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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. The 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.

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1. Introduction

During the life cycle of a pharmaceutical product, Active Pharmaceutical Ingredients (APIs) may be released to the natural environment (Boxall, 2004; Daughton and Ternes, 1999) 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 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 released to the environment. Over half of patients store unused medicines in their home as a consequence of dosage changes, discontinuation of the medication due to, for example, the occurrence of adverse side effects, or because the medications have

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reached their expiry date. It is estimated that anywhere between 3 and 65% of prescribed pharmaceuticals are not used and many of these will ultimately be returned to the pharmacist or disposed of to landfill (Seehusen and Edwards, 2006; Musson and Townsend, 2009).

While numerous publications are available on the metabolism of APIs, the results of these studies can be highly variable. For example, for cyclophosphamide (one of the APIs investigated in the current study), amounts excreted are reported to range from 2 to 25% of the applied dose (Bagley et al., 1973). The observed differences are probably explained by genomically distinct metabolising capacities as well as differences in race, sex, age and health status of the studied subjects, all of which are known to affect the route and rate of metabolism (Dorne, 2010). The method of administration, previous exposure of a patient to the pharmaceutical and simultaneous exposure to other APIs and xenobiotics can also affect the degree of metabolism.

For many APIs, no data exist on the removal in wastewater treatment. In instances where data are available, variations can also be seen in the reported removal efficiencies (Sipma et al., 2010). These variations can be explained by differences in technologies used at different treatment works and differences in operating parameters. Some metabolites may also be re-converted back to the parent compound in wastewater treatment (Heberer et al., 2002). In large catchments it is likely that numerous treatment technologies will be in use and that these will vary in size and performance, so a variety of removal rates may need to be employed in the modelling. The fate of substances in the sewer system is also unknown. Finally, available data on dissipation of APIs in receiving waters is mostly generated under 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 the 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 the 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.

2. Methods

2.1. 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.

2.2. 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 (Janna et al., 2011; Price et al., 2010a, 2010b; Rowney et al., 2009; Williams et al., 2009) and so only the parts salient to this analysis will be described here. LF2000-WQX is the water quality extension model to the Low Flows 2000 (LF2000) software system (Environment Agency, 2004; Young et al., 2003), which is a geographical information system (GIS) based decision support tool designed to estimate river flows at ungauged sites. It combines hydrological models estimating the magnitude and variability of flows across a catchment with a water quality model. The water quality model is driven by discharges from sewage treatment plants (STPs), the locations of which are preset in the model along with data describing the population served, treatment type and dry weather flow of each works. The outputs of the model are mean and 90th and 95th percentile concentrations for each river reach within the catchment being modelled.

Calculation of concentrations in river reaches is based on a simple mass balance mixing equation which is applied in an iterative Monte Carlo simulation using the method of combining distributions proposed by Warn and Brew (1980). Point-source effluent emissions are combined with reach-specific flow statistics to calculate in-river concentrations after mixing at the point of discharge, allowing for upstream concentrations of the pharmaceutical. Flow in the river and flow volume from the sewage works are described as distributions. The other parameters are held constant. The river flow is characterised as log-normal and the sewage work flows as normal. Changes in concentration with 'flow time' due to dilution, from e.g. inputs from tributaries, and degradation also are calculated.

The emissions of an API for a given STP are typically derived from prescription data and STP characteristics. The STP inflow concentration (C_i) is estimated from the projected/actual per capita mass of chemical used/excreted (M, μg/cap/day), and the STP dry weather flow (DWF, L/day), using Eq. (1):

$$C_i = \frac{M \cdot P}{DWF} \quad (1)$$

where P is the population served by the works and was obtained from the water utilities operating each works for all works across England

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