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

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

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

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**

128 *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 μm 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 μL) 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 detections 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 $PEC = \dfrac{consumption * F_{excreta} * (1\text{-WwTP removal})}{inhabitants * WW_{inhab} * dilution}$ (1)

191 Where the numerator represents the river input rate (ng per day): consumption =

192 amount used per day (ng/day); $F_{excreta}$ 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; WW_{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 $F_{excreta}$ 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 $F_{excreta}$ 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 $F_{excreta}$ 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 $F_{excreta}$ 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 $F_{excreta}$ and lowest WwTP removal found in the literature. A PEC (worst

225 case) was also calculated which only considered site-specific dilution (ie. $F_{excreta}$ = 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 complied by Berninger et al. [41].

236 $\quad$ $RQ = \dfrac{PEC*BCF}{C_{max}}$ $\hspace{6cm}$ (2)

237 $\quad$ 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.

RESULTS AND DISCUSSION

241 *Pharmaceutical Occurrence*

242 $\quad$ 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 $F_{excreta}$ 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.

CONCLUSIONS

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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.

SUPPLEMENTAL DATA

407

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 **ACKNOWLEDGEMENT**

420

421   *Data availability*—Data, associated metadata, and calculation tools are available by

422   contacting the corresponding author (alistair.boxall@york.ac.uk).

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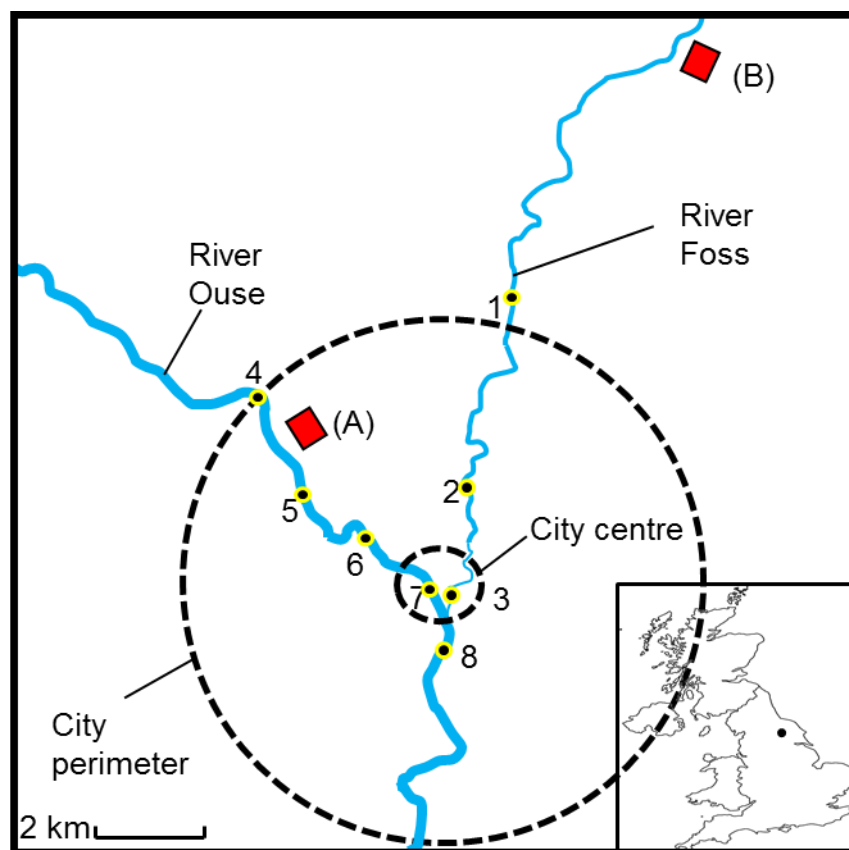
Figure 1. Locations of the 8 sampling sites around the city of York, UK. A and B represent the WwTPs
that service the city. Grab samples were collected in February 2015.

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[a]	Antiviral	4.4	13	7.9	7.9	60	
Albuterol[a]	β2-adrenergic receptor	1.2	0	ND	ND	180	38 – 470[2 e]
Alprazolam	Benzodiazepine	4.3	0	ND	ND	75	
Amitriptyline	Antidepressant	19	25	<MDL	<MDL	250	1.0 – 72[f,g]
Amphetamine	Psychostimulant	4.1	0	ND	ND	76	1.1 -4[f]
Antipyrine[b]	Analgesic	58	20	<MDL	<MDL	87	
Atenolol	Beta blocker	2.7	13	25	25	97	<1 – 530[e]
Benztropine[b,c]	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[e,h]
Carisoprodol	Muscle relaxant	2.5	0	ND	ND	81	
Chlorpheniramine[a,c]	Antihistamine	0.94	13	2.4	2.4	220	
Cimetidine[c]	H2-receptor antagonist	5.6	38	<MDL	<MDL	100	<0.5 – 202[e]
Citalopram[c]	Antidepressant	1.3	50	37	14	170	53[i]
Clonidine	Antihypertensive	30	0	ND	ND	87	
Dehydronifedipine	Nifedepine metabolite	4.9	0	ND	ND	78	
Desmethyl-diltiazem[c]	Degradate of diltiazem	2.5	25	48	44	210	
Desvenlafaxine	Antidepressant, venlafaxine metabolite	3.8	88	85	16	87	7.3 – 290[i,j]

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[a,c]	Cough suppressant	1.6	25	6.7	6.0	140	
Diazepam	Benzodiazepine	0.45	63	1.3	1.0	81	0.6– 1.1[f,g]
Diltiazem[c]	Calcium channel blocker	5.1	63	44	9.1	180	<1 – 49[e]
Diphenhydramine[a]	Antihistamine	2.9	25	6.0	5.6	100	
Erythromycin[c]	Macrolide antibiotic	27	25	180	170	250	<0.5 – 1000[k,l]
Ezetimibe[c]	Cholesterol-reducing agent	13	25	<MDL	<MDL	160	
Fadrozole[b]	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[j]
Fluconazole[a]	Antifungal	36	0	ND	ND	76	
Fluoxetine[c]	Antidepressant	5.4	0	ND	ND	360	6.2 – 34[f,m]
Fluticasone[c]	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[c]	Antifungal	56	0	ND	ND	430	
Lamivudine[c]	Antiretroviral	3.2	0	ND	ND	160	
Lidocaine[a]	Topical anesthetic	3.1	75	9.6	8.9	84	
Loperamide [c]	Antidiarrheal	5.7	0	ND	ND	420	
Loratadine[a]	Antihistamine	1.4	88	8.5	1.5	120	
Pharmaceutical	Source or use	MDL (ng/L)	Detection	Max	Median	Matrix	Detected in

Pharmaceutical	Source or use	MDL (ng/L)	Detection Frequency %	Max (ng/L)	Median (ng/L)	Matrix recovery % (median)	Detected in the UK (ng/L)
Lorazepam	Benzodiazepine (anxiolytic)	58	0	ND	ND	84	
Meprobamate	Anxiolytic	17	0	ND	ND	74	
Metaxalone[b]	Muscle relaxant	7.8	0	ND	ND	80	
Metformin	Antidiabetic	6.6	100	1300	630	120	2300[j]
Methadone[c]	Synthetic opioid	3.8	0	ND	ND	200	10 – 18[g]
Methocarbamol	Muscle relaxant	4.4	25	10	8.7	81	
Methotrexate	Chemotherapy agent	11	0	ND	ND	76	<6.3[n]
Metoprolol[c]	Beta-blocker	14	0	ND	ND	86	<0.5 – 12[e]
Morphine	Analgesic (opioid)	2.8	30	21	19	84	0.6 – 36[f,g]
Nadolol	Beta-blocker	16	0	ND	ND	85	
Nevirapine[c]	Antiretroviral	3.0	25	<MDL	<MDL	81	
Nizatidine[c]	Acid inhibitor (ulcers)	9.5	0	ND	ND	240	
Noreistherone	Oral contraceptive component	2.2	13	<MDL	<MDL	85	<10 – 17[s]
Nordiazepam	Benzodiazepine, diazepam metabolite	21	0	ND	ND	82	0.1 – 6.8[f]
Norverapamil[c]	Verapamil metabolite	1.7	0	ND	ND	400	
Omeprazole[c]	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[f]
Oxycodone	Opioid analgesic	5.0	0	ND	ND	90	0.4 – 7.1[f,g]
Paracetamol[a]	Analgesic	3.6	63	1000	260	88	52 – 2400[d,e]
Paroxetine[c]	Antidepressant	4.1	0	ND	ND	300	
Penciclovir[c]	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)
Pentoxyfylline[c]	Cardiovascular drug	4.7	10	<MDL	<MDL	86	
Phenazopyridine[b]	Urinary tract analgesic	2.7	0	ND	ND	84	
Phendimetrazine[b]	Appetite suppressant	16	0	ND	ND	86	
Phenytoin	Antiepileptic	94	0	ND	ND	78	
Piperonyl butoxide[b]	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[a,c]	Antihistamine	10	50	<MDL	<MDL	190	
Propoxyphene	Opioid analgesic	3.4	0	ND	ND	140	9 -680[k,o]
Propranolol	Beta blocker	13	50	27	18	110	3.9- 220[k,p]
Pseudoephedrine[a]	Decongestant	5.5	13	8.5	8.0	81	12 – 17[g]
Quinine[a,c]	Antimalarial, flavouring agent	16	50	41	23	140	
Raloxifene	Selective estrogen receptor modulator	4.9	0	ND	ND	420	
Ranitidine[a]	Acid inhibitor (ulcers)	38	100	180	72	100	<3 – 73[e,h,q]
Sertraline[c]	Antidepressant	3.3	0	ND	ND	300	
Sitagliptin	Antihyperglycemic	20	25	36	20	81	
Sulfadimethoxine[b]	Sulfonamide antibiotic	33	0	ND	ND	83	
Sulfamethizole[b]	Sulfonamide antibiotic	21	0	ND	ND	82	
Sulfamethoxazole	Sulfonamide antibiotic	13	38	<MDL	<MDL	80	1.8 – 8[e,j]
Tamoxifen[c]	Cancer treatment	11	0	ND	ND	3300	<10 – 210[k,o]
Temazepam	Benzodiazepine (hypnotic)	9.2	25	<MDL	<MDL	81	1.4 – 78
Theophylline	Diuretic	8.3	0	ND	ND	75	
Thiabendazole[b]	Fungicide	0.82	0	ND	ND	83	

Tiotropium[c]	Bronchodilator	8.6	0	ND	ND	220	
Tramadol	Opioid analgesic	3.0	50	77	49	90	3.0 – 7700[e,f]
Triamterene	Diuretic	2.6	25	4.2	<MDL	80	
Trimethoprim	Antibiotic	3.8	75	31	22	86	<1.5 – 180[e,r]
Venlafaxine	Antidepressant	0.90	38	15	12	95	1.1 – 85
Verapamil[c]	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
[a] Available over-the-counter in the UK
[b] Not prescribed in York, UK in January 2015
[c] 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]
[d] Bound & Volvoulis, 2006 [47]
[e] Kasprzyk-Hordern et al., 2008 [48]
[f] Baker & Kasprzyk-Hordern, 2013 [49]
[g] Baker & Kasprzyk-Hordern, 2011 [50]
[h] Kasprzyk-Hordern et al., 2009 [51]
[i] Evans et al., 2015 [52]
[j] Petrie et al., 2015 [53]
[k] Ashton et al., 2004 [54]
[l] Hilton et al., 2003 [55]
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[o] Roberts & Thomas, 2006 [58]
[p] Zhang & Zhou, 2007 [59]
[q] Kasprzyk-Hordern et al., 2007 [60]
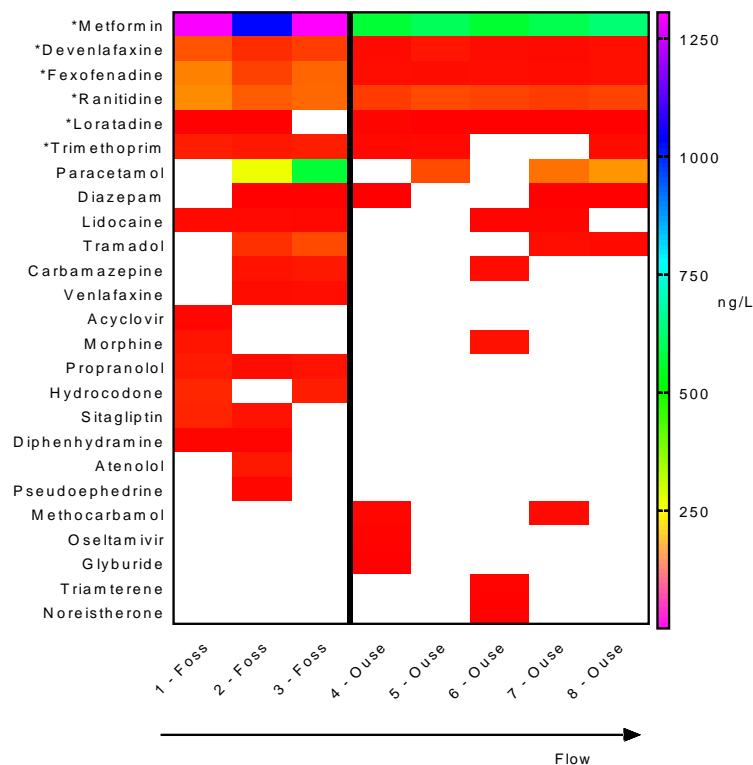[r] Boxall et al., 2011 [61]
[s] Aherne et al., 1985 [62]

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 ≤ 0.05.
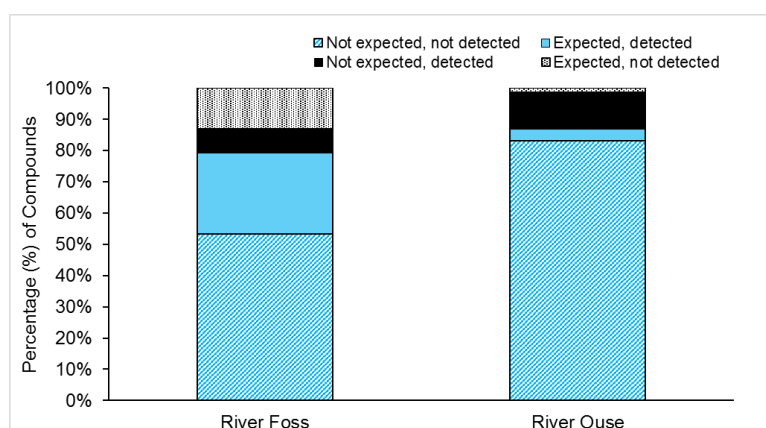

Figure 3. A semi-quantitative analysis of PEC performance in the rivers based on the monitoring campaign results. A compound is expected to be detected when the PEC is greater than the respective analytical method detection limit.
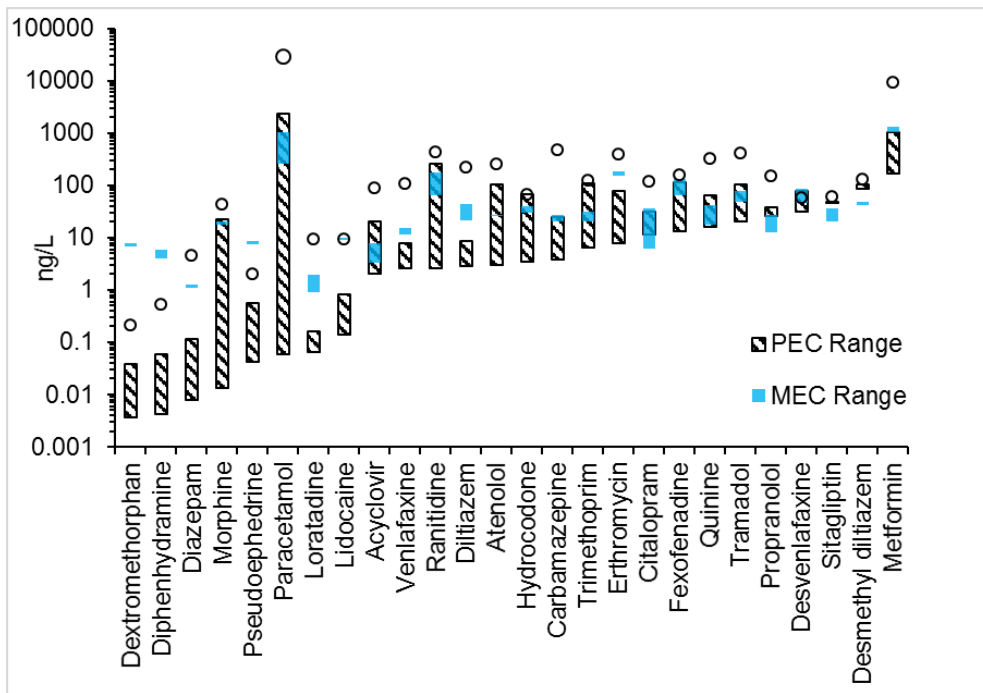
Figure 4. PEC range and MEC range for compounds quantified in the River Foss. The worst case PEC is also plotted (open circles) where $F_{excreta}$ = 1 and WwTP removal = 0. The MEC range is based on the results from sampling sites 1-3 (Figure 1).

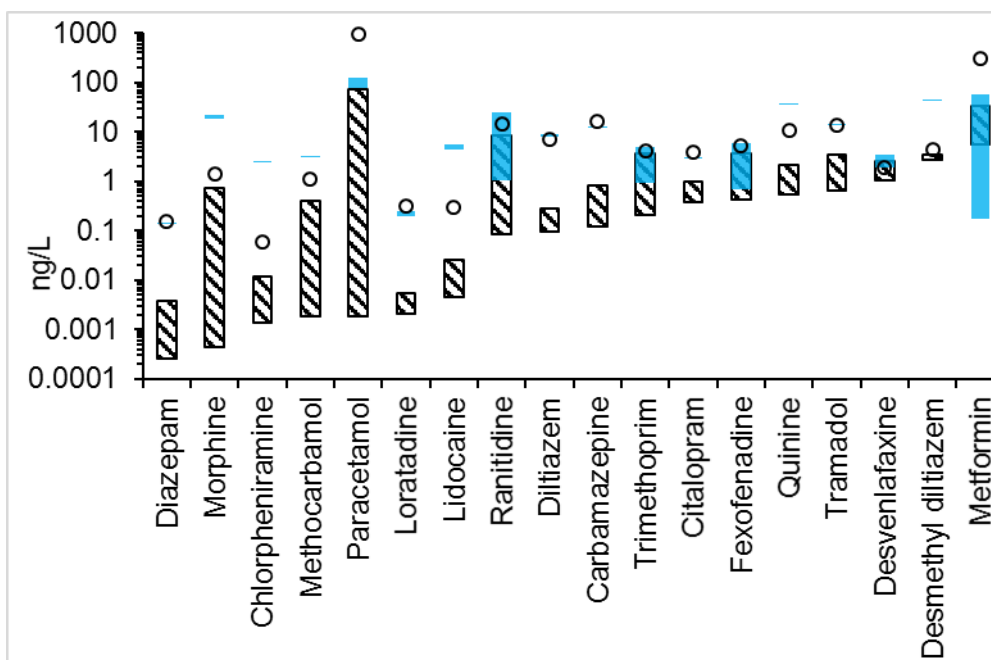Figure 5. PEC range and MEC range for compounds quantified in the River Ouse. The worst case PEC is also plotted (open circles) where $F_{excreta}$ = 1 and WwTP removal = 0.The MEC range is based on the results from sites 5-7 (Figure 1) and corrected for the upstream contributions.
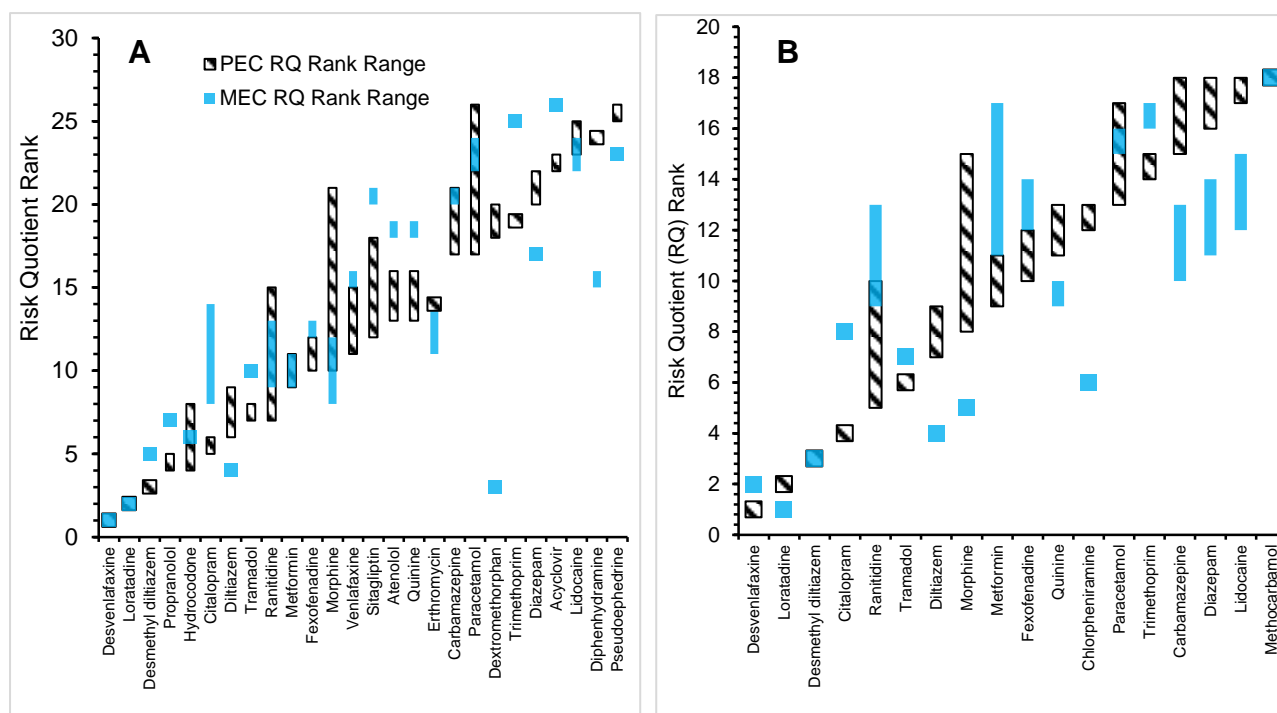
Figure 6. (A) The range of possible ranks resulting from risk quotients calculated using MECs or PECs in the River Foss. (B) The range of possible ranks resulting from risk quotients calculated using MECs or PECs in the River Ouse. Ranks are presented by decreasing risk, where rank 1 corresponds to highest risk.