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Do concentrations of ethinylestradiol, estradiol and diclofenac in European rivers exceed proposed EU environmental quality standards?

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This study used a geographic based water model to predict the environmental concentrations of three pharmaceuticals 17α-ethinylestradiol (EE2), 17β-estradiol (E2) and diclofenac throughout European rivers. The work was prompted by the proposal of the European Community (COM(2011)876) to consider these chemicals as candidates for future control via environmental quality standards (EQS). National drug consumption information, excretion, national water use, and sewage removal rates, were used to derive per capita sewage effluent values for the European countries . For E2, excretion rates of the natural hormone and national demographics were also included. Incorporating this information into the GWAVA model allowed water concentrations throughout Europe's rivers to be predicted. The mean concentration from the expected sewage discharge scenario indicated that 12% by length of Europe's rivers would reach concentrations greater than the proposed 0.035 ng/L EQS for EE2. For several countries, between a quarter and a third of their total river length would fail such an EE2 EQS. For E2, just over 1% by length of rivers would reach concentrations greater than the 0.4 ng/L proposed EQS, whilst just over 2% by length of rivers would reach concentrations greater than the proposed EQS of 100 ng/L for diclofenac.

Key words

Ethinylestradiol, estradiol, diclofenac, river water, model, prediction, environmental quality standard, Europe

Introduction

The control of what are called hazardous substances in Europe falls under the Water Framework Directive (WFD). When an environmental quality standard (EQS) is set for a chemical this can lead to it being phased out of production. However, the very recent addition of the pharmaceuticals 17a-ethinylestradiol (EE2), 17b-estradiol (E2) and diclofenac in the European Community document (COM(2011)876) appear to usher in a new era. This document suggested annual average EQS of 0.035 ng/L for EE2, 0.4 ng/L for E2 and 100 ng/L for diclofenac. Now this document has been amended and these drugs put on a watch list until they are reviewed again in 2014. Thus, there remains the possibility that they will become controlled with an EQS in due course.

Given their societal health benefits, it is unlikely and perhaps undesirable for particular pharmaceuticals to be phased out on the basis of environmental concerns. Thus, as source controls are inappropriate, so end of pipe solutions may have to be sought. A number of studies have examined the efficacy of different sewage tertiary treatments and indeed one European State, Switzerland, is planning to invest in such technology [1]. Based on our current knowledge, most of the proposed techniques would appear to be very expensive to build and maintain [2, 3]. As an EQS would be set for the receiving waters and not the sewage effluent, so the extent of investment will depend on the available dilution. Thus, the magnitude of the challenge for different nations will reflect their unique geographical and hydrological circumstances. Examining the extent of these differences in national exposure would appear to be vital information in engaging not only regulators, water utilities, government and environmental scientists, but also the general public too.

Geographic-based water quality models are a practical tool that can address the question of exposure to pharmaceuticals at a continental scale. Measuring all of these chemicals throughout every European river would be exceedingly costly and time consuming, to say nothing of the problems of consistency. Measuring EE2 throughout Europe's rivers would be impractical, since very few, if any, chemists can confidently claim to quantify EE2 at concentrations of 0.035 ng/L with

current technology. The strengths and weaknesses of water quality modelling vs measuring have been reviewed before, but it is important to note that models have no lower detection limit [4]!

Before considering how to approach this task, it is worth briefly reviewing what evidence brought these chemicals to the attention of the EU. Following a series of surprising observations on the effects of fish being exposed to sewage effluent in the mid 1980s' in the UK, a series of methodical studies were carried out which revealed that something in effluent could provoke endocrine disruption [5]. Field surveys then revealed that endocrine disruption of fish was widespread in wild fish caught in proximity to sewage treatment plants [6] and that the most potent component of that effluent was the fraction containing steroid estrogens [7]. Amongst those steroid estrogens, E2 and the synthetic estrogen EE2 were demonstrated to be the most potent [8]. These observations were repeated by scientists throughout the world. Whilst the disrupting effects of E2 and EE2 at low ng/L exposure concentrations on individual fish are undeniable, the assessment of the effect of that disruption on fish populations is less secure [9]. Diclofenac came to prominence when it was strongly implicated in the poisoning and decline of vulture populations in Asia [10]. A number of studies have suggested that low µg/L concentrations of diclofenac adversely affect fish [11, 12], and raised concern that diclofenac might pose a threat to wild fish. However, a recent study failed to support the results of these earlier studies, and instead found that adverse effects on fish occurred only when the environmental concentration approached 1mg/L [13], which is very much higher than any river concentration is likely to be.

If these pharmaceuticals stay on the watch list and even become priority substances needing control, so it is likely other pharmaceuticals will follow. A stated objective of the European Parliament legislative resolution of 2 July 2013 amending Directives 2000/60/EC and 2008/105/EC as regarding putting chemicals on a watch list (COM(2011)0876 – C7-0026/2012 – 2011/0429(COD)) is that this will stimulate further studies both in terms of monitoring and on the risks they pose. To respond the objectives of this study were:

- To refine and adapt existing models for E2, EE2 and diclofenac using the most recent consumption information to predict European river water concentrations
- To examine how close predicted river concentrations would exceed proposed EQS levels of 0.4 ng/L for E2, 0.035 ng/L EE2 and 100 ng/L diclofenac across Europe
- To identify the European countries most likely to be challenged if such EQS levels had to be achieved.

Materials and methods

Assessing per capita consumption rates. The approach to estimating sewage effluent concentrations takes the drug consumption per capita for a specific nation, less that prevented from being excreted as the free parent compound, and less that removed in sewage treatment. The effluent concentration is then calculated by dividing this figure by the per capita wastewater discharge for that nation:

$$W = \frac{(C - E - S)}{D}$$

Where *C* is consumption of the drug as ng/cap/d; *E* is the amount of the drug that is not excreted (ng/cap/d); *S* is the amount of the drug that is prevented from escaping into sewage effluent (ng/cap/d); *D* is the diluting volume of wastewater as L/cap/d; and *W* is the effluent concentration as ng/L.

The river concentration at the point of the effluent discharge (R_m, ng/L) is calculated by mass balance, and loss of the compound due to aquatic processes such as sedimentation and transformation is accounted for with a first order dissipation process to give the downstream concentration (R_d, ng/L).

99 $$R_d = R_m e^{-k\,t}$$

100 Where, *k* is the decay rate (days^{-1}) and *t* is the time of travel (days). The time of travel is the river
101 reach volume divided by the flow rate [14].

102 The most critical part of any predictive model used to assess concentrations of human
103 derived chemicals in water is obtaining information on usage. National databases and academic
104 studies can be interrogated to assess a per capita consumption value, given the human population of
105 the country at that time (Table 1).

106 **TABLE 1. Range of national pharmaceutical per capita consumption values and their year of origin**

Country	EE2 consumption (µg/cap/d)	Ref source	E2 (HRT) consumption (µg/cap/d)*	Ref Source	Diclofenac consumption (µg/cap/d)	Ref Source
Belgium	2.11 (2007)	[15]	NA	NA	NA	NA
France	1.54 (2007)	[15]	NA	NA	449 (2004)	[16]
Germany	1.69 (2007)	[15]	NA	NA	2613 (2003)	[17]
Italy	0.94 (2007)	[15]	NA	NA	NA	NA
Netherlands	2.59 (2012)	[18]	1.7 (2011)	GIPdatabank (www.gipdatabank.nl)	1205 (2012)	[18]
UK	1.21 (2007)	[15]	5.7 (2010)	NHS dataset (www.ic.nhs.uk)	957 (2010)	NHS dataset (www.ic.nhs.uk)
Spain	1.0 (2003)	[19]	NA	NA	2124 (2003)	[19]
Sweden	0.84 (2010)	Apotekensservice (www.apotekensservice.se)	15.7 (2010)	Apotekensservice (www.apotekensservice.se)	1351 (2010)	Apotekensservice (www.apotekensservice.se)
Poland	1.0 (2000)	[20]	NA	NA	1482 (2000)	[20]
Switzerland	2.0 (2000)	[19]	NA	NA	1459 (2000)	[19]
Denmark	NA†	NA	NA	NA	520 (2009)	Danish medicine statistics (www.ssi.dk)
Czech Republic	1.18 (2012)	SUKL database (www.sukl.cz)	4.1 (2012)	SUKL database (www.sukl.cz)	1075 (2012)	SUKL database (www.sukl.cz)
Norway	1.51 (2011)	Norwegian Prescription Database (www.norpd.no)	7.9 (2011)	Norwegian Prescription Database (www.norpd.no)	1059 (2011)	Norwegian Prescription Database (www.norpd.no)
Mean	**1.47**		**7.0**		**1299**	

107 †NA = Not Available *HRT = Hormone Replacement Therapy

108 **Ethinylestradiol consumption, excretion, and environmental fate.** Recent values for EE2
109 consumption in different European countries that are available show only a small variation in
110 individual EE2 consumption values (Table 1 & 2). The probable excretion rate of EE2 by humans has

111 been extensively reviewed [21] and this also shows only modest variation (Table 2). Information on
112 removal in sewage treatment is available [21-27] and a wide variation in performance is apparent
113 (Table 2). EE2 is still considered the most persistent of the steroid estrogens ,with a modest half
114 life in water of 17 d and also a slow photodegradation rate [28, 29]. The model used here for
115 predicting EE2 concentrations in sewage effluent and receiving waters [21] has been compared
116 previously against measured concentrations [30-32]. An agreement value can be given by dividing
117 the observed by the modelled concentration, such that one is a perfect match, less than one an
118 overestimate and greater than one an underestimate. For EE2 the result is 0.2-2.0 (n=20) for these
119 studies which is within an order of magnitude difference [30, 31].

120 **Estradiol consumption, excretion, and environmental fate**. Estradiol is one of the natural estrogen
121 hormones circulating in the human body and is indeed common to all vertebrates [33]. It is also
122 provided as an active ingredient of many hormone replacement therapies (HRT) and as an ester pro
123 drug (estradiol valerate) in some new contraceptive formulations. The most important contributors
124 of natural E2 are pregnant women, providing an estimated 63% of the natural E2 load in the UK [21],
125 followed by menstrual women (18%). For this study the demographics of each European nation was
126 assessed and the number of males, menstrual, menopausal and pregnant females recorded [34]. To
127 calculate a per capita E2 discharge for each nation, the assumed E2 excretion rate (μg/cap/d) for
128 each population sub-group [21] was multiplied by the number of people in each category. It should
129 be noted that obtaining a value for the number of pregnant women is particularly complex as
130 abortions, foetal deaths, live births and multiple births for each country have to be disentangled
131 from a range of sources. This value was normalised by dividing by the total population to give a per
132 capita natural E2 value. To this natinal natural E2 value was added the per capita HRT E2 value
133 where known, or otherwise a European average value, to calculate a national total E2 discharge
134 value (Table 2). Recently, the topic of human E2 excretion was reviewed [35] for the US and a value
135 of 7.87 μg/cap/d was reported, which is very similar to that previously calculated for E2 [21] in the
136 UK and the range calculated for this study (4-8 μg/cap/d) .

Given the amount of E2 excreted by women on HRT and the proportion present as the parent or glucuronide then only 3-10% of the pharmaceutical E2 ingested would be excreted [21, 36, 37]. This implies that for the countries for which we have data (Table 1), only 1-8% of the total E2 arriving at a sewage treatment plant (STP) would have originated from pharmaceutical sources.

It was assumed that 50% of E2 will convert to E1 in the sewers before arriving at a STP following the suggestion of earlier models [21] (Table 2). Information on removal in sewage treatment is fairly consistent [22-25, 27, 38-40], with a mean removal of 89% being recorded (Table 2). No type of biological sewage treatment (such as between trickling filter and activated sludge) is significantly worse than any other in removing E2 [41]. The ready degradability of E2 in river water samples indicates half-lives of 0.2 to 8.7 d could be expected [28], and the dissipation observed in the field appears to correspond to such rates [42]. This approach to predicting E2 concentrations in sewage effluent and receiving waters has been compared previously against measured concentrations and found to give an observed over modelled agreement ratio of 1.3 (n=3) at one plant effluent [30] and 0.4 (n=19) for 19 STP effluents with an agreement ratio of 0.5-0.7 for a 34 km river stretch [31].

There is a danger that modelling river E2 concentrations on the basis of human inputs alone may underestimate the situation in areas where livestock predominate. Whilst some evidence for a link between the presence of livestock and river estrogens have been made [43] widespread endocrine disruption remains most closely associated with STPs [32] and E2 river predictions at least in the UK can be explained by sewage inputs [31, 44].

Diclofenac consumption, excretion, and environmental fate. Diclofenac (2-[2,6-dichlorophenyl)amino]benzeneacetic acid is a popular non-steroidal anti-inflammatory drug often used to treat rheumatic type pain. The variation in national diclofenac consumption rates appears to be wider than for the other two drugs (Table 1 and 2). The range in diclofenac excretion values has been reviewed previously [45] and appears to be more variable than the range for EE2. Whilst

there again appears to be quite large variability [18, 46-56], the weighted mean sewage removal of diclofenac is poor at only 22% (Table 2). Photodegradation has been put forward as an important removal mechanism in surface waters [57-59]. In reality, leaving darkness aside, conditions in the field are often not ideal for photodegradation, so removal along a river, where residence times are typically much shorter than lakes, can be negligible for diclofenac [57, 60]. Given this uncertainty it was considered prudent to exclude attenuation in predictions for this molecule in river water. The modelling approach for predicting diclofenac concentrations was similar to that carried out previously [45], but now with slightly changed parameters (consumption, excretion and sewage removal) informed by more recent literature. As this diclofenac method has not been tested previously, this was examined using relatively recent sewage effluent measured values from composite samples where inhabitant and flow information permitted predictions to be made [18, 54, 61, 62](Table S1).

TABLE 2. Range of factors affecting the model and their potential impact on the outcome. Note where sufficient data permits a weighted mean is given followed by the best and worst case value given in parenthesis.

Factor	EE2	E2	Diclofenac
Consumption range across nations (μg/cap/d)	0.84-2.59	4.1-8.2[a]	449-2613
Apparent consumption variation	3-fold	2-fold	6-fold
Weighted mean with lowest and highest patient excretion values (%)	40 (21-54)	NA	9.5 (2-23)
Potential effect on influent concentration	3-fold	NA	11-fold
Weighted mean with lowest and highest sewage treatment removal (%)	68 (0-90)	89 (69-99)	22 (0-82)
Potential effect on sewage effluent concentration	10-fold	31-fold	5-fold
Potential effect on drug concentations by combining effects of excretion and sewage treatment removal factors.	26-fold	31-fold	64-fold
In stream half-life in days ($20^{o}C$)	17.3	2.3 (0.3-8.7)	Not used
Range of dilution factors across Europe (m^3/cap/d) **		$2.8 - 2.7 \cdot 10^3$	
Potential effect on water concentration		1000-fold	

[a] As E2 is largely an endogenous hormone we cannot discuss it in terms of consumption and excretion rate. The values given are the concentration excreted by a 'normalised human' [21] modified by national demographics and HRT use differences where known

**10%ile to the 90%ile of dilution values calculated on a cell-by-cell basis using 1970-2000 average river discharge

European river water modelling. To examine potential concentrations of these chemicals throughout European surface waters, the geographic-based water resources model GWAVA run in a water quality mode was used [14]. This model uses geographic data on the location and size of the human European population and their association with STPs. The version of GWAVA used here incorporates a newly available and extensive dataset (2009-2010 information) of locations and number of people connected to sewage discharge points in Europe [63]. The flows through these STPs are incorporated with the natural river discharge adjusted for abstractions (principally for potable supply and agriculture). The hydrology is driven by monthly climate over the period 1970-2000. The ability of GWAVA to simulate river flows has been previously tested against gauged flows across Europe, and other continents. Also modelled water quality determinands have been compared with measured data [14]. The chemical inputs of per capita drug consumption, excretion, removal in sewage, and in-stream half- life were provided by this study (Table 2). The model calculates the water concentrations of chemicals through water courses in a series of 177,470 grid squares (cells) of approximately 6 x 9 km (5 by 5 Arc minutes) dimensions. On a monthly basis, in the water courses in each cell receiving effluent, the concentration is calculated by diluting the mass of chemical discharged in the volume of water in the cell accounting for any loads from upstream cells. The chemicals are transported downstream with the discharge to the next cell. Chemical can be lost through abstraction or a first-order dissipation process. The time of travel though the gridded network (which can comprise rivers, lakes and wetlands) is calculated from the river flow rate and the water volume of each cell. Surface water volumes are estimated using established empirical relationships with width and depth data [14]. Thus, the model was set up using either the national, or mean, per capita consumption for EE2 and diclofenac for each country as appropriate (Table 1).

For E2, a value for each nation was derived from its population demographics plus pharmaceutical E2 use where known (Table 1). The mean value for each grid square was then used as the output. This was considered the most relevant output given that the proposed EQS in the EU (COM(2011)876) document would use an annual average (AA) value. The model output and its statistical analysis can be for a continent, for separate nations or even for individual river basins based on selecting the appropriate cells. Trans-boundary flows and their pollutant load are always accounted for.

Scenario analysis. There are uncertainties in the model parameters determining effluent concentrations, which are critical in estimating river concentrations. In order to assess the impact of this uncertainty, a series of scenarios were run to establish the range of likely river concentrations (and hence likely EQS exceedence) , based on the reported literature values. These scenarios were a best case - low excretion, high sewage removal and high in stream dissipation; a worst case - high excretion, low removal and slow in stream dissipation and an expected case, which used weighted average values for these parameters (Table S2). The envelope of possible effluent concentrations from the best and worse case scenarios was large differing by factors of approximately 26 for EE2, 31 for E1 and 64 for diclofenac (Table 2). The expected scenario based on the mean literature values gives reasonable agreement with the few available measured data (see above and results section), with the other cases giving the extreme values.

Results and Discussion

Ability to predict diclofenac concentrations in effluent. The predicted and measured effluent diclofenac concentrations were compared by dividing the measured by the predicted value to give an agreement ratio (Table S1). Based on this small comparison, with agreement ratios between 0.5

and 8.7, it appears the diclofenac predictions were broadly acceptable (Table S1) but with a tendency to underestimate.

Predicted exceedences of proposed European EQS values. Before starting the water quality modelling, based on the European mean consumption values, excretion values and sewage removal factors (Tables 1 and 2) then 1 ng/L EE2, 3 ng/L E2 and 570 ng/L diclofenac would be expected in European sewage effluents. It should be noted that where data were lacking, such as in some Eastern European countries, European average drug consumption values were used. Apart from predicting the consumption value correctly, it can be seen that variations in the hydrological dilution component will have the biggest impact on the outcome (Table 2). Rivers where an annual average concentration of EE2 would exceed 0.035 ng/L would be fairly widespread with the expected scenario (Fig. 1). Of perhaps greater biological significance is where EE2 concentrations might exceed 0.35 ng/L [8, 64]and this is far less widespread but not negligible (Fig. 1). When all the results are plotted as cumulative frequency distributions, both as the expected (Fig. 2) together with the best and worst case (Fig. S1 and S2) scenarios and compared with the proposed EQS values it can be seen that EE2 would pose the greatest challenge. It can be observed that 74% of Europe's rivers by length receive some sewage input whilst the remaining lengths have negligible human input (Fig. 2). Between 2 and 25% by length of Europe's rivers were predicted to have EE2 concentrations in excess of 0.035 ng/L (best and worst case) with the expected outcome being 12% (Fig. 2). For E2 between 0-6% of river lengths were predicted to exceed 0.4 ng/L (1.5% expected exceedance) and for diclofenac this is predicted to range from 0.1-8.3% of river lengths exceeding 100 ng/L (2.4% expected exceedance) in the three scenarios (Fig. 2, Fig. S1 and S2).

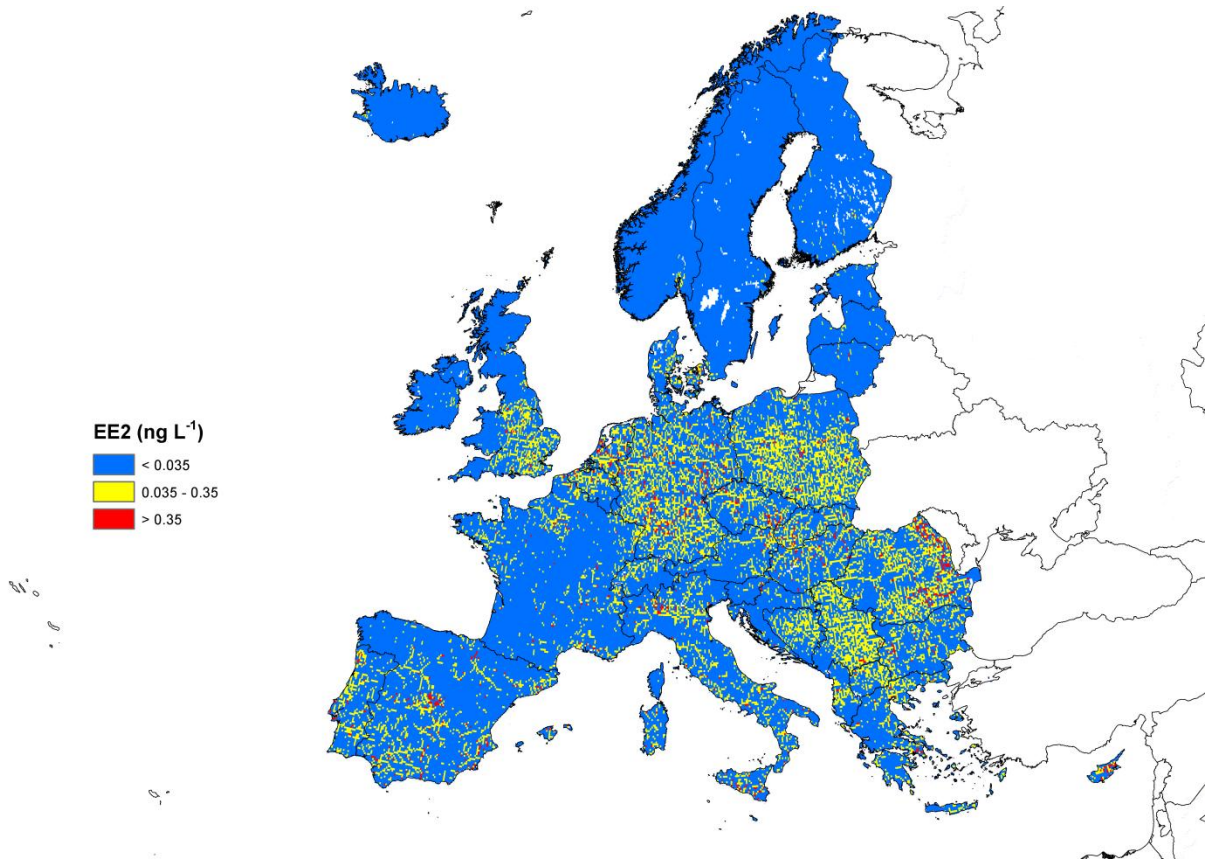

FIGURE 1. Location of European surface waters where EE2 concentrations are predicted to exceed 0.035 ng/L (yellow) and 0.35 ng/L (red) based on expected chemical discharge (mean excretion and mean sewage removal)

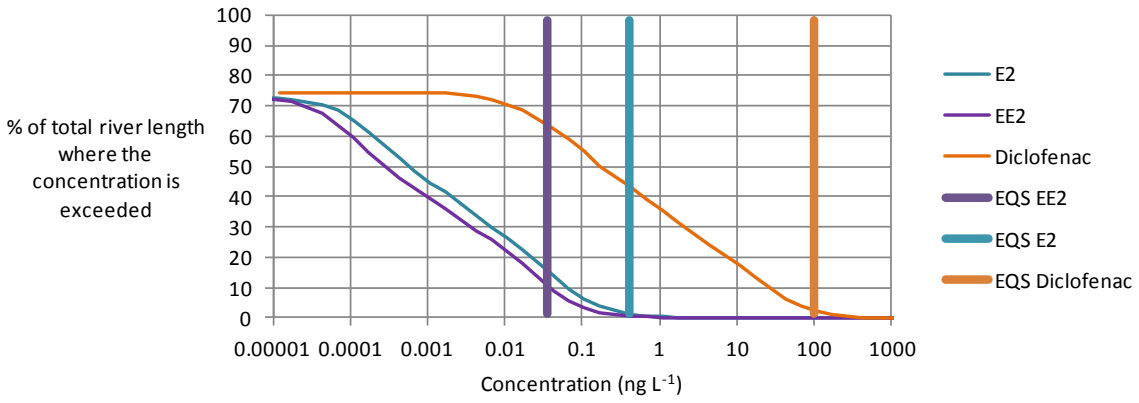

FIGURE 2. Predicted average river water concentrations throughout the European river network based on expected chemical discharge (mean excretion and mean sewage removal) and their proximity to the proposed EQS values in COM(2011)876

TABLE 3. Predicted proportion of national river length that would exceed the suggested annual average EQS based on expected chemical discharge

EE2 (0.035 ng/L AA EQS)		E2 (0.4 ng/L AA EQS)		Diclofenac (100 ng/L AA EQS)	
>30%	Netherlands, Germany, Macedonia, Romania, Poland, Slovakia, Belgium, Bosnia, Serbia	>5%	Romania*, Czech R., Netherlands	>10%	Germany
25-30%	Czech R., Hungary, England	4-5%	Slovakia, Hungary, Germany, Italy, England	8-10%	Spain, Romania, Netherlands
20-25%	Portugal, Albania, Denmark, Bulgaria, Greece	3-4%	Spain, Portugal, Poland, Denmark, Albania, Belgium, Macedonia	5-8%	Poland, Czech R., Hungary, Italy
15-20%	Italy, Switzerland, Austria,	2-3%	Bulgaria, Luxembourg, Serbia,	3-5%	Slovakia, Portugal, Belgium, Serbia, Macedonia, England
10-15%	Spain, Luxembourg, Croatia	1-2%	Greece, Austria, France,	1-3%	Albania, Bulgaria, Luxembourg, Austria, Greece, Denmark, Switzerland
<10%	France, Ireland, Slovenia, Lithuania, Estonia, Wales/Scotland, Finland, Latvia, Sweden, Norway	<1%	Croatia, Switzerland, Ireland, Slovenia, Lithuania, Estonia, Wales/Scotland, Finland, Latvia, Sweden, Norway, Bosnia	<1%	Croatia, Ireland, Slovenia, France, Lithuania, Estonia, Wales/Scotland, Finland, Latvia, Sweden, Norway, Bosnia

*Values provided for 32 European nations. The UK was separated into England and Wales/Scotland/Northern Ireland. Cyprus and Iceland were not included due to uncertainties in the ability to simulate their chemical concentrations.

It is possible to examine the proportion of river length that would exceed the suggested EQS on a national basis in the expected scenario (Table 3). Some countries, such as the Netherlands, Czech Republic, Romania and Germany appear to have the most exposed rivers, whilst the rivers in the Scandinavian countries and Baltic Republics are typically least exposed. The high, or low, exposure of some countries does not always seem intuitive and it is worth reviewing the principal controlling factors captured in the model predictions:

- High populations discharging into small rivers.
- Above, or below average national consumption of the specific drug.
- Low sewer connection (eg in Belgium only considered to be 60%) as septic tanks are assumed to not be directly connected to rivers.
- Receiving waste from upstream neighbouring countries, such as the Netherlands (important where in-stream attenuation is low).
- It is the nature of averages that they can be highly influenced by transient very low flows, which can occur more frequently in some countries than others (eg Spain, Romania and UK).
- Where the GWAVA model does not have specific information on the sewage effluent discharge points (eg Poland, Bosnia Herzegovina, Serbia), it estimates a discharge point relative to the population centre and the nearest water course. This could lead to too high modelled concentrations as discharge may be incorrectly ascribed to small tributaries.
- The range of predicted concentrations can be rather narrow in some country's rivers. The choice of the EQS value can then dramatically change the percentage of river length exceeding that EQS.

The national exposure to these chemicals can only be considered a preliminary guide, but nevertheless it will hopefully stimulate further study and debate.

Implications. Given the enormous difficulties in measuring picogram concentrations of E2 and EE2 in rivers, currently our best hope in assessing exposures throughout Europe is through

291 modelling. With its global scope, models like GWAVA can be applied to continents, such as Europe,
292 to assess possible river concentrations of pollutants originating from the human population.
293 However, with a 6 x 9 km grid cell, its precision is limited and in some countries the sewage effluent
294 discharge locations are also only estimated. Similarly, in this modelling exercise where the precise
295 national consumption of a drug was not known, a European mean had to be applied. Despite these
296 limitations, the clear message from this modelling exercise was that using the expected scenario
297 over 10% of continental Europe's rivers (25% assuming a worst case scenario) would exceed a 0.035
298 ng/L EE2 AA EQS. For many European countries, a quarter to a third of their rivers would fail such a
299 standard. If a 0.035 ng/L EE2 AA EQS were to be applied across Europe, it would represent an
300 enormous technical and financial challenge to meet, given the extent of likely failure predicted here.

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304 **Supporting Information Available**

305 Details on the corroboration of predicted and measured diclofenac concentrations in sewage
306 effluent, cumulative frequency curves for best and worst case scenarios for the pharmaceuticals in
307 European rivers together with parameters used in the modelling are available free of charge via the
308 Internet at http://pubs.acs.org.

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