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

Emily E. Burns,[†] Jane Thomas-Oates,[†] Dana W. Kolpin,[‡] Edward T. Furlong,[§] Alistair B.A. Boxall*[‖]

[†]Chemistry Department, University of York, York, United Kingdom

[‡] U.S. Geological Survey, Iowa City, IA, United States

[§] U.S. Geological Survey, National Water Quality Laboratory, Denver CO, United States

[‖]Environment Department, University of York, York, United Kingdom

*Address correspondence to alistair.boxall@york.ac.uk

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

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

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

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

Consequently, many risk-based prioritisation methods have employed exposure prediction models or algorithms to derive predicted environmental concentrations (PECs) in order to prioritise pharmaceuticals that have no monitoring data and/or to provide conservative estimates of environmental concentrations [16]. PECs are typically derived based on data on pharmaceutical usage, degree of metabolism in humans, removal in wastewater treatment plants (WwTP) and environmental dilution. The method most commonly used is based on the approach recommended in the European Medicines Agency (EMEA) guidelines for assessment of the risk of human pharmaceuticals in the environment [6,9,11,17–23]. Default parameters (e.g. for dilution of wastewater) proposed by the EMEA guidance are regularly used in these prioritisation exercises, regardless of their suitability [6,10,19,20]. The use of site-specific data when performing these calculations for prioritisation is a rarity [21].

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

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

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

METHODS

Study site and sampling

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

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

Analytical Methods

Samples were analysed using a direct injection (100 µL) high-performance liquid chromatography/tandem mass spectrometry with an electrospray ionization source (LC-ESI-MS/MS) method for the determination of 110 pharmaceuticals, pharmaceutical degradates, and wastewater indicator compounds [31]. Of the 110 compounds, 95 pharmaceuticals were targeted in the present study with method detections limits (MDL) as defined by the US Environmental Protection Agency (USEPA) [32] down to 0.45 ng/L (Table 1). Instrumentation included an Agilent 6410 triple quadrupole MS/MS system coupled with an Agilent 1200 Series HPLC. Mobile phases were HPLC-grade water modified with 1M formic acid and 1M ammonium formate (A) and 100% HPLC grade methanol (B). Chromatography gradient and conditions are detailed in Supplemental Data, Table S2. Quantification and identification was achieved by external calibration with known standards for each of the pharmaceuticals and completed using Agilent Mass Hunter software in accordance with the USGS methodology described in Furlong et al. [31]. The MS/MS was operated in multiple reaction monitoring (MRM) mode, where two MRM transitions and correct retention times were required for ion qualification, while quantification was based on the major transition (Supplemental Data, Table S3). Additionally, ion ratios between the major and secondary transitions were required to fall within a compound-specific range determined from the corresponding analytical standard [31]. Concentrations reported in the present study are the median of three aliquots taken from each site.

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

Quality control samples were analysed to (1) assess matrix recovery efficiency and identify the presence of matrix interferences that could induce ion suppression or enhancement [34], and (2) identify any blank contamination from sampling and analysis. For recovery assessment, an environmental sample was amended with the pharmaceuticals of interest (matrix spike) to a concentration of 400 ng/L. The aforementioned field blank samples were analysed to identify any potential contributions of pharmaceuticals during sample collection, laboratory processing and analysis. In addition to the field blank and matrix spike samples, analogous laboratory spike and blank samples, using high purity HPLC-grade water, also were analysed with each batch of environmental samples.

PEC Modelling

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

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

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

Pharmaceutical usage was generated from localised prescription data released monthly by the National Health Service for January 2015 [35]. Relevant medical practices were selected by postal code (Supplemental Data, Table S4). The $F_{excreta}$ term was obtained from either the peer-reviewed literature or online databases such as Drugbank, MedSafe and RXmed, as well as publicly available pharmaceutical data sheets released by government organisations such as MedSafe New Zealand or the Food and Drug Agency (Supplemental Data, Table S5). When a pharmaceutical was metabolised to conjugated metabolites (e.g. glucuronide or sulfato-conjugates), the portion released as a conjugate was added to the unchanged parent excretion estimate. These metabolites can undergo reactions during water treatment such as cleavage and thus be converted back into their parent compounds, increasing the parent pharmaceutical load in wastewater effluent [36]. Estimates of unchanged pharmaceutical excretion varied across sources; this led to a range of possible unchanged excretion estimates, which were used to calculate a PEC range. For ophthalmic and topical preparations, metabolism was assumed to be zero and therefore the $F_{excreta}$ was set to 1 [19].

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

Evaluation of PECs

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

Prioritisation Approach

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

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

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

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

RESULTS AND DISCUSSION

Pharmaceutical Occurrence

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

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

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

Evaluation of Modelled Concentrations with Monitoring Data

The EMEA PEC model describes an annual average concentration for the region the consumption data cover; in general, usage data from the whole of a country is averaged to give a single PEC [4]. Evaluating this approach with localised, temporally limited samples would introduce a source of potential error as it has been shown that seasonal usage is important for some pharmaceuticals and that demographics in a specific area may differ substantially from the national average [25,26]. To reduce these potential biases, local usage data, corresponding to time of sampling, was used. In addition, site-specific dilution factors were incorporated to avoid the use of EMEA [23] default dilution factors (i.e. 10). The WW_{inhab} term could not be refined to actual discharge because both WwTPs are highly variable and discharge measurements were not available for the sampling dates. This permits a focus on other factors that could be affecting the suitability of PECs such as WwTP removal and metabolism.

Overall PEC Performance

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

The large difference in dilution between the two rivers, factors of 17.8 and 540 for the Foss and Ouse respectively, led to larger PECs in the River Foss and therefore a higher number of expected detections. A larger proportion of expected detections were not identified in our monitoring campaign in the Foss in comparison to the Ouse; it could be that pharmaceuticals were missed by our sampling effort, however our results indicate that pharmaceutical concentrations are stable throughout the River Foss over an 8-hour period (Figure 2), which diminishes the likelihood of missing a detection. Conversely, the metabolism or WwTP removal selected from the literature may have produced PECs larger than real-world concentrations. The number of unexpected but detected pharmaceuticals is greater in the River Ouse, despite corrections for upstream contributions detected at site 4, (Figure 2). The River Ouse could be subject to a greater number of sources not reflected in our usage estimate in contrast to the more rural River Foss. Sources of pharmaceuticals beyond the scope of localised prescription data exist within the city include, for example, a substantial tourism industry and two post-secondary institutions. Recent studies have demonstrated the impact of post-secondary institutions [44] and music festivals [45] on MECs, and it is likely that MECs in the Ouse are influenced by demographic factors not inclusive of localised prescription-based usage estimates.

Impact of Metabolism and WwTP Removal Uncertainty on PECs

Underestimated PECs: A breakdown of how each pharmaceutical PEC performed in comparison to the MEC is shown for the River Foss (Figure 4) and the River Ouse (Figure 5). While the overall semi-quantitative performance of PECs in the River Ouse was slightly better than the Foss, these results were not repeated when quantitative data were compared. In the Foss and the Ouse, 38% and 78% respectively, of the MEC ranges were entirely greater than the corresponding PEC range. This drops to 12% and 44% respectively when the PEC (worst case) is considered. The PEC (worst case) does not include metabolism or WwTP removal, only dilution, and when this PEC still falls below the MEC it indicates a problem with the consumption estimate. The analytical matrix spike recoveries indicated that matrix enhancement is occurring, which could affect the comparisons with PECs. To investigate, each compound with a MEC range greater than the PEC range was theoretically corrected based on the compound specific matrix recovery. All of the theoretically corrected MEC ranges were still greater than the corresponding PEC ranges in the River Ouse and Foss with one exception, erythromycin, where the MEC range corresponded with the top of the PEC range in the River Foss. Therefore we do not expect our results to be significantly altered by the distribution in matrix recoveries.

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

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

Our results indicate that consideration of metabolism and WwTP removal is essential when calculating PECs because PEC (worst case) is a large overestimate of actual concentrations in the majority of cases (Figure 4), also shown by others [6,10,22]. In the River Foss, prescription pharmaceuticals are described well using the PEC approach. This is in sharp contrast in the River Ouse, where multiple consumption sources are likely affecting concentrations of the pharmaceuticals in the environment, making it impossible to evaluate the effect of the fate parameters with the current dataset. Further monitoring that incorporates sampling WwTP influents and effluents to compute actual removals will be critical to assessing PECs relative to MECs. In addition, the uncertainty in measured concentrations can be limited by incorporating time-averaged composite samples representative of the average conditions [14]. Further work which includes a seasonal monitoring campaign is suggested to quantify the seasonal variability and magnitude of influence that tourism and post-secondary institutions have on MECs in addition to serving as a check of the findings from the present initial scoping study.

Implications for prioritisation

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

CONCLUSIONS

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

SUPPLEMENTAL DATA

Table S1 National grid references of sampling site locations

Tables S2-S3 Analytical operating conditions.

Tables S4-S5 PEC parameters.

Equations S1-S5 Bioconcentration factor equations.

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

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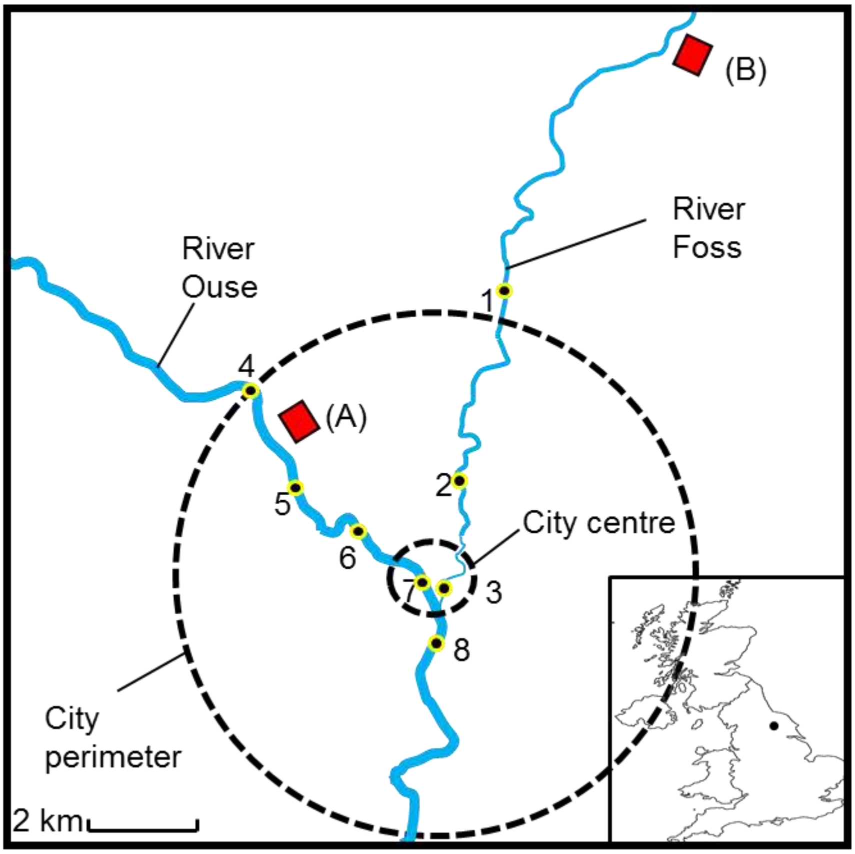

Figure 1. Locations of the 8 sampling sites around the city of York, UK. A and B represent the WwTPs that service the city. Grab samples were collected in February 2015.

Table 1. Occurrence data for the 8 water samples collected during February 2015 from the sampling network with matrix recovery and method detection 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

			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[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	
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[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]
[m]Roberts & Bersuder, 2006 [56]
[n]Aherne et al., 1990 [57]
[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]

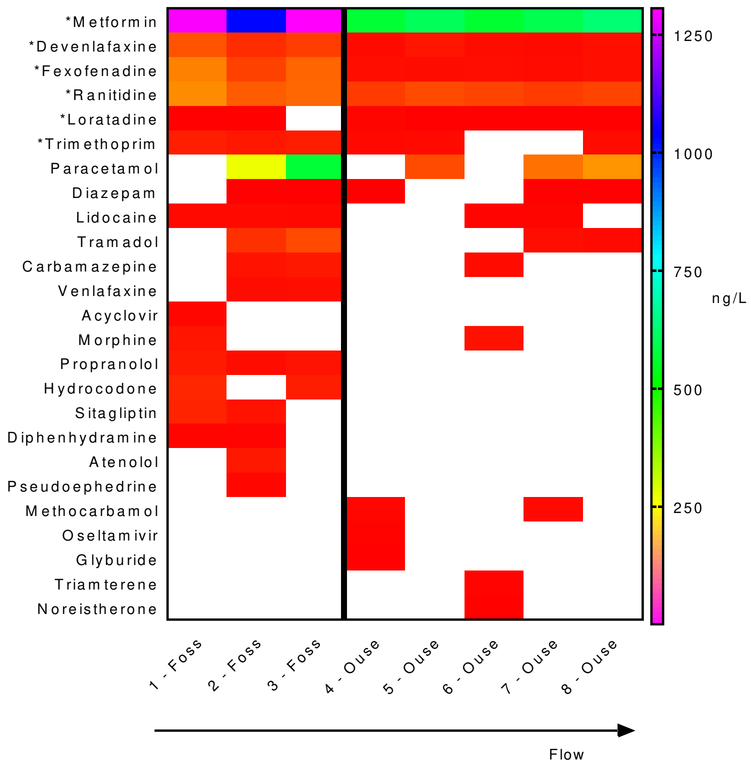

Figure 2. A heat map of the mean pharmaceutical concentration at each of the 8 sampling sites along the Rivers Ouse and Foss. Numbers refer to the specific sampling sites listed in Figure 1. Significant differences in concentrations between the River Ouse and Foss were found for the 6 pharmaceuticals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

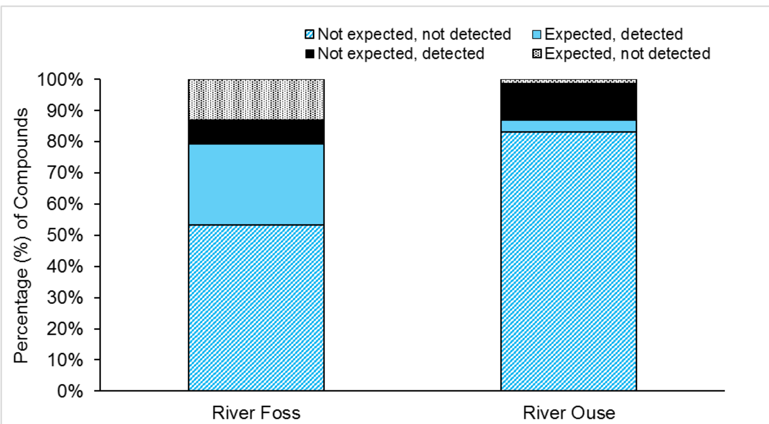

Figure 3. A semi-quantitative analysis of PEC performance in the rivers based on the monitoring campaign results. A compound is expected to be detected when the PEC is greater than the respective analytical method detection limit.

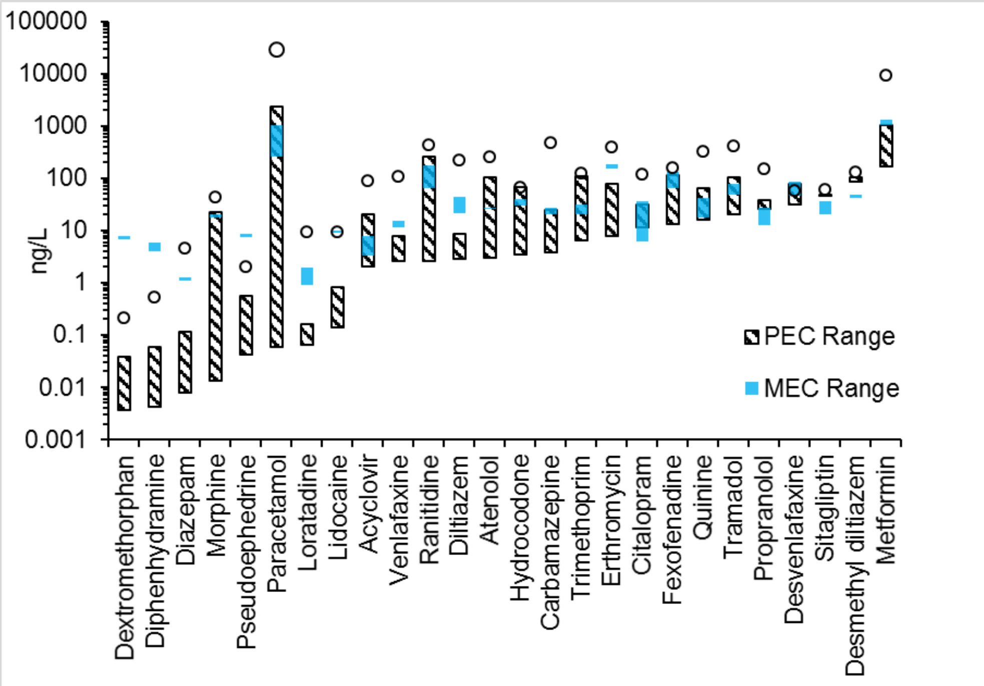

Figure 4. PEC range and MEC range for compounds quantified in the River Foss. The worst case PEC is also plotted (open circles) where $F_{excreta}$ = 1 and WwTP removal = 0. The MEC range is based on the results from sampling sites 1-3 (Figure 1).

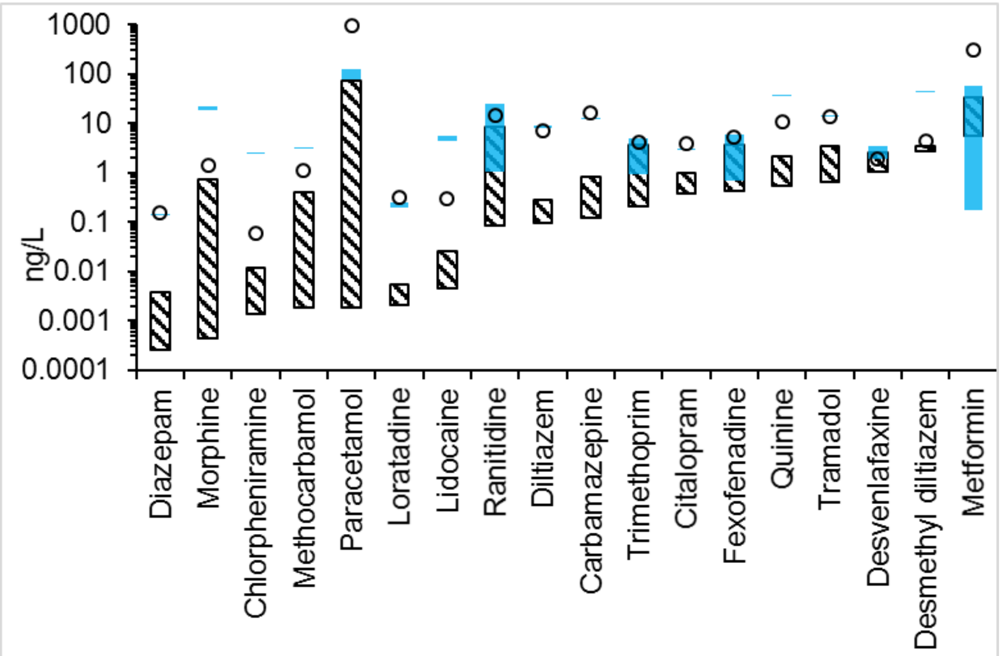

Figure 5. PEC range and MEC range for compounds quantified in the River Ouse. The worst case PEC is also plotted (open circles) where $F_{excreta}$ = 1 and WwTP removal = 0.The MEC range is based on the results from sites 5-7 (Figure 1) and corrected for the upstream contributions.

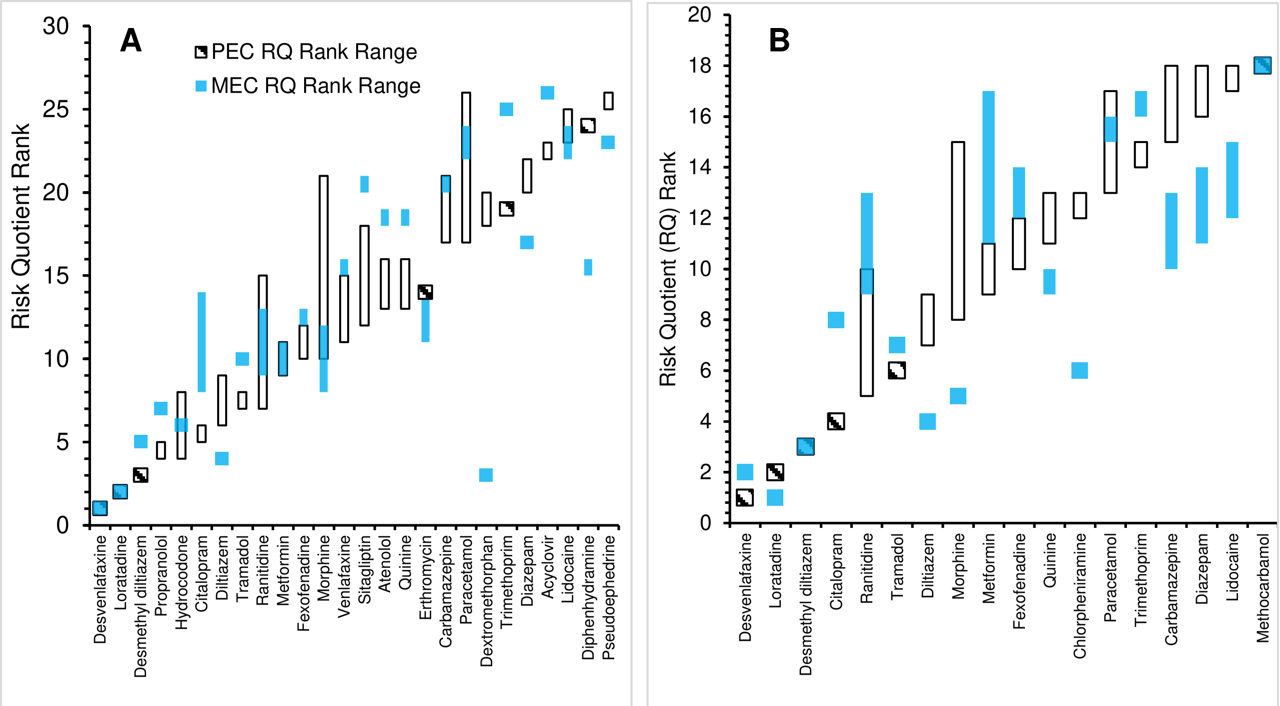

Figure 6. (A) The range of possible ranks resulting from risk quotients calculated using MECs or PECs in the River Foss. (B) The range of possible ranks resulting from risk quotients calculated using MECs or PECs in the River Ouse. Ranks are presented by decreasing risk, where rank 1 corresponds to highest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