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1 **Title**

2 A high-resolution spatial model to predict exposure to pharmaceuticals in European surface  
3 waters – ePiE

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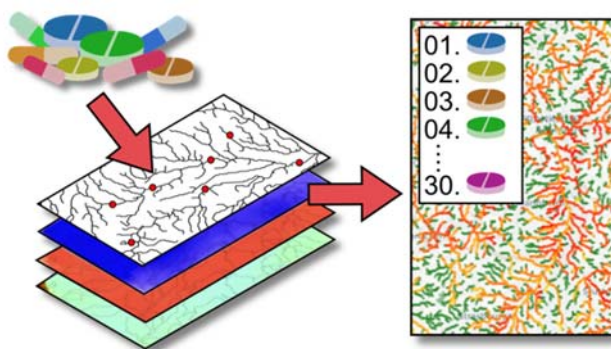
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12 **Graphical abstract**



13

14 **Abstract**

15 Environmental risk assessment of pharmaceuticals requires the determination of their  
16 environmental exposure concentrations. Existing exposure modelling approaches are often  
17 computationally demanding, require extensive data collection and processing efforts, have a  
18 limited spatial resolution, and have undergone limited evaluation against monitoring data.  
19 Here, we present ePiE (exposure to Pharmaceuticals in the Environment), a spatially explicit  
20 model calculating concentrations of active pharmaceutical ingredients (APIs) in surface  
21 waters across Europe at ~1 km resolution. ePiE strikes a balance between generating data on  
22 exposure at high spatial resolution while having limited computational and data  
23 requirements. Comparison of model predictions with measured concentrations of a diverse  
24 set of 35 APIs in the river Ouse (UK) and Rhine basins (North West Europe), showed around  
25 95% were within an order of magnitude. Improved predictions were obtained for the river  
26 Ouse basin (95% within a factor of 6; 55% within a factor of 2), where reliable consumption  
27 data were available and the monitoring study design was coherent with the model outputs.  
28 Application of ePiE in a prioritisation exercise for the Ouse basin identified metformin,  
29 gabapentin, and acetaminophen as priority when based on predicted exposure  
30 concentrations. After incorporation of toxic potency, this changed to desvenlafaxine,  
31 loratadine and hydrocodone.

## 32 **Introduction**

33 Over the past decades, human consumption of pharmaceuticals has steadily increased.<sup>1, 2</sup> In  
34 combination with continuing improvements in our analytical capabilities,<sup>3, 4</sup> this has led to the  
35 detection of many active pharmaceutical ingredients (APIs) in surface waters worldwide.<sup>5, 6</sup>  
36 The environmental presence of 631 different pharmaceuticals has been reported in 71  
37 countries covering all continents,<sup>5</sup> but the actual number of APIs present in surface waters is  
38 likely higher due to the self-fulfilling selection bias of many monitoring campaigns.<sup>7</sup>

39 A crucial step in the environmental risk assessment of chemicals is the determination of their  
40 environmental exposure potential. Since there are currently at least 1500 distinct APIs in  
41 use,<sup>8, 9</sup> monitoring all of them everywhere and continuously is practically impossible.  
42 Moreover, APIs under development will not be present in the environment so monitoring will  
43 provide no information on exposure of these molecules. There is therefore a need for  
44 exposure modelling approaches that can help us prioritize our monitoring efforts, support  
45 more robust environmental risk assessment of new APIs, and that can be used to take  
46 targeted measures.<sup>10</sup> These should preferably be spatially explicit, acknowledging that  
47 geographical variability can lead to substantial differences in the concentrations of APIs across  
48 and within regions.<sup>11, 12</sup> For example, rankings of APIs established at the continental European  
49 level may lead to misguided allocation of resources when adopted at a regional level.<sup>12</sup> Such  
50 mismatches between EU-level and regional level prioritization of APIs might, for example, be  
51 the result of geographical variation in API consumption, a heterogeneous distribution of  
52 emission sources, or spatially varying environmental conditions driving the fate of APIs after  
53 emission.

54 The environmental exposure potential of chemicals is reflected by the measured (MEC) or  
55 predicted (PEC) environmental concentrations at which they occur in the environmental  
56 compartment of interest. PECs can be derived using multimedia fate models, such as the  
57 EUSES model<sup>13</sup> and our previously developed prioritization tool for APIs.<sup>11</sup> These are based  
58 on mass-balance equations for interconnected compartments that represent the relevant  
59 environmental media (e.g., fresh and salt waters, air, urban and agricultural soils, et cetera),  
60 and are therefore especially useful for larger scale (regional, continental) assessments where  
61 multiple media might be relevant. However, they are less suitable for answering locally  
62 specific questions (e.g., hotspot identification, scenario analyses for optimal mitigation  
63 measures), because they assume a homogenous distribution of chemicals within their  
64 compartments and do not account for any spatial variation at that scale.<sup>14, 15</sup> This also  
65 inherently limits the options for model corroboration with local measurement data.

66 APIs tend to largely remain in the compartment where they are emitted,<sup>16</sup> implying that the  
67 use of single-media models is also an option. Examples of geographically-based single-media  
68 models for down-the-drain chemicals are GREAT-ER,<sup>17</sup> PhATE,<sup>18</sup> GWAVA,<sup>19</sup> LF2000-WQX,<sup>20</sup>  
69 iSTREEM,<sup>21</sup> and the recent unnamed model by Grill et al.<sup>15</sup> Combined, these models have been  
70 applied to assess the distribution of APIs in many river basins worldwide. Invariably, they  
71 integrate information on API consumption, human metabolism, removal in wastewater  
72 treatment plants (WWTPs), and dilution and dissipation in receiving surface waters, to  
73 estimate PECs throughout river basins. The characterization of hydrology is broadly done in  
74 one of two ways: via gridded approaches incorporating extensive process-based hydrological  
75 models,<sup>15, 19</sup> or via segmentation of the river network into discrete river segments with  
76 calibration against measured hydrology and extrapolation to ungauged sites.<sup>17, 18, 20, 21</sup> Both

77 approaches have their own drawbacks, related to the computational demands of large scale  
78 hydrological models, the extensive data collection and processing efforts required for the  
79 parameterization of river basins, and the limited spatial resolution determined by the grid-  
80 cell size or the length of individual river segments.

81 Here, we present ePiE (exposure to Pharmaceuticals in the Environment), a new spatially  
82 explicit model, developed in the frame of the Innovative Medicines Initiative iPiE project, that  
83 can calculate concentrations of APIs in surface waters throughout river basins in Europe. It is  
84 designed to strike a balance between generating data on exposure at high spatial resolution  
85 while having limited computational and data requirements. It does so by employing FLO1K  
86 for the underlying hydrology, a global geographic dataset with annual predictions of  
87 streamflow metrics (annual mean flow, highest and lowest monthly mean flow) spatially  
88 distributed at 30 arc seconds (~1 km).<sup>22</sup> This is a resolution ten times higher than the most  
89 detailed global hydrological models or land surface models currently available.<sup>23, 24</sup> In ePiE,  
90 river networks are represented as collections of interconnected nodes describing emission  
91 points, river junctions, river mouths and inlets and outlets of lakes and reservoirs. It thus  
92 provides a modelling architecture supporting linkage and integration of geographic  
93 information in vector format, i.e., the nodes of the river networks, and rasterized information  
94 on climatic, hydrological, and geochemical conditions.<sup>25</sup> We developed a custom routing  
95 scheme to follow APIs through the river network, along the way accounting for dissipation  
96 from the water via the processes of biodegradation, photolysis, hydrolysis, volatilization and  
97 sedimentation.

98 In this article, we present the structure of ePiE and evaluate its performance against  
99 measured concentration data from the open literature for a combined total of 35 APIs in two

100 European river basins. Finally, to illustrate the utility of the model, we apply ePiE to rank APIs  
101 in the river Ouse basin (UK), based on predicted concentrations in surface waters and  
102 predicted risks to fish.

## 103 **Methods**

### 104 *Model structure*

105 Central to ePiE are a set of network nodes derived from the global databases HydroSHEDS<sup>26</sup>  
106 and HydroLAKES,<sup>27</sup> and agglomerations and WWTPs from the UWWTD-Waterbase.<sup>28</sup> This  
107 latter database contains information on the location and characteristics (i.e., generated load,  
108 design capacity and level of treatment) of 30,043 European urban WWTPs and 27,695  
109 agglomerations with generated wastewater loads above 2,000 population equivalents (p.e.).  
110 After curation of the UWWTD-Waterbase (see Supporting Information S1), agglomerations  
111 and WWTPs were incorporated into the river network based on their proximity to the nearest  
112 water body. Direct emissions into the sea were excluded from the model. Finally, gridded  
113 information on air temperature, wind speed, slope, and streamflow was extracted to all nodes  
114 in the network. To optimize its flexibility and accessibility, ePiE is entirely constructed in the  
115 open-source software environment R,<sup>29</sup> and a description of the model construction can be  
116 found in Supporting Information S2.

117 The ePiE model has a modular structure based on the georeferenced river basins provided by  
118 the global HydroBASINS database<sup>25</sup> which includes basins below of 60 °N. Depending on the  
119 river basin of interest, a subset of the total network of nodes is geographically selected. As a  
120 starting point, ePiE then requires yearly consumption data for the API of interest (kg/year) for  
121 all countries the river basin covers. When the API of interest is formed as a metabolite from  
122 another API, i.e. its prodrug, consumption data for that prodrug are also needed. Yearly

123 emissions into the river network from WWTPs ( $E_{w,wwtp}$ ; kg/year) and from agglomerations  
 124 with incomplete WWTP connectivity ( $E_{w,agg}$ ; kg/year) are calculated via Equation 1 and  
 125 Equation 2, respectively. The country-specific yearly consumption data ( $M$ ) include the  
 126 prescription of pharmaceuticals in hospitals. This means that hospital emissions are not  
 127 included as location-specific point sources, but spatially distributed according to the  
 128 wastewater loads per agglomeration (i.e., a proxy for population density).

$$129 \quad E_{w,wwtp} = (M \cdot f_{pc} + M_{pd} \cdot f_{met}) \cdot \frac{\sum_{j=1}^n (V_{ww,agg,j} \cdot f_{conn,agg,j} \cdot f_{wwtp,agg,j})}{V_{ww,cnt}} \cdot (1 - f_{rem}) \quad \text{Equation 1}$$

130 Where  $M$  and  $M_{pd}$  are the yearly consumption of the API of interest and its prodrug in the relevant country (kg/year);  $f_{pc}$  is  
 131 the fraction of the administered parent compound excreted/egested unchanged or as reversible conjugates via urine and  
 132 faeces (-);  $f_{met}$  is the fraction of prodrug metabolized to the API of interest, and subsequently excreted/egested via urine  
 133 and faeces (-);  $n$  is the number of agglomerations  $j$  connected to the WWTP (-);  $f_{conn,agg,j}$  is the level of WWTP connectivity  
 134 per agglomeration  $j$ ;  $f_{wwtp,agg,j}$  is the fraction of agglomeration  $j$  connected to the WWTP;  $f_{rem}$  is the API-specific removal  
 135 efficiency per WWTP (-); and  $V_{ww,agg,j}$  and  $V_{ww,cnt}$  are the wastewater loads generated per agglomeration  $j$  and the total in  
 136 the relevant country, respectively (p.e.).

$$137 \quad E_{w,agg} = (M \cdot f_{pc} + M_{pd} \cdot f_{met}) \cdot \frac{V_{ww,agg} \cdot (1 - f_{conn,agg})}{V_{ww,cnt}} \quad \text{Equation 2}$$

138 The SimpleTreat 4.0 model<sup>30</sup> was incorporated into ePiE to estimate the removal efficiency  
 139 during wastewater treatment ( $f_{rem}$ ). It requires basic physicochemical properties as input, as  
 140 well as solids-water partitioning coefficients for primary sewage ( $Kp_{ps}$ ; L/kg) and activated  
 141 sludge ( $Kp_{as}$ ; L/kg), and (pseudo-)first order biodegradation rate constants ( $k_{bio,wwtp}$ ;  $s^{-1}$ ).  
 142 Removal efficiencies were assigned to individual WWTPs depending on their associated level  
 143 of treatment, using either the full SimpleTreat 4.0 model for those employing consecutive  
 144 primary and secondary treatment, or the module for primary treatment only.



145 After their emission, API residues are followed through the river network using a routing  
 146 procedure ordered from the most upstream to the most downstream nodes. As such, the  
 147 contribution of all upstream emissions to local concentrations is considered. Along the way,  
 148 ePiE accounts for dilution in the water column and five (pseudo-)first order loss processes,  
 149 three being degradation processes, i.e. biodegradation, photolysis and hydrolysis, and two  
 150 being intermedia transport processes, i.e. sedimentation and volatilization. Equation 3  
 151 calculates concentration  $C_i$  ( $\mu\text{g/L}$ ) at any node  $i$  in the river network; Equation 4 calculates  
 152 concentrations in lakes and reservoirs, following an approach similar to Grill et al.<sup>15</sup> in which  
 153 they are modelled as single completely stirred tank reactors.

$$154 \quad C_i = \frac{E_{w,i} + \sum_{j=1}^n \left( E_{w,j} \cdot e^{-\left[ \sum_{m=1}^5 k_{m,d_{j-i}} \right] \frac{d_{j-i}}{v_{d_{j-i}}}} \right)}{Q_i} \quad \text{Equation 3}$$

155 Where  $E_{w,i}$  and  $E_{w,j}$  are the emissions into the river network at node  $i$  and at node  $j$  upstream from node  $i$ , respectively  
 156 ( $\text{mg/s}$ );  $n$  is the total number of nodes upstream from node  $i$  (-);  $d_{j-i}$  is the distance over the river network between node  $j$   
 157 and node  $i$  ( $\text{m}$ );  $k_{m,d_{j-i}}$  is the average (pseudo-) first order rate constant for loss process  $m$  over  $d_{j-i}$  ( $\text{s}^{-1}$ );  $v_{d_{j-i}}$  is the average  
 158 river flow velocity over  $d_{j-i}$  ( $\text{m/s}$ ); and  $Q_i$  is the total river flow at node  $i$  ( $\text{m}^3/\text{s}$ ), including any discharges.

$$159 \quad C_i = \frac{\sum_{p=1}^n (E_{w,p})}{(V_i / \text{HRT}_i) + \sum_{m=1}^5 (k_{m,i}) \cdot V_i} \quad \text{Equation 4}$$

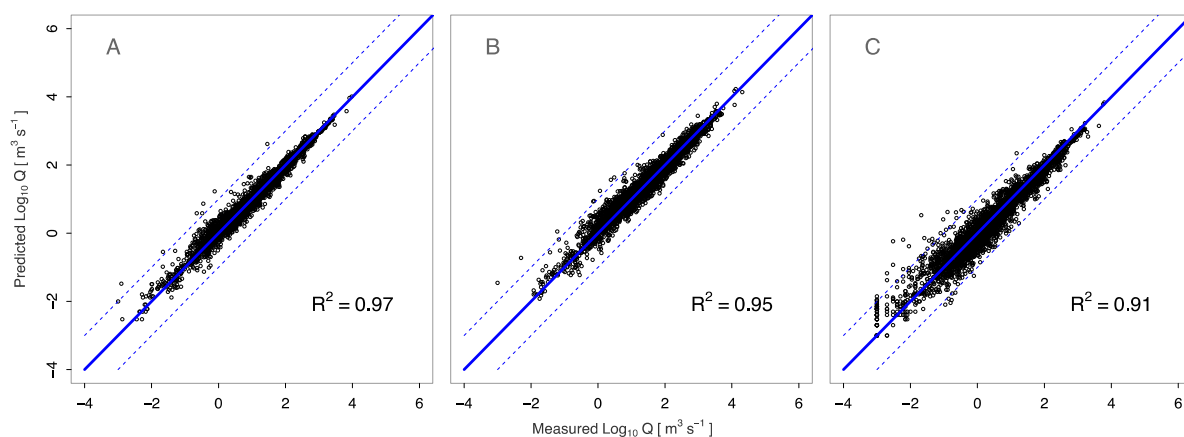
160 Where  $E_{w,p}$  is the emission into lake or reservoir  $i$  coming from node  $p$  ( $\text{mg/s}$ ), which can either be a direct emission source  
 161 (i.e., a WWTP or an agglomeration), or an inlet point carrying API residues from upstream the river network;  $n$  is the total  
 162 number of nodes emitting into lake or reservoir  $i$  (-);  $\text{HRT}_i$  is the hydraulic retention time of lake or reservoir  $i$  ( $\text{s}$ );  $V_i$  is the  
 163 volume in lake or reservoir  $i$  ( $\text{m}^3$ ); and  $k_{m,i}$  is the (pseudo-) first order rate constant for loss process  $m$  in lake or reservoir  $i$   
 164 ( $\text{s}^{-1}$ ).

165 Individual loss rate constants are extrapolated from test to field conditions by accounting for  
 166 temperature differences, sorption to suspended solids and dissolved organic carbon,<sup>32</sup> and

167 reduced light intensity.<sup>33</sup> Local sedimentation and volatilization rate constants are  
168 implemented via mass transport velocities between media.<sup>34</sup> Detailed information on the  
169 extrapolation to field conditions can be found in Supporting Information S3.

170 For characterization of annual mean flow, and highest and lowest monthly mean flow, the  
171 recent global FLO1K dataset was implemented in ePiE.<sup>22</sup> FLO1K is based on an ensemble of  
172 artificial neural networks regressions, with upstream-catchment physiography (area, slope,  
173 elevation) and year-specific climatic variables (precipitation, temperature, potential  
174 evapotranspiration, aridity index and seasonality indices) as covariates. It provides  
175 estimations of flow at a spatial resolution of 30 arc seconds (~1 km) for the years 1960-2015,  
176 which are in good agreement with independent data (global  $R^2$  of single-year metrics up to  
177 0.91). An additional comparison with independent data obtained from 1,007 European  
178 monitoring stations for the period 2010-2015,<sup>35</sup> showed that year-specific annual mean flow,  
179 and highest and lowest mean monthly flow in European rivers are predicted well, with  $R^2$   
180 values of 0.97, 0.95 and 0.91, respectively (Figure 1).

181 Additional hydrological parameters flow velocity  $v_i$  (m/s) and river depth  $h_{w,i}$  (m), were  
182 calculated via the Manning's equation for open channel flow, rewritten under the assumption  
183 of a wide rectangular river cross section as proposed by Pistocchi and Pennington.<sup>36</sup> In this  
184 approach, river width was related to river flow using their power law equation for European  
185 rivers ( $R^2$  of 0.87).<sup>36</sup>



186  
 187 **Figure 1.** Validation results for year-specific annual mean flow (A), highest monthly mean flow (B) and lowest monthly mean  
 188 flow (C). Independent validation dataset consisted of yearly measurements (2010-2015) from 1,007 GRDC European stations.  
 189 The solid line represents perfect model fit (1:1 line) and the dashed lines represent a difference of one order of magnitude.

190 *Model evaluation*

191 We performed a model evaluation exercise with measured concentrations for 35 APIs  
 192 consumed in Europe and covering a wide range of pharmaceutical classes. Excretion, sorption  
 193 and degradation data were extracted from open literature by cross-referencing a set of  
 194 reviews on human metabolism, sludge sorption, sediment sorption, biodegradation and  
 195 photolysis. The data obtained were supplemented with additional API-specific searches. The  
 196 resulting dataset was extensive, containing a total of 430 sorption coefficients and 342  
 197 degradation rate constants, but not homogeneously distributed over the 35 APIs. Complete  
 198 experimental datasets were available for 13 APIs, while 12 were missing data on at least one  
 199 sorption process and 11 on at least one degradation process. No experimental sorption or  
 200 degradation data were found for sitagliptin and triamterene. Missing sorption coefficients  
 201 were substituted by combining default mass fractions of organic carbon for sludge<sup>30</sup> or  
 202 sediments<sup>37</sup> with QSAR predictions of organic carbon-water partition coefficients.<sup>38, 39</sup>  
 203 Moreover, if only ready biodegradability screening test data were available, APIs were  
 204 assigned a biodegradation rate constant as proposed by Jager et al.<sup>40</sup> When experimental  
 205 degradation rate constants were lacking altogether, no degradation was assumed. Table S4.1

206 and Table S4.2 show the physicochemical and environmental fate properties of the 35 APIs,  
207 respectively.

208 Predicted environmental concentrations were compared with measured concentrations  
209 extracted from a database compiled by the German national environmental protection  
210 agency,<sup>5</sup> and a limited number of more recent literature studies. Individual studies were  
211 included in the model evaluation if 1) measurements were performed after 2010, 2)  
212 measurement locations were provided, 3) at least 10 of our APIs were measured above their  
213 limit of detection at least 10% of the time, and 4) multiple consecutive measurements were  
214 performed over time. These criteria resulted in the selection of three literature studies, being  
215 those by Burns et al.,<sup>41</sup> who measured APIs in the river Ouse basin in the United Kingdom, and  
216 by Ruff et al.<sup>42</sup> and Munz et al.,<sup>43</sup> who both measured APIs in the river Rhine basin in North-  
217 western Europe (Figure 2). Burns et al.<sup>41</sup> included a total of 30 of our preselected APIs in a  
218 monthly grab-sampling campaign throughout 2016. They reported the coordinates of their  
219 11 sampling locations, of which six were located along the river Ouse and five along its  
220 tributary, the river Foss, and we integrated these as such into ePiE. The yearly average of the  
221 Burns et al.<sup>41</sup> dataset was compared to the PEC obtained under annual mean flow conditions  
222 for 2015. Ruff et al.<sup>42</sup> measured a total of 23 of our preselected APIs in a weekly flow-  
223 proportional composite sampling campaign during “a remarkably dry period with constant  
224 low flow conditions” in the early spring of 2011. To reflect these low flow conditions, we used  
225 PECs derived under lowest monthly mean flow for 2011 in the quantitative evaluation of  
226 model performance. Out of their 16 sampling locations, ten were sampling stations along the  
227 river Rhine, but their coordinates were not reported. We georeferenced these sampling  
228 locations based on the proximity of the cities mentioned by the authors to sampling stations

229 in the GRDC Station Catalogue.<sup>35</sup> In addition, they sampled six tributaries of the river Rhine.  
230 We assumed these were sampled directly before their confluence with the main river. Finally,  
231 Munz et al.<sup>43</sup> included a total of 11 of our preselected APIs in two distinct grab-sampling  
232 campaigns in 2013 and 2014. Their 24 sampling locations were split evenly over these two  
233 campaigns and were all located directly downstream of WWTPs in Switzerland. Two sampling  
234 locations outside the river Rhine basin were excluded from our model evaluation. Similar to  
235 Ruff et al.<sup>42</sup>, Munz et al.<sup>43</sup> explicitly chose their sampling times to capture low flow conditions.  
236 Therefore, we used PECs derived under lowest monthly mean flow conditions for 2013 (site  
237 1-12) and 2014 (site 13-24).

238 For estimations in the river Ouse basin, we used consumption data for 2016 from the  
239 Prescription Cost Analysis.<sup>44</sup> For the river Rhine basin, consumption data for the Netherlands  
240 were obtained from the Dutch National Health Care Institute.<sup>45</sup> German, French and Swiss  
241 consumptions during the years of interest were mostly extrapolated from per capita  
242 consumption in other years.<sup>46</sup> Consumption data were not available for 5 APIs in France, 1  
243 API in Switzerland, and all APIs in Austria, Belgium and Luxembourg. In these cases, we  
244 averaged the per capita consumption from the basin's other countries. All consumption data  
245 are presented in Supporting Information S5.

246 To assess the predictive accuracy of ePiE, we computed the median symmetric accuracy  $\xi$  per  
247 study included in the evaluation exercise (Equation 5).<sup>47</sup> This metric reflects the typical  
248 percentage error of the predictions compared to the measurements. For example, a  $\xi$  of 100%  
249 indicates that predicted concentrations will typically be within a factor of 2 of the  
250 measurements. Contrary to metrics based on scale-dependent errors (e.g., root-mean-square  
251 error RMSE),  $\xi$  assigns equal importance to deviations of the same order rather than the same

252 magnitude. This is especially relevant for our data where concentrations ranged from low  
 253 ng/L to µg/L levels. In other words, a situation where the PEC is 1 ng/L and the MEC is 10 ng/L  
 254 (absolute error 9 ng/L) receives an equal penalty to that where the PEC is 100 ng/L and the  
 255 MEC is 1 µg/L (absolute error 900 ng/L). Moreover, since  $\xi$  bases on the median of the  
 256 accuracy ratios of individual pairs of predictions and measurements, it penalizes under- and  
 257 overpredictions equally. This is an advantage over the often-applied mean absolute  
 258 percentage error MAPE, which penalizes overpredictions more heavily.<sup>47</sup>

$$259 \quad \xi = 100 \cdot \left( e^{[M(|\ln(PEC_i/MEC_i)|)]} - 1 \right) \quad \text{Equation 5}$$

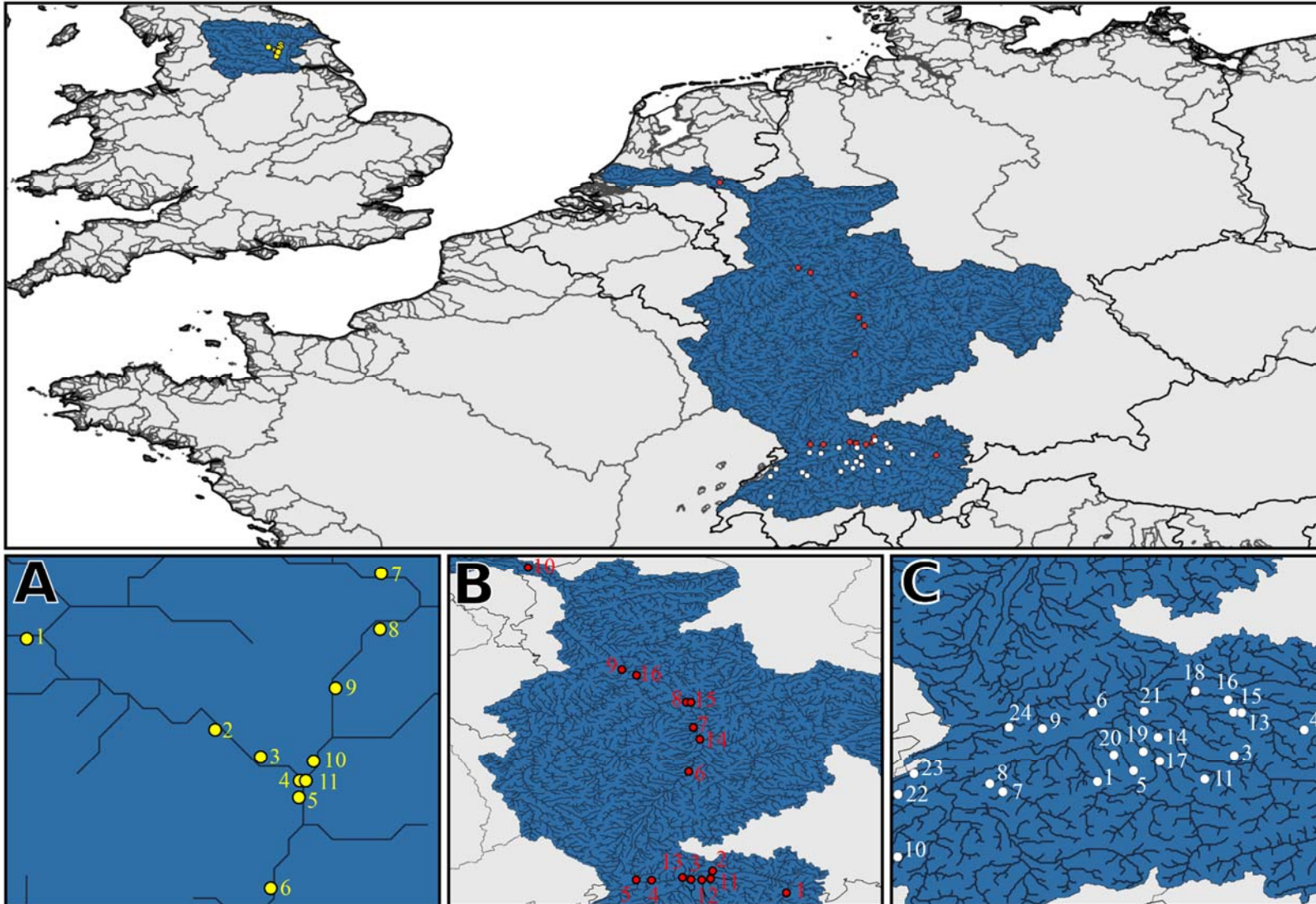
260 Additionally, we assessed the prediction bias of ePiE by computing the symmetric signed  
 261 percentage bias (SSPB) (Equation 6), which is closely related to the median symmetric  
 262 accuracy  $\xi$ .<sup>47</sup> The SSPB can be interpreted similarly to a mean percentage error, but is not  
 263 affected by the likely asymmetry in the distribution of percentage error.

$$264 \quad SSPB = 100 \cdot \text{sgn}(M(\ln(PEC_i/MEC_i))) \cdot \left( e^{[M(\ln(PEC_i/MEC_i))]} - 1 \right) \quad \text{Equation 6}$$

### 265 *Model application*

266 To illustrate the utility of the model, we applied ePiE to prioritise APIs in the Ouse river basin,  
 267 the basin with the best model performance and most APIs included. Additional nodes were  
 268 integrated into the network at evenly spaced one-kilometre distances, enabling a basin-wide  
 269 prioritisation using geographically homogeneous aggregate statistics. In addition to a ranking  
 270 based on concentrations, we ranked the APIs based on their potential risks to fish. For this we  
 271 followed a similar method as Burns et al.,<sup>48</sup> based on the fish plasma model approach.<sup>49, 50</sup>  
 272 We extrapolated concentrations in surface water to concentrations in fish plasma using  
 273 bioconcentration factors computed according to Fitzsimmons et al.<sup>51</sup> for neutral compounds,

274 and Fu et al.<sup>52</sup> for ionizing compounds. The latter were derived assuming a surface water pH  
275 of 7.4.<sup>53</sup> Risk quotients (RQ) for fish were then calculated as the ratio of concentrations in fish  
276 plasma over therapeutic concentrations in human plasma, which we obtained from the  
277 MaPPFAST database.<sup>54</sup> A risk quotient exceeding 1 thus indicates that the concentration of  
278 an API in surface water is expected to cause a pharmacological effect in fish, assuming  
279 equivalent pharmacological activity as in humans.<sup>55</sup> Finally, to enable exploration of local  
280 concentration and risk patterns, model results were geographically visualized as interactive  
281 html-maps, using the leaflet package “leafletR” in the R environment.<sup>56</sup>



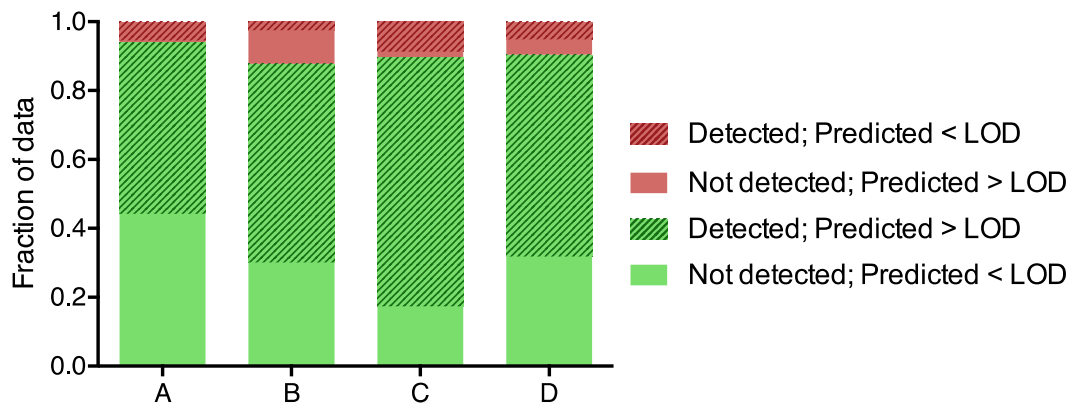
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**Figure 2.** Overview of studies included in the model evaluation exercise, with numbered sampling locations from Burns et al.<sup>41</sup> (A), Ruff et al.<sup>42</sup> (B) and Munz et al.<sup>43</sup> (C).



304 **Results and discussion**

305 Out of the 940 predicted values used for model evaluation, 36% were qualified as non-detects  
306 in the measurement campaign. We qualified a substance as a non-detect in case it was below  
307 the limit of detection (LOD) in at least 40% of the samples taken at that location. Such non-  
308 detects are less suitable for a quantitative evaluation of model performance. We did,  
309 however, include them in a binary comparison between predicted min-max concentration  
310 ranges, resulting from the temporal variation in flow conditions, and measurements in  
311 relation to their LOD (Figure 3). Assigning comparisons to one of 4 bins (detected,  
312 predicted<LOD; not detected, predicted>LOD; detected, predicted>LOD; not detected,  
313 predicted<LOD), there was 94%, 88% and 90% coherence of predictions and measurements  
314 for the Burns et al.,<sup>41</sup> Ruff et al.,<sup>42</sup> and Munz et al.<sup>43</sup> studies, respectively (green bars in Figure  
315 3).



316 **Figure 3.** Binary comparison of measurements and min-max range of predictions, relative to their limit of detection (LOD).  
317 All combinations of location and API from Burns et al.<sup>41</sup> (A), Ruff et al.<sup>42</sup> (B), Munz et al.<sup>43</sup> (C), and all studies combined (D).  
318

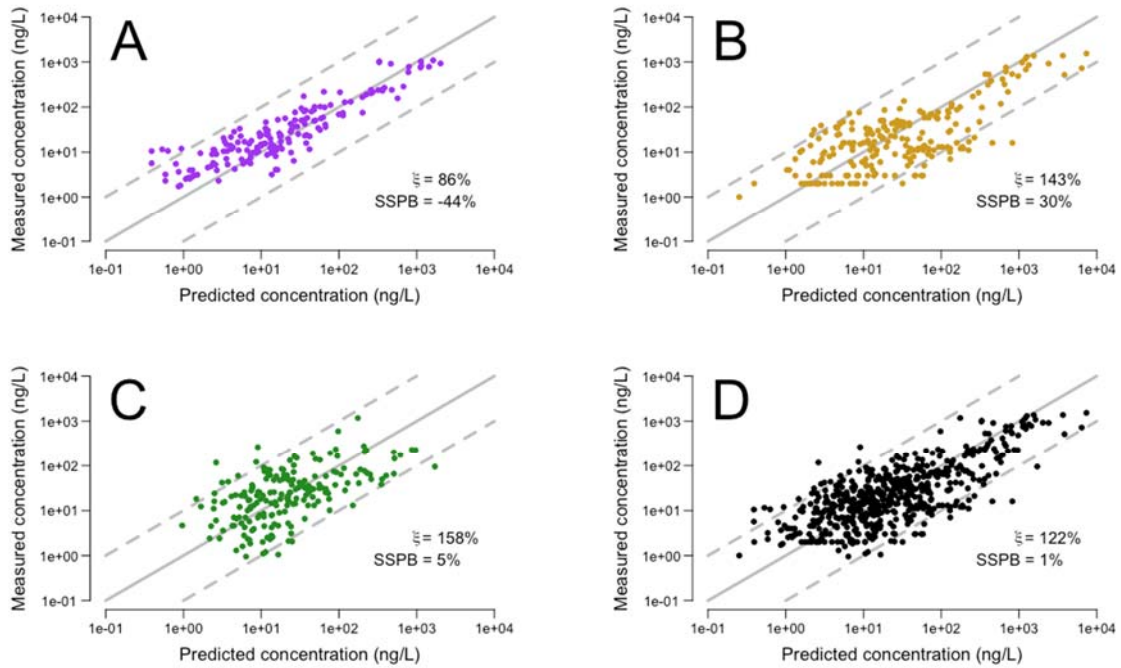
319 For a quantitative assessment of model performance, we included all detects at locations  
320 downstream of a WWTP, i.e., for which  $PEC > 0$ . In case measured values were below the LOD  
321 (i.e. always less than 40%), these measurements were replaced by  $\frac{1}{2}\sqrt{2} \cdot LOD$ .<sup>48</sup> The resulting  
322 comparison of predicted versus measured values (Figure 4) revealed a substantial variation

323 between the three studies. Model accuracy was best for predictions in the Ouse river basin,  
324 with a typical percentage error of 86% (Figure 4A; Burns et al.<sup>41</sup>). Predictions in the river Rhine  
325 basin had typical percentage errors of 143% (Figure 4B; Ruff et al.<sup>42</sup>) and 158% (Figure 4C;  
326 Munz et al.<sup>43</sup>). Model performance was similar if data points were included for which  
327 PEC>LOD and for which more than 40% of the measurements were below the LOD (Figure  
328 S6.1).

329 The worse performance of ePiE in the river Rhine basin might relate to the quality of the  
330 consumption data used in the calculations. Firstly, Swiss and German consumption data were  
331 often reported as “greater-than” values instead of exact amounts.<sup>46</sup> Secondly, we  
332 extrapolated the consumption in 2009 to that in the actual years of sampling (2011-2014),  
333 based on changing demographics and the assumption of a constant per capita consumption  
334 over the years (Table S5.1). However, actual per capita consumption has increased  
335 significantly for at least some pharmaceuticals, e.g., antidiabetics like sitagliptin<sup>57</sup> or  
336 antidepressants like venlafaxine.<sup>58</sup> These were therefore underestimated by ePiE due to the  
337 temporal extrapolation. In addition, errors might have been introduced when sampling sites  
338 from Ruff et al.<sup>42</sup> were allocated to the river network, because limited geographical detail was  
339 available on their specific locations. Inaccuracies may also be due to the fact that HydroSHEDS  
340 does not provide the real geometry of a river network in a basin, but most likely flow paths  
341 between individual cells according to flow accumulation. Similarly, errors might have been  
342 introduced during the allocation to the river network of the WWTPs sampled by Munz et al.<sup>43</sup>  
343 These were all located at smaller streams in the upper Swiss catchment of the Rhine river  
344 basin, without other upstream emission sources. In such smaller upstream catchments,  
345 proximity-based allocation is more prone to errors because the main stream within the

346 floodplain is less easily identified. Nevertheless, the  $\xi$  values and the scatterplots in Figure 4  
347 indicate that concentrations were typically predicted within a factor of 2-3, with  
348 approximately 95% of predictions within a factor of 10.

349 Concentrations measured by Burns et al.<sup>41</sup> were typically underestimated by ePiE, with a  
350 symmetric signed percentage bias (SSPB) of -44% (Figure 4A). From the scatterplot in Figure  
351 4A, underestimations seem to be more prominent at lower concentrations. This can at least  
352 partly be explained by the fact that measured concentrations have a lower bound in the form  
353 of their LOD, while model predictions do not. As a consequence, underestimations are more  
354 likely than overestimations in the vicinity of that LOD, since non-detects are excluded from  
355 the comparison. Indeed, model performance slightly improved if data points were included  
356 for which  $PEC > LOD$ , and which had more than 40% of the measurements below the LOD  
357 which were replaced by  $\frac{1}{2}\sqrt{2} \cdot LOD$  (Figure S6.1). Additionally, the reliability of measured  
358 concentrations decreases closer to the LOD. This complicates the evaluation of model  
359 performance, because any difference between predicted and measured concentrations might  
360 then be attributed to errors in either of them. Finally, inputs from tourism, specific point  
361 sources (e.g., hospitals), operation of combined sewer overflows at selected times of the year  
362 and use of over the counter medicines may also explain the slight mismatch between  
363 measurements and predictions in the river Ouse basin.

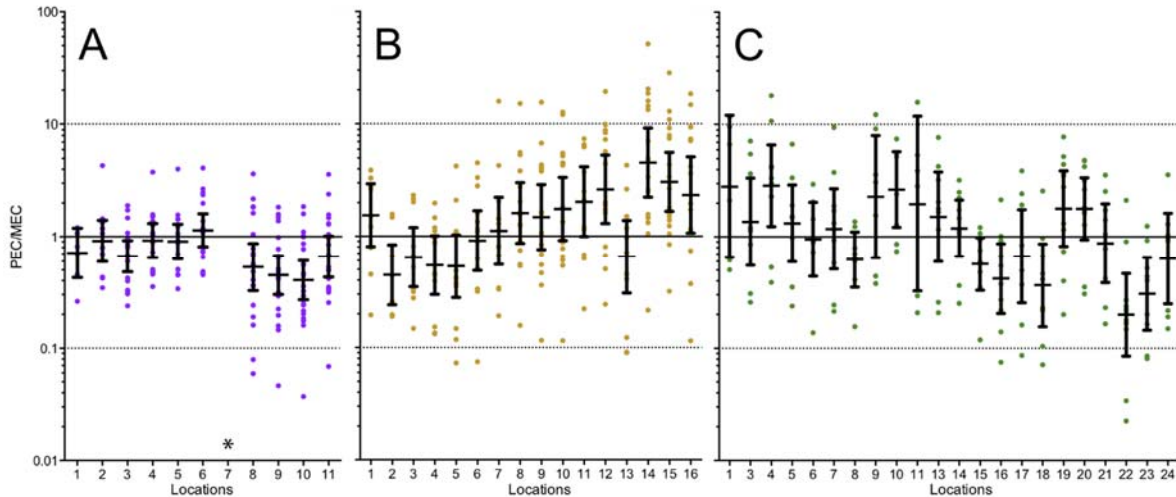


364  
 365 **Figure 4.** Predicted concentrations (i.e., >0) versus detects (i.e., <40% of the measurements below LOD), separately for data  
 366 from Burns et al.<sup>41</sup> (purple; A), Ruff et al.<sup>42</sup> (golden; B), Munz et al.<sup>43</sup> (green; C), and for all studies combined (black; D).  
 367 Concentrations predicted under annual mean flow conditions (A) or lowest monthly mean flow conditions (B and C). Solid  
 368 line represents 1:1 relationship; dashed lines represent 1:10 and 10:1 relationships.  $r^2$ : median symmetric accuracy; SSPB:  
 369 symmetric signed percentage bias.

370 In contrast to the river Ouse basin, concentrations measured in the river Rhine basin were  
 371 typically slightly overestimated, with SSPB values of 30% and 5% (Figures 4B and 4C). When  
 372 we ran ePiE under annual mean flow settings, these values dropped considerably to -70% and  
 373 -313%, respectively. This indicates that actual streamflow during sampling was probably  
 374 somewhere between lowest monthly mean flow and annual mean flow conditions.

375 Ratios of predicted over measured concentrations (PEC/MEC ratios) provide further insights  
 376 into the performance of ePiE (Figure 5). PEC/MEC ratios are grouped according to study and  
 377 sampling location, numbered as in Figure 2. Similar graphs grouped according to API are  
 378 included in the Supporting Information (Figure S6.2). Figure 5A shows that the spread around  
 379 predictions in the river Ouse (locations 1-6) is smaller than around those in its tributary river

380 Foss (locations 7-11). This indicates that ePiE predicts concentrations in larger rivers better  
381 than in smaller ones. While concentrations in larger rivers reflect an accumulation of APIs  
382 over a larger upstream catchment area, concentrations in smaller rivers and streams are more  
383 directly influenced by specific local conditions, i.e. water extraction and retention or small  
384 scale discharges. Indeed, comparison of predicted and measured mean annual flow at two  
385 gauging stations, i.e. one in the river Ouse and one in the river Foss (Table S6.1), shows that  
386 our flow prediction is less accurate for the smaller river Foss. The impact of local conditions  
387 can furthermore be observed at the most upstream location on the river Foss (location 7),  
388 where multiple APIs were detected but ePiE predicted zero concentrations for all of them.  
389 This deviation was likely due to the presence of a small upstream WWTP not included in the  
390 UWWTD-Waterbase because its size was below the reporting threshold of 2,000 p.e. National  
391 consumption data and default WWTP characteristics might thus not always suffice to  
392 estimate concentrations in locally influenced rivers. The same likely holds for the tributaries  
393 of the river Rhine sampled by Ruff et al.<sup>42</sup> (locations 11-16) and by Munz et al.<sup>43</sup> However, the  
394 pattern is less obvious here, probably due to errors introduced by the aforementioned  
395 incoherent flow conditions, consumption data, and geographical detail on sampling locations  
396 and emission sources. One option to improve predictions in upstream tributaries is to extend  
397 the UWWTD-Waterbase with WWTPs smaller than 2,000 p.e.

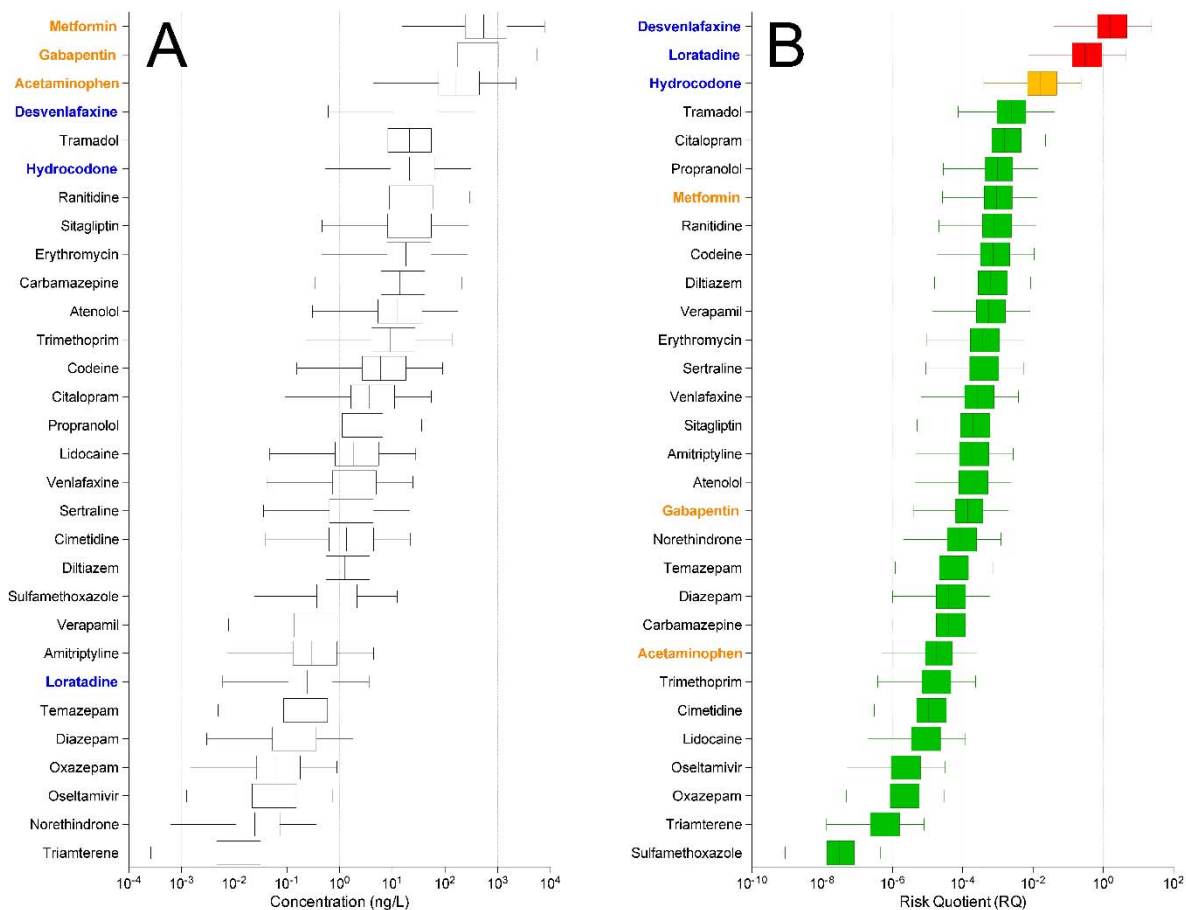


398  
 399 **Figure 5.** Ratios of predicted over measured concentrations (PEC/MEC), reported by Burns et al.,<sup>41</sup> (A), Ruff et al.,<sup>42</sup> (B) and  
 400 Munz et al.<sup>43</sup> (C). Coloured dots are individual combinations of API and location, measured above the LOD; black bars  
 401 represent 95<sup>th</sup> percentile and median over all measurements per location (numbered as in Figure 2). Concentrations  
 402 predicted under annual mean flow conditions (A) or lowest monthly mean flow conditions (B and C). \* = The PEC/MEC ratio  
 403 of location 7 in panel A equals zero.

404 Figure 6A shows that predicted concentrations in the river Ouse basin were highest for  
 405 metformin, gabapentin and acetaminophen, mainly resulting from their large consumption  
 406 volumes, high excretion fractions and/or relatively poor degradation (Supporting Information  
 407 S4.2 & S5). The prioritisation of APIs shifts when based on potential risks to fish instead of  
 408 concentrations (Figure 6B). Metformin, gabapentin and acetaminophen drop down the list  
 409 and are replaced by other more pharmacologically active APIs. Desvenlafaxine, loratadine and  
 410 hydrocodone (highlighted in Figure 6A) then become APIs of particular interest. Their risk  
 411 quotients for fish were larger than 0.1 in one or more locations in the river basin, with risk  
 412 quotients for desvenlafaxine and loratadine even exceeding 1 in ~26% and ~10% of the river  
 413 length, respectively. Interestingly, desvenlafaxine is formed as a metabolite of its prodrug  
 414 venlafaxine but is not administered as a separate medication in the United Kingdom. This  
 415 provides a strong argument for more focus on active metabolites in the environmental risk  
 416 assessment of pharmaceuticals. Finally, Figure 7 shows that higher risks are mainly found in

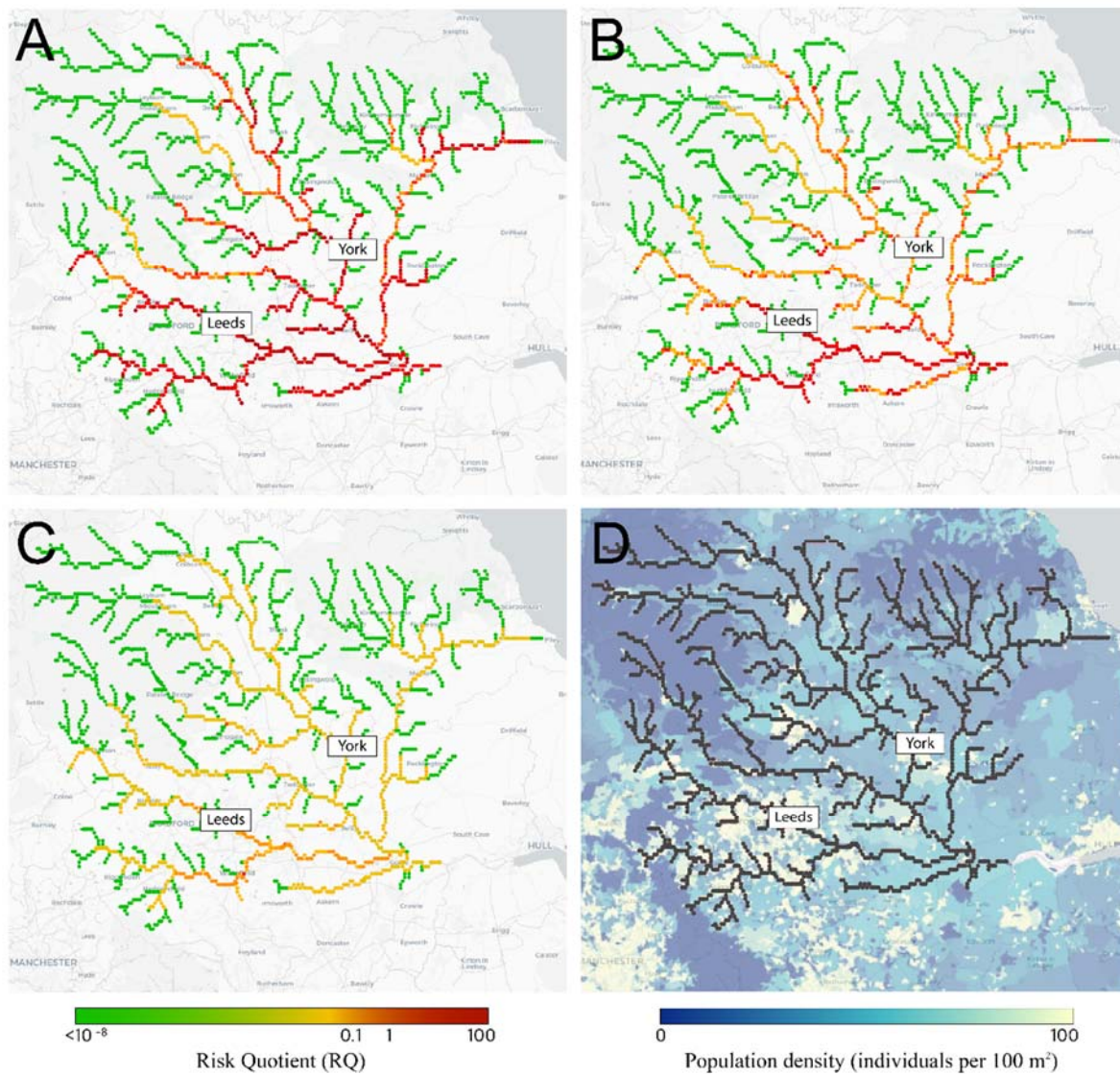
417 more densely populated areas, e.g., around the city of Leeds. The geographical distribution  
418 of surface water concentrations and risk quotients for all APIs is visualised in interactive html-  
419 maps in Supporting Information S7.

420 Our model evaluation showed that ePiE generally predicts concentrations in surface waters  
421 within one order of magnitude of measured concentrations for a wide range of  
422 pharmaceutical classes. While other models have been shown to predict PECs of APIs to  
423 within a factor 2-15 of measured concentrations,<sup>60</sup> none of these models have been evaluated  
424 using such an extensive dataset on a diverse range of APIs. To further strengthen confidence  
425 in the model, future model development and evaluation should extend towards additional,  
426 more hydrologically and climatically diverse river basins. As part of the IMI funded project  
427 iPiE, we are currently monitoring additional river basins in Denmark, Germany, Spain and the  
428 UK to develop a broader dataset against which to evaluate the model. Because of its flexible  
429 set-up and the use of global high-resolution gridded streamflow,<sup>22</sup> ePiE can be extended to  
430 new basins worldwide in a relatively straightforward way. Our model results also showed that  
431 a proper assessment of model performance requires measured concentrations derived under  
432 the same conditions as those modelled. This means that further model development should  
433 ideally be supported by long-term annual sampling efforts. In addition, incorporation of local  
434 consumption patterns, point sources (e.g., hospitals and pharmaceutical production plants),  
435 WWTP characteristics, and environmental conditions, would be especially relevant for  
436 adequate estimation of concentrations in smaller river stretches.



437  
 438 **Figure 6.** Ranking of all APIs modelled with ePiE in the Ouse river basin, based on concentrations (A) and risk quotients for  
 439 fish (B) predicted throughout the river basin, excluding zero concentrations. Boxes indicate interquartile range including  
 440 median; whiskers indicate 1<sup>st</sup>-99<sup>th</sup> percentile range for the total river length. Red boxes: RQ exceeds 1 at least somewhere in  
 441 the river network; amber boxes: RQ exceeds 0.1 at least somewhere in the river network; green boxes: RQ below 0.1  
 442 throughout the river network.





443

444 Figure 7. The spatial distribution of risk quotients for the three top ranked APIs in the river Ouse basin (UK): desvenlafaxine

445 (A), loratadine (B), and hydrocodone(C). Panel D depicts the spatial variation in population density in the river Ouse basin

446 (individuals/100 m<sup>2</sup>).

447 **Supporting Information**

448 S1. Curation of UWWTD-Waterbase

449 S2. Model construction

450 S3. Loss processes

451 S4. Chemical model parameterization

452 S5. Consumption data

453 S6. Additional results

454 S7. Interactive html-maps

455 **Acknowledgments**

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