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Exploiting Monitoring Data in Environmental Exposure Modelling and Risk Assessment of Pharmaceuticals

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Abstract

In order to establish the environmental impact of an active pharmaceutical ingredient (API), good information on the level of exposure in surface waters is needed. Exposure concentrations are typically estimated using information on the usage of an API as well as removal rates in the patient, the wastewater system and in surface waters. These input data are often highly variable and difficult to obtain, so model estimates often do not agree with measurements made in the field. In this paper we present an approach which uses inverse modelling to estimate overall removal rates of pharmaceuticals at the catchment scale using a hydrological model as well as prescription and monitoring data for a few representative sites for a country or region. These overall removal rates are then used to model exposure across the broader landscape. Evaluation of this approach for APIs in surface waters across England and Wales showed good agreement between modelled exposure distributions and available monitoring data. Use of the approach, alongside estimates of predicted no-effect concentrations for the 12 study compounds, to assess risk of the APIs across the UK landscape, indicated that, for most of the compounds, risks to aquatic life were low. However, ibuprofen was predicted to pose an unacceptable risk in 49.5% of the river reaches studied. For diclofenac, predicted exposure concentrations were also compared to the Environmental Quality Standard previously proposed by the European Commission and 4.5% of river reaches were predicted to exceed this concentration. While the current study focused on pharmaceuticals, the approach could also be valuable in assessing the risks of other 'down the drain' chemicals and could help inform our understanding of the important dissipation processes for pharmaceuticals in the pathway from the patient to ecological receptors.

Key words

Active pharmaceutical ingredient, inverse modelling, ibuprofen, diclofenac

Introduction

During the life cycle of a pharmaceutical product, Active Pharmaceutical Ingredients (APIs) may be released to the natural environment (Daughton and Ternes, 1999; Boxall, 2004) and a wide range of APIs have been detected in surface waters (Hirsch *et al*., 1999; Kolpin *et al*., 2002; Monteiro and Boxall, 2010). Even though the reported concentrations are generally low (i.e. sub-µg/l), questions have been raised over the potential impacts of APIs in the environment on flora and fauna and human health. Environmental risk assessments are also now required in many regions as part of the marketing authorisation process of a new API (Breton and Boxall, 2003). In order to establish the risks of APIs, it is essential to have a good understanding of the levels of exposure that occur in natural systems.

A range of exposure modelling approaches is currently being applied in the assessment of the environmental risks of APIs. These include simple deterministic algorithms through to more complex models such as the GREAT-ER, PhATE and LF2000-WQX models (EMA, 2006; Schowanek and Webb, 2002; Schwab *et al*., 2005; Williams *et al*., 2009) which use data on flow in rivers to estimate how APIs will be distributed within river catchments. In order to accurately estimate concentrations in the environment, these models traditionally require comprehensive information on the usage of an API within the system of interest, the extent of metabolism of the API within treated humans and the degree of removal in wastewater treatment processes and in receiving waters.

Many countries collate detailed information on the quantities of APIs used. For example, in the UK, the National Health Service collect monthly information on the number of prescriptions made for different products in different regions. From this freely available information, it is possible to determine the amounts of different APIs prescribed in an area over time. Similar systems are in place in Denmark, Germany and Australia. However, the estimation of API usage, based on prescription volumes, may over-estimate what is actually

66 released to the environment. Over half of patients store unused medicines in their home as a
67 consequence of dosage changes, discontinuation of the medication due to, for example, the
68 occurrence of adverse side effects, or because the medications have reached their expiry date.
69 It is estimated that anywhere between 3 and 65% of prescribed pharmaceuticals are not used
70 and many of these will ultimately be returned to the pharmacist or disposed of to landfill
71 (Seehusen and Edwards, 2006; Musson and Townsend, 2009).
72 While numerous publications are available on the metabolism of APIs, the results of these
73 studies can be highly variable. For example, for cyclophosphamide (one of the APIs
74 investigated in the current study), amounts excreted are reported to range from 2 to 25% of
75 the applied dose (Bagley *et al.*, 1973). The observed differences are probably explained by
76 genomically distinct metabolising capacities as well as differences in race, sex, age and
77 health status of the studied subjects, all of which are known to affect the route and rate of
78 metabolism (Dorne, 2010). The method of administration, previous exposure of a patient to
79 the pharmaceutical and simultaneous exposure to other APIs and xenobiotics can also affect
80 the degree of metabolism.
81 For many APIs, no data exist on removal in wastewater treatment. In instances where data are
82 available, variations can also be seen in the reported removal efficiencies (Sipma *et al.*,
83 2010). These variations can be explained by differences in technologies used at different
84 treatment works and differences in operating parameters. Some metabolites may also be re-
85 converted back to the parent compound in wastewater treatment (Heberer *et al.*, 2002). In
86 large catchments it is likely that numerous treatment technologies will be in use and that
87 these will vary in size and performance, so a variety of removal rates may need to be
88 employed in the modelling. The fate of substances in the sewer system is also unknown.
89 Finally, available data on dissipation of APIs in receiving waters is mostly generated under
90 controlled laboratory conditions and dissipation in natural aquatic systems is often much

slower than in the laboratory (Fono *et al*., 2006). When all of these different factors are considered, it is perhaps not surprising that the selection of the input parameters for exposure modelling for APIs can be challenging and that, while some exposure modelling of this type has been successful for some contaminants (Ort *et al*., 2009), predictions do not always agree with observed measurements of APIs in the field (Metcalfe *et al*., 2008).

One approach to overcome the problem of the parameter selection process is to use monitoring data alongside inverse modelling to derive model input parameters. In this approach, data on measured concentrations of APIs within a study system are used in the models to back calculate one or more model input parameter. The derived parameters can then be employed to model exposure in other scenarios. The advantage of this approach in API exposure modelling is that it accounts for variability in factors such as metabolism of APIs within the population in the catchment; dissipation in the sewer network; effects of different types of treatment technologies that are employed; and the different dissipation processes that occur in surface waters. Inverse modelling, based on data on environmental occurrence, has already successfully been used to estimate usage of illicit drugs for different regions around the world (Zuccato *et al*., 2011) and emissions and half-lives of selected APIs into/in European surface waters (Pistocchi *et al*., 2012).

In this paper we present and evaluate a combined monitoring and modelling approach that uses prescription and monitoring data to estimate removal of pharmaceuticals between the point of use and emission into surface waters. We then show how the removal estimates can be used to estimate concentration distributions for API in water bodies at the landscape scale. We illustrate the utility of the approach by assessing the risks of 12 commonly used APIs across surface waters in England and Wales.

1. Methods

1.1.Monitoring data

The measured data on concentrations of APIs in surface waters was taken from a recent study into the occurrence of APIs in surface and drinking waters in England and Wales (Boxall *et al*., 2012a). The twelve study APIs (Table 1) covered a range of chemical classes and varied in terms of their physico-chemical properties. The study was carried out at four catchments, which varied in terms of the population served and in the type of wastewater treatment technologies employed (Table 2). Triplicate samples of surface water (2.5 L) were taken from a single point in each catchment every 4 weeks for a period of 12 months. Following collection, these were immediately transported back to the laboratory where they were extracted onto HLB solid phase extraction cartridges before being analysed by LC-MS/MS using a Waters Acquity Ultra-Performance Liquid Chromatography (UPLC) system (Waters, Milford MA, US) fitted with a UPLC HSS T3 C18 column. Gradient elution was used with mobile phases consisting of 5 mM ammonium acetate in water and methanol. Concentrations were determined by comparison of peak areas with those of known matrix-matched standards. For a number of analytes (atenolol, carbamazepine, fluoxetine and ibuprofen), internal standards, comprising the deuterated form of the compound, were used to correct for losses during the extraction process and/or suppression or enhancement of the MS signal. In the event that internal standards were not available, sample over-spiking at a range of concentrations was used to assess recovery of a compound. Seven of the 12 study compounds were detected in surface waters at sub-µg/l concentrations. Mean concentrations and concentration ranges are shown in Table 1.

1.2.Model Description

The modelling was carried out using the LF2000-WQX model (Williams et al., 2009), which is a spatially-based modelling framework that has been widely applied to a number of chemicals discharged down-the-drain (Williams *et al*., 2009; Rowney *et al*., 2009; Price *et al*.,

141 2010a and b; Janna *et al*., 2011) and so only the parts salient to this analysis will be described
142 here. LF2000-WQX is the water quality extension model to the Low Flows 2000 (LF2000)
143 software system (Young *et al*., 2003; Environment Agency, 2004), which is a geographical
144 information system (GIS) based decision support tool designed to estimate river flows at
145 ungauged sites. It combines hydrological models estimating the magnitude and variability of
146 flows across a catchment with a water quality model. The water quality model is driven by
147 discharges from sewage treatment plants (STPs), the locations of which are preset in the
148 model along with data describing the population served, treatment type and dry weather flow
149 of each works. The outputs of the model are mean and 90th and 95th percentile
150 concentrations for each river reach within the catchment being modelled.
151 Calculation of concentrations in river reaches is based on a simple mass balance mixing
152 equation which is applied in an iterative Monte Carlo simulation using the method of
153 combining distributions proposed by Warn and Brew (Warn and Brew, 1980). Point-source
154 effluent emissions are combined with reach-specific flow statistics to calculate in-river
155 concentrations after mixing at the point of discharge, allowing for upstream concentrations of
156 the pharmaceutical. Flow in the river and flow volume from the sewage works are described
157 as distributions. The other parameters are held constant. The river flow is characterised as
158 log-normal and the sewage works flows as normal. Changes in concentration with 'flow time'
159 due to dilution, from e.g. inputs from tributaries, and degradation also are calculated.
160 The emissions of an API for a given STP are typically derived from prescription data and
161 STP characteristics. The STP inflow concentration (C_i) is estimated from the projected/actual
162 per capita mass of chemical used/excreted (M, µg/cap/day), and the STP dry weather flow
163 (DWF, L/day), using Equation 1:
164
165 $$C_i = \frac{M \cdot P}{DWF}$$ Equation 1

Where P is the population served by the works and was obtained from the water utilities operating each works for all works across England and Wales. A normal distribution is assumed for DWF. The other parameters are fixed for each sewage treatment works.

The model allows removal in treatment efficiency to be considered using a global removal rate (r) including sewer removal, primary treatment and secondary treatment. The value of r can be specific to each STP modelled and can be varied according to the type of plant and levels of treatment applied. The final concentration in the effluent (C_{eff}), is thus

$$C_{eff} = C_i \cdot (1 - r) \qquad \text{Equation 2}$$

Equations 1 and 2 describe the STP process. They are calculated in turn for each of the Monte Carlo iterations, so that the point source emission is expressed as a distribution.

Within LF2000-WQX, the whole catchment is structured as a network of interconnected model reaches. Reaches are defined as river stretches between model features, which are usually defined by significant tributaries, confluence of model reaches and STPs. Within the river, the model can simulate either conservative (no in-stream removal) or degradable (in-stream removal) substances. Modelling a degradable determinand, the concentration downstream (C_{DS}), after in-stream removal is defined with a first order exponential decay:

$$C_{DS} = C_{EP}\, e^{-k\,t} \qquad \text{Equation 3}$$

Where C_{EP} is the concentration in the river at the point of entry of an STP discharge, k (day^{-1}) is the decay rate, and t (day) is the time of travel along a reach defined as the reach length divided by the velocity of the river.

1.3. *Estimation of removal of APIs using inverse modelling and comparison with removal estimates using standard modelling approach*

Inverse modelling was used to estimate the mean, maximum and minimum removal of the study APIs between the point of use and the point at which surface water was sampled for the four study sites. Estimates of use of APIs were based on UK usage in 2009 (IMS Health, 2012) and were expressed as a per capita consumption per day (derived using the estimated UK population of 61,126,832; Eurostat, 2012). The LF2000-WQX model was run for all of the monitoring study sites, using only the per capita usage data (Table 1). It was assumed that all the prescribed drugs were consumed and excreted and that there was no removal in the STPs. For each API, percentage effective removals were calculated by dividing the measured value for an API at each of the study sites by the predicted mean value for the specific site.

To allow comparison of the inverse modelling removal estimates with removal estimates from the 'standard' forward approach to API exposure modelling, removal percentages were also calculated for each of the monitoring study sites based on published data on metabolism, removal in treatment and dissipation in surface waters (Table 3). Where a range of values were reported for these input parameters, lowest and highest values were used to produce 'worst' and 'best' case estimates of removal. For use in broader modelling, a correction was made, using dissipation data from Table 3, to the inverse modelled removal rates to account for the in stream-dissipation of a study compound between the points of emission to the catchments and the monitoring points.

1.4. Evaluation of modelling approach against monitoring data

To evaluate the performance of the approach, predictions of concentrations in river catchments in England and Wales were compared with measured environmental concentrations from a range monitoring studies that have been performed in the UK over the

216 past eleven years (Boxall *et al*., 2012b; Hilton *et al*., 2003; Ashton *et al*., 2004; Thomas and
217 Hilton, 2004; Bound and Voulvoulis, 2006; Roberts and Bersuder, 2006; Roberts and
218 Thomas, 2005; Kasprzyk-Hordern *et al*., 2007 and 2009; Kasprzyk-Hordern and Baker, 2012;
219 Zhang and Zhou, 2007; Zhou *et al*., 2009; Table 4). Mean concentrations were then obtained
220 for each sampling point and these mean MECs were then collated into one single distribution
221 using the approach described by Straub (2008) and Metcalfe *et al*. (2008). Median and upper
222 and lower quartiles were derived for the concentration distributions. Concentrations of
223 monitored APIs were then estimated for all river reaches in the monitored catchments using
224 the mean, minimum and maximum removal rates that were derived from the inverse
225 modelling and corrected for in stream dissipation. Concentration distributions and associated
226 summary statistics from the monitoring data analyses and the modelling were then compared.
227
228 *1.5. Assessment of pharmaceutical risks to aquatic systems in England and Wales*
229 The average, maximum and minimum removal estimates and corrected for in-stream
230 dissipation data were then used in the LF2000-WQX model to predict concentrations of the
231 12 study APIs in 3117 river reaches distributed across 22 large catchments in England and
232 Wales serving a population of 21 million people. Annual mean predicted environmental
233 concentrations (PECs) were obtained for each pharmaceutical for every reach in each
234 catchment.
235 To assess the implications of the predicted exposure distributions in terms of ecological risks,
236 data on the acute and chronic (growth and reproduction) toxicity of the study APIs to algae,
237 invertebrates and fish were extracted from the literature (Table 5). With the exception of
238 naproxen, these data were used to derive predicted no-effect concentrations (PNECs) for each
239 study pharmaceutical using assessment factors recommended by the European Chemicals
240 Agency (ECHA, 2010). Studies reporting non-regulatory endpoints (e.g. biomarker,

histological and behavioural responses) were not considered in the derivation of PNECs. For naproxen, the Environmental Reference Concentration (ERC) proposed by Murray-Smith *et al* (2012) was used. Risk characterisation ratios (RCRs) were then calculated for each river reach using equation 4.

$$RCR = \frac{PEC}{PNEC \text{ or } ERC} \qquad \text{Equation 4}$$

Estimated RCRs for all the reaches in all the 22 catchments were then combined in order to develop risk distributions for each pharmaceutical. An RCR ≥1 was considered as indicative of an unacceptable risk posed by an API to the aquatic population in a reach. In the past, diclofenac has been identified as a potential priority substance under the European Water Framework Directive and an environmental quality standard (EQS) of 0.1 μg/l was proposed for this API. Therefore, in addition to deriving RCR distributions for diclofenac, we also compared exposure predictions to the proposed EQS value to see what the implication of the EQS would have been had it been introduced.

2. Results

2.1. *Comparison of removal using forward with removal based on monitoring data at the study sites*

Mean inverse modelling-based estimates of removal between the point of prescription/sale and the point of monitoring into the surface waters for the monitoring study sites ranged from 90.63 (carbmazepine) to 99.86% (ibuprofen) (Table 6). Concentrations of cyclophosamide, fluoxetine, ketoprofen, orlistat and simvastatin were below detection limits in the monitoring study, so it was only possible to estimate a minimum removal rate for these substances – these were all greater than 95.5% (Table 6). In comparison, estimates of effective removal,

266 based on forward modelling using data on usage, metabolism and dissipation in wastewater
267 treatment and surface waters resulted in 'worst' case estimates of between 4 (atenolol) and
268 97.1% (naproxen) and 'best' case estimates of between 70.2 (trimethoprim) and 99.8%
269 (ibuprofen) removal between use by the patient and the sampling points for the four study
270 sites (Table 6). Mean percentage removal values for carbamazepine, diclofenac, fluoxetine,
271 furosemide and trimethoprim, obtained from usage, metabolism and wastewater and surface
272 water dissipation data were lower than removal values obtained using inverse modelling of
273 the monitoring data and for selected compounds (e.g. trimethoprim), there was a large
274 difference between the two approaches. Due to a lack of data, it was not possible to estimate
275 removal percentages for cyclophosphamide, ketroprofen, orlistat and simvastatin using the
276 forward modelling approach.
277 Correction of the inverse modelling data for in-stream dissipation of the study compounds
278 indicated that on average between 90.01 (atenolol) and 99.84% (ibuprofen) is removed
279 between the point of prescription/use and the points of emission from treatment plants within
280 the monitoring study catchments (Table 6). With the exception of atenolol where on average
281 3% of the compound was estimated to have dissipated in the rivers within the catchment, in-
282 stream dissipation was found to actually play a negligible role in the overall dissipation of the
283 study compounds and the monitoring sites. Never-the-less, the corrected values were
284 employed in the subsequent landscape scale exposure modelling.
285
286 *2.2. Comparison of exposure predictions against monitoring data*
287 It was possible to obtain good datasets on mean concentrations of atenolol, carbamazepine,
288 diclofenac, ibuprofen and trimethoprim in surface waters at different points within 10
289 catchments allowing concentration distributions to be derived (Figure 1). Mean, minimum
290 and maximum estimated removal rates between the point of use and emission to surface

291 waters were used in the LF2000-WQX model to estimate mean concentrations of the study
292 compounds for every river reach in the 10 monitored catchments in England and Wales.
293 Summary statistics for the distributions of mean predicted concentrations for all river reaches
294 in the monitored catchments, obtained from the modelling, are shown in Table 7. With the
295 exception of ibuprofen, there was good agreement between the monitored and modelled
296 distributions (Table 7; Figure 1). For ibuprofen, the modelled median concentrations and
297 upper and lower quartiles for the distributions were substantially smaller than the summary
298 statistic values obtained from monitoring studies.
299
300 *2.3. Assessment of risks of APIs to surface waters in England and Wales*
301 To assess the implications of the distributions of concentrations of the APIs, concentrations
302 were used alongside ecotoxicity data to characterise the level of risk posed by each API in
303 each of the river reaches modelled. Risk characterisation ratios for the study APIs for the 22
304 catchments (Figure 2) show that, for trimethoprim, furosemide, diclofenac and atenolol,
305 RCRs were 0.008 or lower, indicating that these substances pose a very low risk to aquatic
306 systems in England and Wales (Figure 2A). While the maximum RCRs of greater than one
307 were obtained for carbamazepine, fluoxetine and simvastatin in one of the 3312 river reaches
308 and for orlistat in 12 river reaches, simvastatin exceeded one, in the vast majority of reaches a
309 RCRs were lower than one indicating that these substances generally pose an acceptable risk
310 to the aquatic environment. For orlistat, simvastatin and fluoxetine, exposure estimates are
311 based on limits of detection so in reality RCRs will be lower still. However, the maximum
312 RCR for ibuprofen was 174 and, for this compound, 49.5% of river reaches across the 22
313 catchments were predicted to be at risk. When the catchments were considered individually
314 (Figure 2B), nine of the catchments were found to have median concentrations for ibuprofen
315 greater than the PNEC. The proposed EQS for diclofenac is 320-times lower than the

316 calculated PNEC. Comparison of this value with the exposure data suggested that 4.5% of
317 river reaches in the 22 catchments would have concentrations higher than the proposed
318 standard (Figure 2A), while none would have a concentration higher than the PNEC.
319
320 **3. Discussion**
321 A number of studies over the past few years have applied modelling approaches to predict the
322 occurrence and risks of APIs in surface waters in different regions of the world (Williams *et*
323 *al*., 2009; Hannah *et al*., 2009; Letzel *et al*., 2009). Typically, the modelling uses information
324 on the usage of an API in an area, metabolism, fate in wastewater treatment systems and fate
325 in receiving waters to estimate surface water concentrations. Comparison of estimates of
326 removal, obtained using these information, with estimates of total removal, obtained using
327 inverse modelling based on monitoring data for the four study sites, indicates that the
328 standard modelling approach can either over- or under-estimate removal of pharmaceuticals
329 in the real environment. This is probably one reason why previous studies have often shown
330 little correlation between measured and modelled data (e.g. Metcalfe *et al*. 2008). The
331 mismatch between the inverse modelled removal rates and rates obtained from usage,
332 metabolism and dissipation data are likely explained by a number of factors, including: not
333 all of a prescribed API is released to the wastewater system; metabolism in the actual
334 population is greater or lower than indicated by literature studies on a few individuals; and
335 variability in the types and performance of wastewater treatment works. When ranges of
336 values are available for a particular model input parameter, there were also large differences
337 between the maximum and minimum removal percentages for some compounds. This was
338 particularly true for atenolol and furosemide, where removal was estimated to range from 4.0
339 to 97.9% and from 10 to 77.5%, respectively, highlighting the difficulty in selecting model
340 input data. Smaller variation was seen for the inverse-modelling derived total removal rates

341 across the four study sites. Differences in demographic characteristics and the treatment
342 technologies across the sites may contribute to the differences between the forward and
343 inverse modelling derived values across the sites.
344 For six of the seven study compounds, where extensive datasets were available on
345 concentrations in rivers in England and Wales, there was close agreement between the results
346 of the exposure modelling and the monitoring data. The disagreement between modelled and
347 measured distribution statistics for ibuprofen may be partly explained by the fact that the
348 ibuprofen monitoring dataset was dominated by measurements made in 2003 during periods
349 of low precipitation when dilution of effluent through the wastewater treatment plants and
350 dilution by receiving waters would be small. In addition, IMS Health data indicate that usage
351 of ibuprofen in 2003 was higher than in 2009 when our study was performed (i.e. 293,802 kg
352 in 2003 compared with 277,465 kg in 2009). There have also been significant advances in
353 analytical methodologies since 2003, which have reduced the occurrence of analytical
354 artefacts such as matrix interferences. In a recent large-scale monitoring study involving
355 analysis of around 8,000 samples of undiluted wastewater effluents at over 160 treatment
356 works, median concentrations for ibuprofen have been reported to be 330 ng/l (95 percentile
357 concentration = 2.48 µg l^{-1}) suggesting the monitoring data from the earlier study are likely
358 not typical of concentrations across the broader landscape (UKWIR, 2012). The inverse
359 model results better reflect the much smaller values measured for ibuprofen in the most
360 recent monitoring studies performed in 2006, 2007 and 2009.
361 PNECs were derived from available acute and chronic ecotoxicity studies using standard
362 endpoints such as mortality, reproduction and growth and assessment factors recommended
363 by ECHA. Numerous studies have also explored effects of APIs on non-standard endpoints
364 such as behaviour, histology and biochemical effects, sometimes at concentrations much
365 lower than the standard endpoints (Hoeger *et al.*, 2005; Ankley *et al.*, 2007; Stanley *et al.*,

366 2007; Boxall *et al*., 2012b). However, in this study we did not use these data to inform the
367 PNEC derivation. This approach is consistent with the recent Technical Guidance Document
368 for deriving Environmental Quality Standard (EQSs) in the scope of the European Water
369 Framework Directive (EQS-TGD, 2011). With the exception of diclofenac, these non-
370 standard effects are seen at concentrations higher than the estimated PNECs, providing re-
371 assurance that the PNEC values for most of the study substances are protective against more
372 subtle effects. For diclofenac, the EQS value is slightly higher than concentrations where
373 histological and biochemical effects have been reported. A recent study (Memmert *et al*.,
374 2103) has questioned the reliability of the conclusions on the histopathology studies on which
375 the EQS is based and it is possible that the EQS is overly conservative.
376 With the exception of ibuprofen, where a risk was identified for 49.5% of river reaches,
377 RCRs for the other study compounds in river reaches in England and Wales were generally
378 lower than one (for carbamazepine, orlisat, fluoxetine and simvastatin a risk was identified in
379 one, one and 12 of the 3312 river reaches respectively), indicating that the other compounds
380 pose an acceptable risk to the UK environment. The findings for ibuprofen agree with
381 conclusions from other studies into the risks of APIs in aquatic systems, where ibuprofen has
382 been highlighted as a drug of potential concern in river systems (Christensen *et al*., 2009;
383 Lienert *et al*., 2007). We would therefore advocate that further work is carried out to explore
384 the wider occurrence of ibuprofen in surface waters in England and Wales and to explore
385 whether effects are occurring in the catchments where a significant proportion of river
386 reaches are predicted to be at risk; the PNEC may also need to be re-assessed as well.
387 Comparison of exposure predictions for diclofenac with the previously proposed EQS for
388 diclofenac, indicated that 4.5% of river reaches would have exceeded the EQS had it been
389 adopted. This percentage is in agreement with the value of 3-5% previously predicted for

EQS exceedences in rivers in England using the forward modelling approach (Johnson *et al*., 2013).

Overall, this study demonstrates the potential of using inverse modelling alongside monitoring data to generate model input data in exposure and risk assessment. As a total removal rate is estimated for a broad scale, the approach offers a number of advantages, i.e. it takes into account factors such as the non-use of prescribed drugs by patients; it addresses differences in metabolism across the population; it accounts for dissipation processes in the local sewerage network and it accounts for differences in effectiveness of different wastewater treatment technologies in a catchment. The four study sites used in this study were based in four different counties located in the South East and Midland regions of England so the approach appears to be effective at estimating exposure for different regions in a country the size of England. This is backed up by the comparisons of exposure predictions for the catchments that have been monitored in England and Wales with the experimentally-derived data.

The approach is, however, reliant on the availability of good quality monitoring data and cannot be applied to compounds that are not yet in use. Cultural and demographic differences might mean that the total removal predictions from this study cannot be applied to other countries. However, there is no reason why a similar monitoring and modelling strategy to that employed in the current study could not be applied elsewhere in order to generate state- or country-specific removal rates and hence assess the broad scale exposure risks of APIs in other regions of the world. The concept could also be applied at different stages in the pathway of a pharmaceutical from the patient to environmental receptors to better understand key dissipation processes for pharmaceuticals to inform future modelling initiatives.

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Table Legends

Table 1. Usage and mean concentrations (expressed in ng l^{-1}) measured at the four study sites. Values in parentheses for the study sites indicate the measured concentration range over the 12 month study period (Measured data taken from Boxall *et al*, 2012a).

Table 2. Characteristics of study catchments in terms of population served, types of sewage treatment plants present and average residence time between discharge points and the monitoring points.

Table 3. Information on percentage of API excreted, percentage API removed in wastewater treatment removal rates, and half lives for in stream dissipation used in the modelling of the study APIs.

Table 4. Summary of the monitoring studies used in the evaluation of the modelling approach.

Table 5. Ecotoxicological data used alongside the model predictions to establish the level of risk of the study compounds across the 18 study catchments in England and Wales.

Table 6. Summary of removal percentages for the 12 study APIs at the monitoring sites, obtained using the inverse modelling approach and the traditional forward modelling approach.

Table 7. Comparison of summary statistics for modelled and measured distributions of mean concentrations of APIs for river reaches in catchments that have been monitored for APIs in England and Wales.

Figure legends

Figure 1. Cumulative distributions of mean concentrations of pharmaceuticals in river reaches in catchments in England and Wales derived from the LF2000-WQX model or from

monitoring data. Modelled distributions are developed for the catchments where a pharmaceutical has been monitored and are based on mean, maximum and minimum inverse-modelled rates of removal. Monitoring data were taken from: Hilton *et al*., 2003; Ashton *et al*., 2004; Thomas and Hilton, 2004; Bound and Voulvoulis, 2006; Roberts and Bersuder, 2006; Roberts and Thomas, 2006; Kasprzyk-Hordern *et al*., 2007, 2009, 2012; Zhang and Zhou, 2007; Zhou *et al*., 2009; Boxall *et al*., 2012. In instances where a number of samples were taken from sites in a catchment, mean concentrations were estimated for each site. If a measured concentration was reported as < LOD then half of the LOD was used in the calculation of means.

Figure 2. Box and whisker plots (indicating median, upper and lower quartile and maximum and minimum values) of PEC/PNEC ratios for A) a range of APIs, obtained from LF-2000-WQX exposure predictions for 2950 river reaches across 22 large river catchments in England and Wales and PNEC values derived from published literature on the effects of the study compounds on aquatic organisms. Removal rates for the grey bars were based on non-detect data so are a 'worst' case indication of risks; and B) for ibuprofen in the individual 18 large river catchments modelled in England and Wales.

Table 1.

Compound	Class	Use in UK in 2009 (Kg/yr)	Site 1	Site 2	Site 3	Site 4
Atenolol	β-blocker	32944	43.8 (18.1 – 66.3)	54.2 (31.2 – 91.2)	26.7 (8.2 – 67.6)	41.1 (19.6 – 114)
Carbamazepine	anti-epileptic	49781	103.6 (49.4 – 199)	138.8(45.0 – 277)	272.3 (34.3 – 555)	182.6 (16.4 – 480)
Cyclophosphamide	chemotherapy agent	281	<1	<1	<1	<1
Diclofenac	non steroidal anti-inflammatory	34720	10.3 (<10 – 24.3)	18.1 (<10 – 39.0)	20.5 (<10 – 76.3)	15.9 (<10 – 47.1)
Fluoxetine	antidepressant	6377	<5	<5	<5	<5
Furosemide	diuretic	20872	10.2 (<5 – 28.9)	19.8 (6.59 – 43.1)	9.1 (<5 – 36.0)	17.4 (5.34 – 63.5)
Ibuprofen	non steroidal anti-inflammatory	277466	17.6 (6.33 – 30.8)	11.8 (<2 – 38.4)	8.4 (<2 – 21.5)	18.2 (<2 – 38.2)
Ketoprofen	non steroidal anti-inflammatory	1878	<1	<1	<1	<1
Naproxen	non steroidal anti-inflammatory	67672	18.2 (10.2 – 26.4)	18.1 (6.93 – 42.2)	13.6 (4.85 – 28.9)	23.1 (11.1 – 44.4)
Orlistat	anti-obesity	16669	<10	<10	<10	<10
Simvastatin	hypolipidemic	50070	<50	<50	<50	<50
Trimethoprim	antibiotic	13094	10.0 (<5 – 13.8)	9.5 (<5 – 13.8)	4.1 (<5 – 8.27)	8.9 (<5 – 26.4)

Table 2.

Site	Location	Population	Number of treatment plants upstream of sampling point	Types of STPs†	Average water residence between discharge and sampling (d)
1	Midlands	402227	17	SAS 1 SB 5 TA 3 TB 8	1.27
2	Southern England	2071445	81	SAS 12 SB 22 TA 19 TB 28	2.33
3	Southern England	395581	27	SAS 2 SB 11 TA 8 TB 6	2.42
4	South East England	177801	14	SAS 2 SB 3 TA 4 TB 5	1.46

†General classification of sewage treatment plants: SAS - Secondary Activated Sludge; SB - secondary biological filter; TA - Activated Sludge with tertiary treatment; TB - Biological filter with tertiary treatment.

Table 3.

Compound	Proportion of administered compound excreted by patient (%)	Proportion of compound removed in wastewater treatment plants	Dissipation half-life in receiving water (d)
Atenolol	69 – 96	-93 - 97	3 - 30
Carbamazepine	26 – 31	-122 – 58	82 - 100
Cyclophosphamide	2.5 – 20	0	43
Diclofenac	6 – 26	-143 – 80	5
Fluoxetine	20 – 26	33	112 – 113
Furosemide	90	-119 – 75	-
Ibuprofen	11 – 47	52 – 99.7	~20
Ketoprofen	-	40–100	-
Naproxen	0.6 – 5.6	48 – 93	10.2 – 14.6
Orlistat	83.1	~90	-
Simvastatin	-	-17 – 91	7.8
Trimethoprim	50 – 70	-40 – 40.4	5.7 – 100

Data collated from: Anderson et al., 2004; Andreozzi et al., 2003; Araujo et al., 2011; Bagley et al., 1973; Boxall et al., 2002; Bürge et al., 2003; Buser et al., 1999; Garcia-Ac et al., 2009; ; Gros et al., 2010; Heberer et al., 2002; Kasprzyk Hordern, 2012; Kovalova et al., 2011; Kwon; & Armbrust, 2006; Küster et al., 2010; Lam et al., 2004, LeClerq et al., 2009; Lee et al., 2009; Lienert et al., 2007; Paffoni et al., 2006, Paxeus, 2004; Piecha et al., 2010; Roche, unpublished; Runkel et al., 1972; Sipma et al., 2010; Ternes et al., 2001; Upton et al., 1980; Wu et al., 2011; Yamamoto, 2009; Zhi et al., 1995; Zuccato et al., 2001.

Table 4.

Compound	River catchments	References
Atenolol	Blackwater, Derwent, Ely, Great Ouse, Taff, Thames	1,2
Carbamazepine	Blackwater, Derwent, Ely, Great Ouse, Taff, Thames	1-3
Diclofenac	Blackwater, Derwent, Ely, Great Ouse, Lea, Nene, Sussex Ouse, Taff, Thames, Welland	1-4
Furosemide	Blackwater, Derwent, Ely, Great Ouse, Taff, Thames	1,2
Ibuprofen	Blackwater, Derwent, Ely, Great Ouse, Lea, Nene, Sussex Ouse, Taff, Thames, Tyne, Welland	1-6
Naproxen	Blackwater, Derwent, Ely, Great Ouse, Taff, Thames	1,2
Trimethoprim	Blackwater, Derwent, Ely, Great Ouse, Lea, Nene, Taff, Thames, Tyne, Welland	1-3,6

1-Kasprzyk Hordern et al., (2008); 2- Boxall et al., (2012); Zhang and Zhou (2007); 4- Environment Agency (2003); 5 – Bound and Volvoulis (2006); 6 – Roberts and Thomas (2006)

Table 5.

	Test	EC50 (mg/l)	NOEC (mg/l)	AF (REACH)	PNEC (µg/l)	Source
Atenolol	*Pseudokirchneriella subcapitata* 72 h growth		128.8			Küster et al., 2010
	Daphnia magna 21 d reproduction		8.872			Küster et al., 2010
	Daphnia magna 21 d second generation reproduction test started with 1st gen. brood		1.48	10	148	Küster et al., 2010
	Pimephales promelas 32 d hatching, survival, growth		3.2			Winter et al., 2008
Carbamazepine	*Daphnia magna 48 h*	13.8				Ferrari et al., 2009
	Pseudokirchneriella subcapitata 96 h growth		100			Ferrari *et al*., 2003
	Ceriodaphnia dubia 7 d reproduction		0.025	10	2.5	
	Danio rerio 10 d ELS		25			
Cyclophosphamide	*Pseudokirchneriella subcapitata* 96 h growth	930		100	560	Zounkova *et al*., 2007; SFT, 2006
	Daphnia magna 48 h immobilisation	>1000				
	Daphnia magna reproduction		56			
Diclofenac	Proposed EQS under the Water Framework Directive				0.1	SCHER, 2011a
	Rainbow trout reproduction		0.32	10	32	Novartis (personal comm)
	Zebra fish reproduction		0.32	10	32	
Fluoxetine	*Daphnia magna* chronic		0.089			Brooks *et al*., 2005; Lister *et al*., 2009;
	Danio rerio reproduction		0.0032			Oaks *et al*., 2010
	Desmodesmus subspicatus growth		0.0006	10	0.06	
	Thamnocephalus platyurus 24 h		0.76			Nalecz-Jawecki, 2007
Furosemide	*Pseudokirchneriella subcapitata* 96 h growth		70	1000	70	Isidori *et al*., 2006
	Daphnia magna 48 h immobilisation	60.62				
Ibuprofen	*Scenedesmus subspicatus* 72 h growth	342		10	0.01	Han *et al*., 2010; Cleuvers, 2004
	Daphnia magna 21 d reproduction		<1.23			
	Oryzias latipes 120 d (post hatch) survival		0.0001			
Naproxen	*Daphnia magna* 48 h	37				Straub and Stewart, 2007
	Lepomis macrochirus 96h	560				
	Pseudokirchneriella subcapitata 96 h growth		0.032			Brun et al., 2006
	Ceriodaphnia dubia 7 d reproduction		0.032	100		
	ERC value developed from chronic studies				4.2	Murray-Smith et al, 2012

	Test	EC50 (mg/l)	NOEC (mg/l)	AF (REACH)	PNEC (µg/l)	Source
Orlistat	*Selenastrum capricornutum* 10 d		1.92			GSK 2008
	Daphnia magna 21 d NOEC		0.0016	50	0.032	
	Oncorhyncus mykiss 96 h	>18.5				
Simvastatin	*Dunaliella tertiolecta* 96 h EC50	22.8				Delorenzo and Fleming, 2008
	Fundulus heteroclitus 96 h EC50	2.68				Key et al., 2009
	Palaemonetes pugio	1.18		1000	1.20	
Trimethoprim	*Pseudokirchneriella subcapitata* 72 h		16			Yang et al., 2008
	8 species of cyanobacteria 144 h		3.1–200	50	62	Ando et al., 2007
	Daphnia magna 21 d reproduction		6			Park & Choi, 2008
	Oryzias latipes 96 h	>100	20			Kim et al., 2007

Table 6.

Compound	Removal between point of use and point of monitoring using inverse modelling (%)	'Best' and 'Worst' case removal between point of use and monitoring points based on published metabolism, treatment and dissipation data (%)	Inverse modelled removal rate corrected for in-stream dissipation (%)
Atenolol	93.92 (86.94-97.27)	4.0 – 97.9	90.92 (81.87-95.28)
Carbamazepine	90.63 (85.20-96.07)	69.0 – 89.1	90.01 (84.89-93.95)
Cyclophosphamide	95.36 (93.75-96.73)	—	94.74 (93.75-95.38)
Diclofenac	98.24 (97.20-99.42)	74.0 – 95.2	97.64 (96.51-99.00)
Fluoxetine	98.97 (98.63-99.26)	82.6 – 86.6	98.87 (98.66-99.03)
Furosemide	98.18 (96.67-99.10)	10 – 77.5	97.67 (95.81-98.82)
Ibuprofen	99.86 (99.81-99.92)	77.4 – 99.97	99.84 (99.80-99.91)
Ketoprofen	99.31 (99.07-99.50)	—	99.25 (99.11-99.37)
Naproxen	99.18 (98.74-99.48)	97.1 - 99.6	99.01 (98.59-99.31)
Orlistat	98.11 (97.45-98.63)	—	97.94 (97.52-98.30)
Simvastatin	98.42 (97.86-99.02)	—	98.01 (97.52-98.38)
Trimethoprim	97.85 (96.39-99.07)	30-70.2	97.14 (95.54-98.73)

Table 7.

	Median concentration (ng/l)		Lower quartile concentration (ng/l)		Upper quartile concentration (ng/l)	
	Monitoring data	Modelled data	Monitoring data	Modelled data	Monitoring data	Modelled data
Atenolol	140	92	46	43	435	172
Carbamazepine	61	193	14.5	89	265	321
Diclofenac	20	24	6.4	11	61	46
Furosemide	10.4	19	3.1	8.9	34	32
Ibuprofen	125	14	25	6.4	475	26
Naproxen	13	24	4.2	11	42	46
Trimethoprim	6.7	11	2.1	4.9	21	21

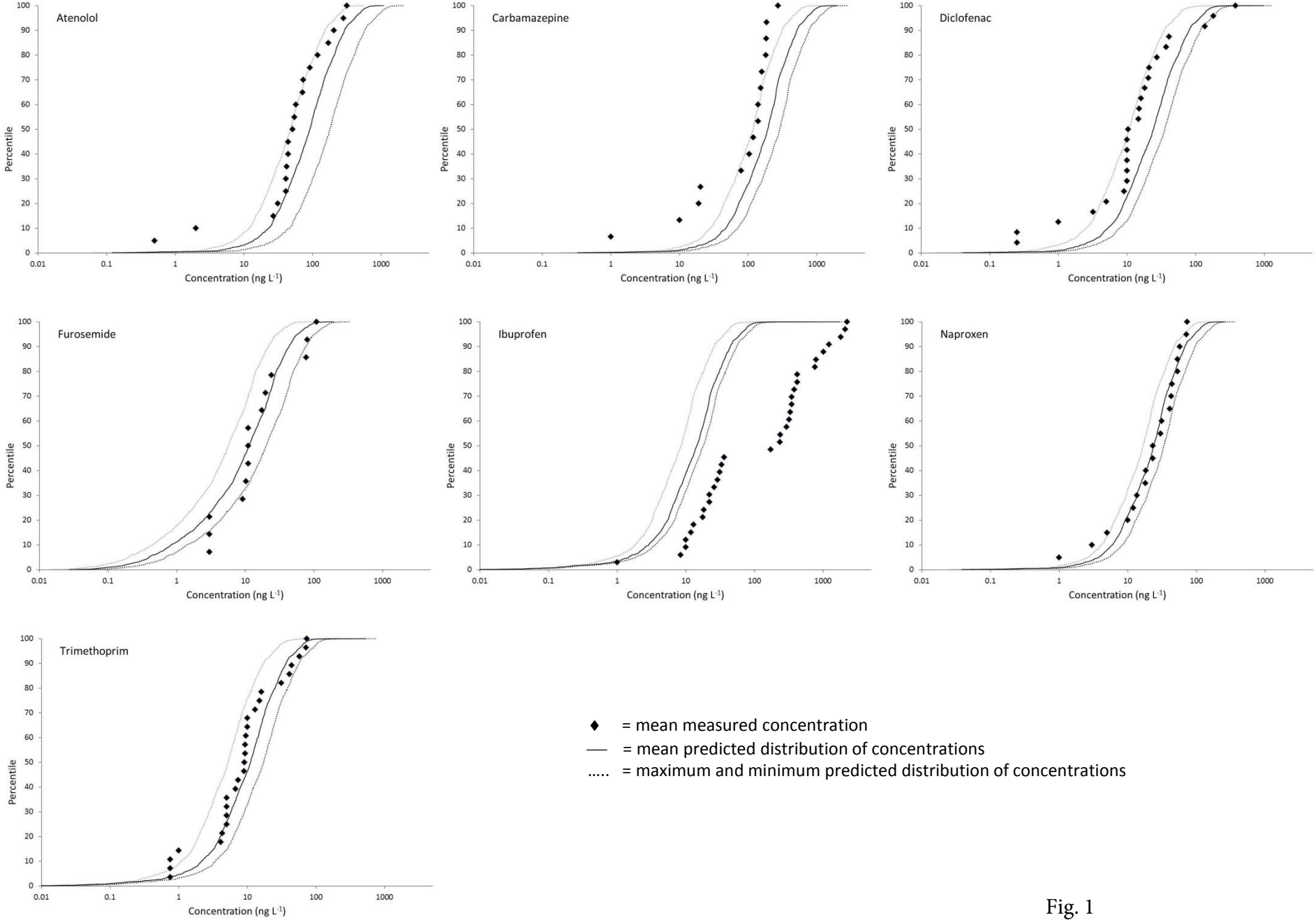
Atenolol
Carbamazepine
Diclofenac
Furosemide
Ibuprofen
Naproxen
Trimethoprim
Percentile
Concentration (ng L-1)
♦ = mean measured concentration
— = mean predicted distribution of concentrations
..... = maximum and minimum predicted distribution of concentrations

Fig. 1

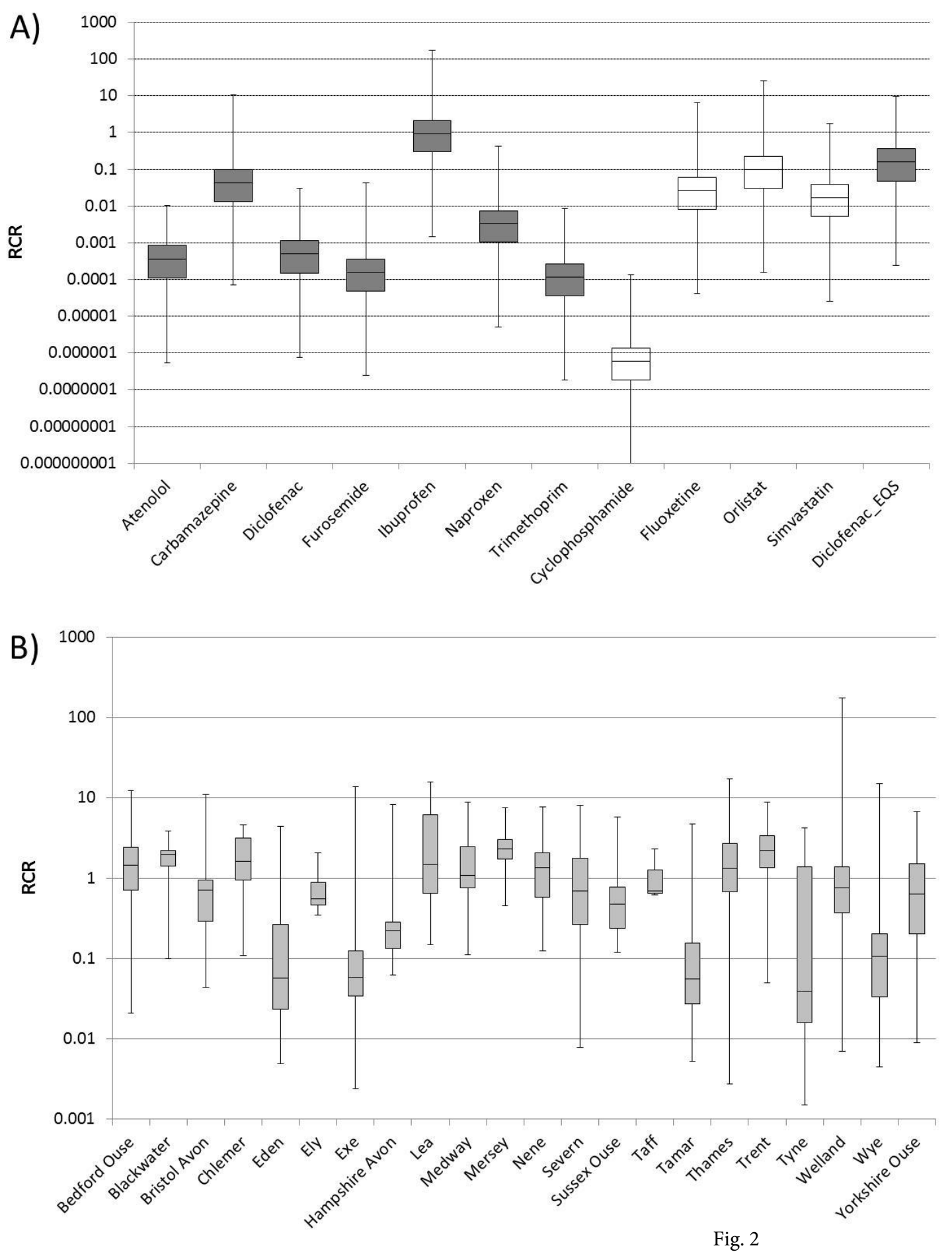
A)
RCR
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
0.00000001
0.000000001
Atenolol
Carbamazepine
Diclofenac
Furosemide
Ibuprofen
Naproxen
Trimethoprim
Cyclophosphamide
Fluoxetine
Orlistat
Simvastatin
Diclofenac_EQS
B)
RCR
1000
100
10
1
0.1
0.01
0.001
Bedford Ouse
Blackwater
Bristol Avon
Chlemer
Eden
Ely
Exe
Hampshire Avon
Lea
Medway
Mersey
Nene
Severn
Sussex Ouse
Taff
Tamar
Thames
Trent
Tyne
Welland
Wye
Yorkshire Ouse

Fig. 2