Predicting concentrations of human pharmaceuticals throughout the river systems of Europe

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Introduction

Human pharmaceuticals are produced in significant amounts with high production volume. Not surprisingly, pharmaceuticals have been detected around the world in a wide range of environmental media, such as urban and hospital wastewater effluents, surface waters, ground waters and drinking waters (e.g., Fatta-Kassinos et al., 2011). Consequently, the discharge of pharmaceuticals in wastewater into the aquatic environment has been a source of discussion and concern in scientific and regulatory circles for more than a decade (Daughton & Ternes, 1999; Halling-Sørensen et al., 1998). 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 recent addition of the pharmaceuticals 17α-ethinylestradiol (EE2), 17β-estradiol (E2) and diclofenac in the European Community document (COM(2011)876) appear to usher in a new era. The document suggested annual average EQS of 0.035 ng/L for EE2, 0.4 ng/L for E2 and 100 ng/L for diclofenac.

If these three pharmaceuticals stay on the watch list and even become priority substances needing control, so it is likely other pharmaceuticals will follow. Chemotherapy drugs in the group known as cytostatic, cytotoxic, or antineoplastic (referred to collectively as cytostatic) are often featured on lists of pharmaceuticals of concern that are discharged into our river systems (Fent et al., 2006; Sanderson et al., 2004), due to their possess fetotoxic, genotoxic and teratogenic properties, which have already been shown in fish (Grisolia, 2002) and invertebrates (Anderson et al., 1995).

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. 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 and technical feasibility.

Here, the results of two separate but related studies are presented, in which we attempted to predict the range of possible concentrations of pharmaceuticals in surface waters for various countries in the European Union. Based on publically available consumption data, literature data on human excretion values, and sewage removal rates, we predict concentrations of four cytostatics (i.e., cyclophosphamide; CP, carboplatin, 5-fluorouracil; 5FU, and capecitabine, as well as the three "WFD-compounds" E2, EE2, and, using the geographic-based Global Water Availability model (GWAVA; Dumont et al., 2012). For the latter three compounds, we examined whether and where predicted river concentrations would exceed proposed EQS levels of 0.4 ng/L for E2, 0.035 ng/L for EE2 and 100 ng/L across Europe.

Method

Estimation of effluent concentrations

The approach to estimating sewage effluent concentrations takes the drug consumption per capita for a specific country, 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 (Equation 1).

$$W = \frac{(C-E-S)}{D} \qquad (1)$$

Where *C* is consumption of the drug (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 (L/cap/d); and *W* is the effluent concentration (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) (Equation 2).

$$R_d = R_m \cdot e^{-k \cdot i} \qquad (2)$$

Where k is the decay rate (days^{-1}) and t is the time of travel (days). The time of travel is the river reach volume divided by the flow rate (Dumont et al., 2012).

Assessing consumption, excretion and sewage removal

The most critical part of any predictive model to assess concentrations of human derived chemicals in water is obtaining information on usage. Fortunately, some national annual consumption data on cytostatic drugs are publically available. These were interrogated to assess a per capita consumption value, given the population of the country at a particular time.

Next, the extent to which the parent compound is excreted unchanged by the patient has to be considered. Not surprisingly, humans vary in their excretion behaviour, with such factors as age, health, and co-medication all influencing the percentage excreted. This especially holds for the cytostatic compounds assessed. We therefore surveyed a wide range of literature on excretion rates before arriving at a mean value. Similarly to excretion rates, natural variations in sewage performance can influence pharmaceutical removal rates in treatment. Moreover, the literature on removal in sewage treatment for many (cytostatic) pharmaceuticals is still limited.

European river water modelling

To examine potential concentrations of the pharmaceuticals throughout European surface waters, the geographic-based water resources model GWAVA was used (Dumont et al., 2012). This model uses geographic data on the location and size of the human European population and their association with sewage treatment plants (STPs) (EEA, 2011). 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 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. 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 (Equation 2). The time of travel through 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 (Dumont et al., 2012).

Results

The GWAVA model provides predictions for 1.2 million km of European rivers receiving the waste from 602.8 million people. As such, a single run of the model with its 177 000 grid squares and 31 years of climate data generates 66 million results per chemical. All of the variables discussed will play a role. However, the most important factor in correctly predicting river concentrations, apart from consumption, is dilution. Different interpretations on human excretion, or sewage removal rates, could change the values by up to 20-fold, but dilution could change the values by up to 1000-fold.

Predictions for the four cytostatics

The results from model runs are displayed in a map showing the 50th percentile concentrations across Europe for CP based on a mean excretion rate and mean sewage treatment removal (Fig. 1). This is broadly equivalent to the concentration that would be recorded at a median flow for that part of a river and, as such, might represent the typical exposure for surface waters. When potential worst-case river concentrations are modelled, such as might be associated with low summer flows, the simulations indicate that 99% of European river locations would be below 0.2 ng/L for carboplatin and below 0.6 ng/L for 5FU. With CP, only 0.1% of locations could exceed 1 ng/L, whereas for capecitabine, 2.2% could exceed 1 ng/L in rivers.

Predicted exceedances of proposed European EQS values for EE2, E2 and diclofenac

Before starting the water quality modelling, based on the European mean consumption values, excretion values and sewage removal

factors, then 1 ng/L EE2, 3 ng/L E2, and 570 ng/L diclofenac would be expected in European sewage effluents. At mean excretion and mean sewage removal, rivers where an annual average concentration of EE2 would exceed 0.035 ng/L would be fairly widespread with the expected scenario (Fig. 2). Of perhaps greater biological significance is where EE2 concentrations might exceed 0.35 ng/L (Caldwell et al., 2008), and this is far less widespread but not negligible (Fig. 2). When all the results are plotted as cumulative frequency distributions and compared with the proposed EQS values, it can be seen that EE2 would pose the greatest challenge (Fig. 3). 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. 4).

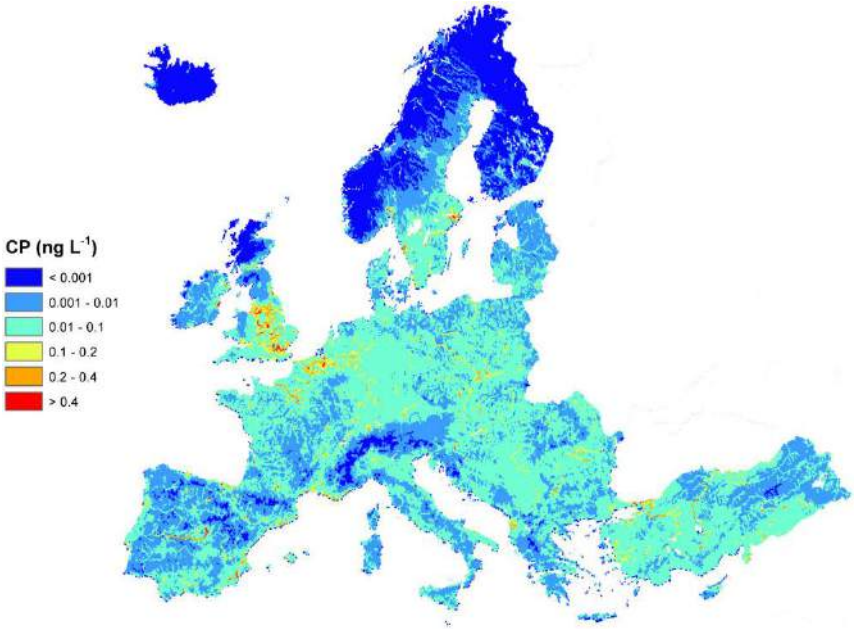

Figure 1. Predicted cyclophosphamide (CP) concentrations in surface water based on mean excretion rate, mean sewage treatment removal, and 50th percentile flow across the European continent, taking into account differing national per capita consumption and wastewater discharge values from the Global Water Availability model (GWAVA).

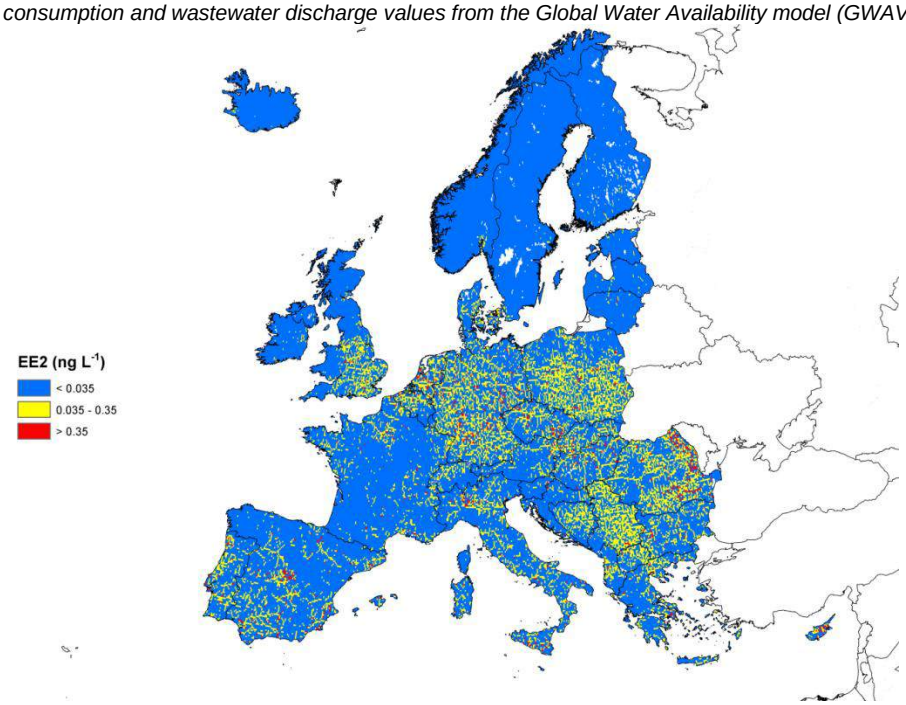

Figure 2. Location of European surface waters where EE2 concentrations are predicted to exceed 0.035 ng/L (yellow) and 0.35 ng/L (red) based on expected chemical discharge (mean excretion and mean sewage removal).

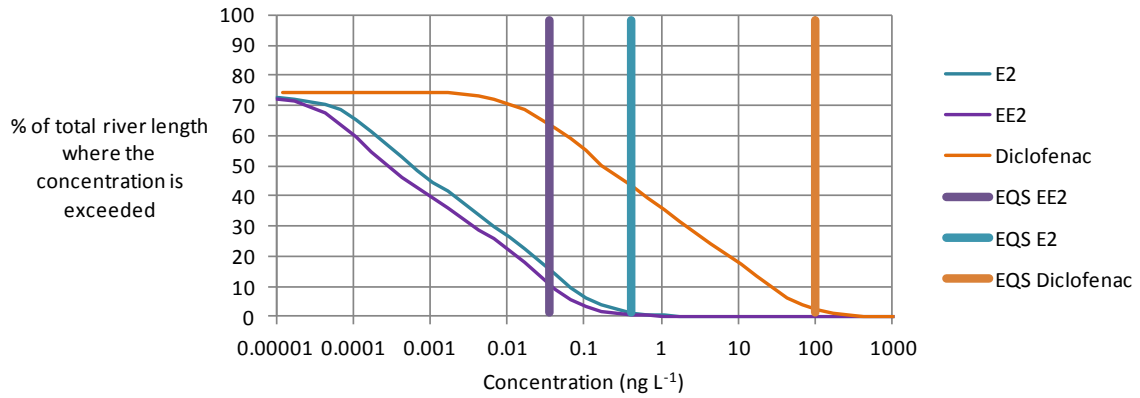

Figure 3. Predicted average river water concentrations throughout the European river network based on expected chemical discharge (mean excretion and mean sewage removal) and their proximity to the proposed EQS values in COM(2011)876.

Conclusion

Concentrations predicted for cytostatics

We found a surprising difference in the popularity of the four cytostatics drugs across European nations, with differences of up to 28-fold. The predicted mean effluent concentrations ranged from 2 ng/L to 40 ng/L for CP, from 0.8 ng/L to 2.5 ng/L for carboplatin, from 0.3 ng/L to 2.5 ng/L for 5FU, and from 8.5 ng/L to 87 ng/L for capecitabine. In the majority of cases, where data are available, it is possible to predict CP concentrations in sewage effluent to within an order of magnitude of that observed (data not shown here). By linking with the geographic-based water quality model, it is expected that the majority of European rivers would have concentrations below 1 ng/L for these cytostatics drugs.

Comparison with proposed EQS values and implications

Given the enormous difficulties in measuring pictogram concentrations of E2 and EE2 in rivers, currently our best hope in assessing exposures throughout Europe is through modelling. With its global scope, models like GWAVA can be applied to continents, such as Europe, to assess possible river concentrations of pollutants originating from the human population. Despite limitations with respect to the resolution (6 x 9 km grid cells) and limited national consumption data for some countries (for which a European mean had to be applied), the clear message from this modelling exercise was that over 10% of continental Europe's rivers would exceed the proposed EQS for EE2 of 0.035 ng/L. If such an EQS were to be applied across Europe, it would represent an enormous technical and financial challenge to meet, given the extent of likely failure predicted here.

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