	15	12	95	1.1 – 85
Verapamil <sup>c</sup>	Calcium channel blocker	3.1	0	ND	ND	550	
Warfarin	Anticoagulant	3.0	25	<MDL	<MDL	84	

% = percentage; ng/L = nanograms per litre; MDL = Method detection limit; ND = Not detected

<sup>a</sup> Available over-the-counter in the UK

<sup>b</sup> Not prescribed in York, UK in January 2015

<sup>c</sup> API reported as estimate due to being only qualitatively confirmed (<MDL) or environmental matrix recovery quality assurance criteria (60-120%) according to Furlong et al. [42], reported values are not corrected for percentage of analyte recovered in environmental matrix spikes according to Wershaw et al. [43]

<sup>d</sup> Bound & Volvoulis, 2006 [47]

<sup>e</sup> Kasprzyk-Hordern et al., 2008 [48]

<sup>f</sup> Baker & Kasprzyk-Hordern, 2013 [49]

<sup>g</sup> Baker & Kasprzyk-Hordern, 2011 [50]

<sup>h</sup> Kasprzyk-Hordern et al., 2009 [51]

<sup>i</sup> Evans et al., 2015 [52]

<sup>j</sup> Petrie et al., 2015 [53]

<sup>k</sup> Ashton et al., 2004 [54]

<sup>l</sup> Hilton et al., 2003 [55]

<sup>m</sup> Roberts & Bersuder, 2006 [56]

<sup>n</sup> Aherne et al., 1990 [57]

<sup>o</sup> Roberts & Thomas, 2006 [58]

<sup>p</sup> Zhang & Zhou, 2007 [59]

<sup>q</sup> Kasprzyk-Hordern et al., 2007 [60]

<sup>r</sup> Boxall et al., 2011 [61]

<sup>s</sup> Aherne et al., 1985 [62]

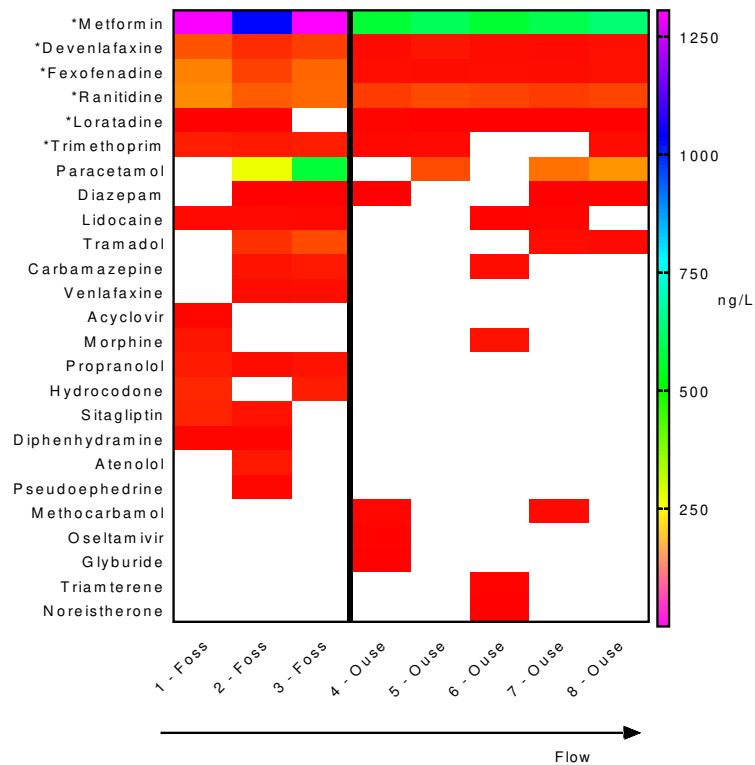


Figure 2. A heat map of the mean pharmaceutical concentration at each of the 8 sampling sites along the Rivers Ouse and Foss. Numbers refer to the specific sampling sites listed in Figure 1. Significant differences in concentrations between the River Ouse and Foss were found for the 6 pharmaceuticals that were detected frequently enough to compute a student's t-test, \* indicates a  $p \leq 0.05$ .

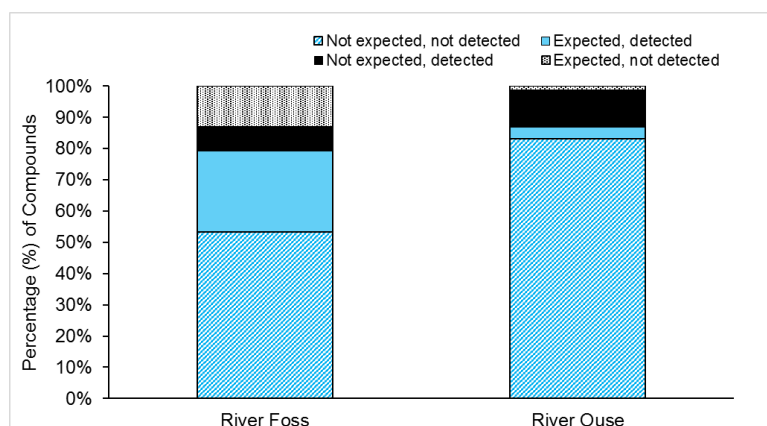


Figure 3. A semi-quantitative analysis of PEC performance in the rivers based on the monitoring campaign results. A compound is expected to be detected when the PEC is greater than the respective analytical method detection limit.

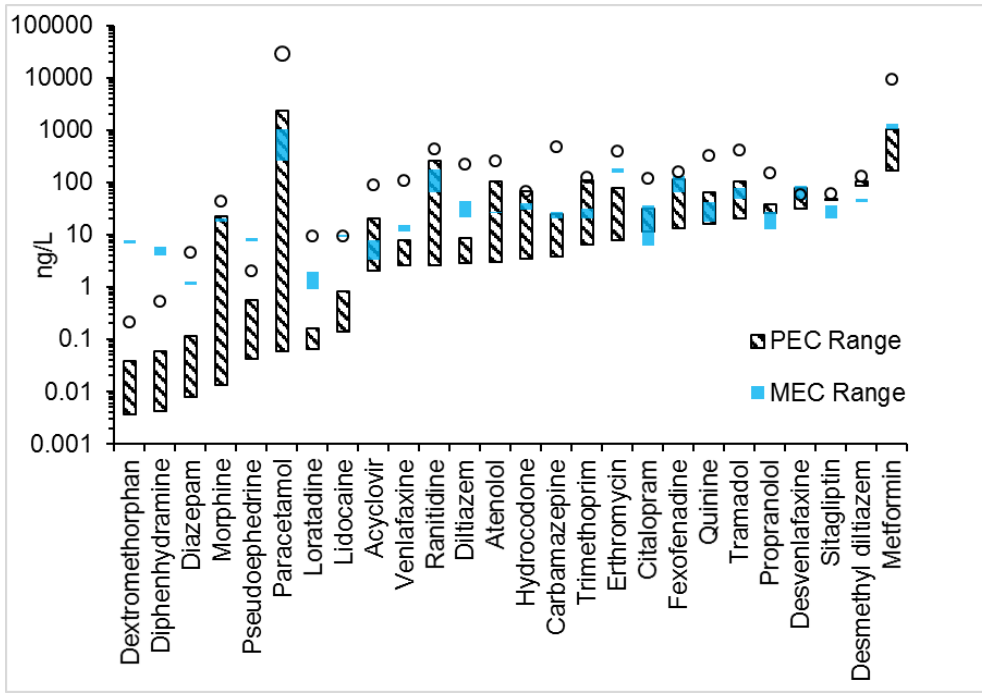


Figure 4. PEC range and MEC range for compounds quantified in the River Foss. The worst case PEC is also plotted (open circles) where  $F_{\text{excreta}} = 1$  and WwTP removal = 0. The MEC range is based on the results from sampling sites 1-3 (Figure 1).

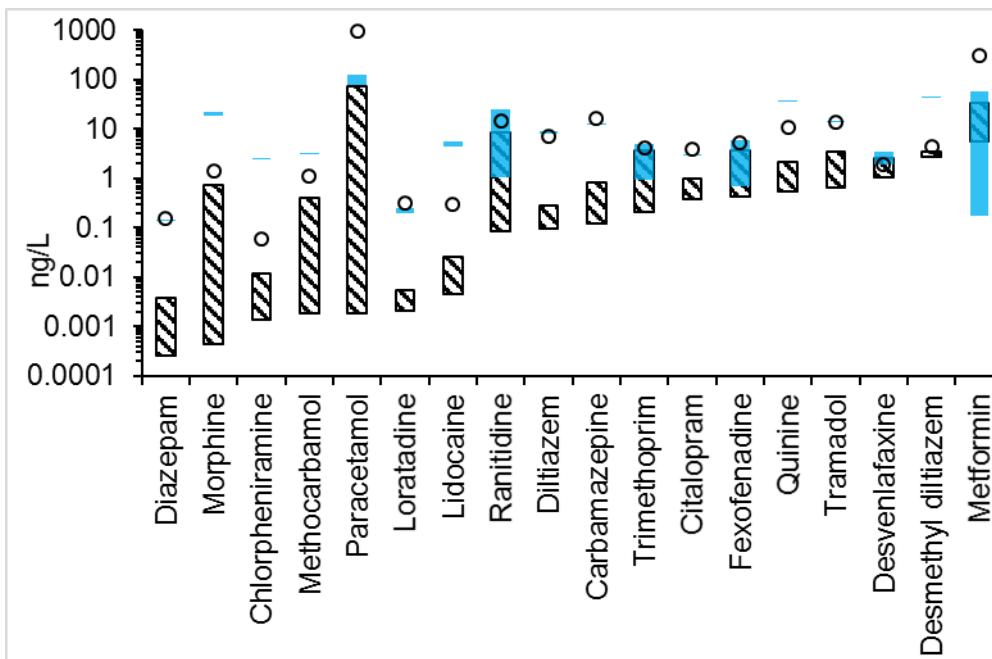


Figure 5. PEC range and MEC range for compounds quantified in the River Ouse. The worst case PEC is also plotted (open circles) where  $F_{\text{excreta}} = 1$  and WwTP removal = 0. The MEC range is based on the results from sites 5-7 (Figure 1) and corrected for the upstream contributions.

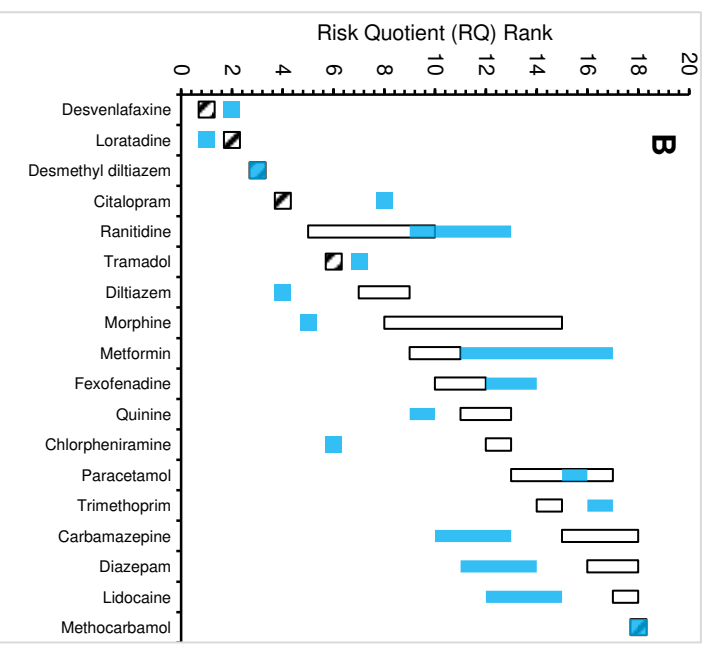
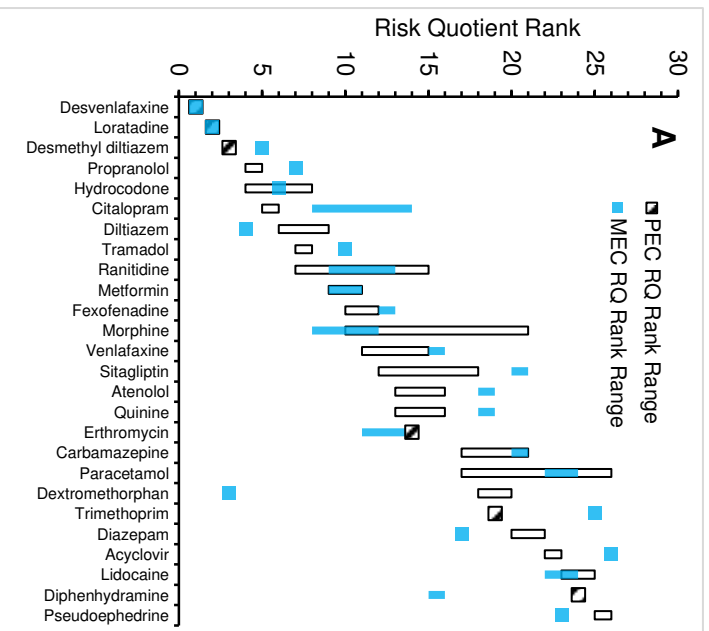


Figure 6. (A) The range of possible ranks resulting from risk quotients calculated using MECs or PECs in the River Foss. (B) The range of possible ranks resulting from risk quotients calculated using MECs or PECs in the River Ouse. Ranks are presented by decreasing risk, where rank 1 corresponds to highest risk.