Ibuprofen exposure in Europe; ePiE as an alternative to costly environmental monitoring

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ABSTRACT

The EU Water Framework Directive and Priority Substance Directive provide a framework to identify substances that potentially pose a risk to surface waters and provide a legal basis whereby member states are required to monitor and comply with environmental quality standards (EQSs) set for those substances. The cost and effort to continuously measure and analyse real world concentrations in all water bodies across Europe are high. Establishing the reliability of environmental exposure models to predict concentrations of priority substances is key, both to fill data gaps left by monitoring campaigns, and to predict the outcomes of actions that might be taken to reduce exposure. In this study, we aimed to validate the ePiE model for the pharmaceutical ibuprofen by comparing predictions made using the best possible consumption data with measured river concentrations. The results demonstrate that the ePiE model makes useful, conservative exposure predictions for ibuprofen, typically within a factor of 3 of mean measured values. This exercise was performed across a number of basins within Europe, representative of varying conditions, including consumption rates, population densities and climates. Incorporating specific information pertaining to the basin or country being assessed, such as custom WWTP removal rates, was found to improve the realism and accuracy of predictions. We found that the extrapolation of consumption data between countries should be kept to a minimum when modelling the exposure of pharmaceuticals, with the per capita consumption of ibuprofen varying by nearly a factor of 10.

1. Introduction

The trend in the use of active pharmaceutical ingredients (APIs) to treat common ailments via self-care continues to increase globally (Bennadi, 2014; IQVIA, 2019). With the improved access to self-care that many of us consider a cornerstone of modern-day living, comes the potential for over consumption and the inappropriate disposal of pharmaceutical products. This is no doubt a contributing factor to the volumes of the pharmaceuticals found in surface waters around the globe (aus der Beek et al., 2016; Pereira et al., 2020a, 2020b; Petrie and Camacho-Muñoz, 2020; Sousa et al., 2018).

Within Europe, the Water Framework Directive (WFD) (EC, 2000) and Priority Substance Directive (EC, 2008, 2013) provide a framework to identify substances that potentially pose a risk to surface waters and provide a legal basis whereby member states are required to monitor and comply with environmental quality standards (EQSs) set for those substances. Where concentrations in surface waters exceed EQSs, a number of actions might be taken to reduce the surface water concentrations to safe levels. In order to ensure the best course of action is taken, whilst maintaining the societal benefits of the substance to the greatest degree possible, it is vital to have a thorough understanding of the emission, fate and exposure of the substance in question, including identifying all important sources and the size of their contribution. This is a key aspect of assessing the effectiveness of any measures taken to reduce environmental exposure to safe levels. The cost and effort to continuously measure and analyse real world concentrations in all water bodies across Europe are high and can be quite focussed on the relatively short list of substances identified as a priority under the Water Framework Directive (WFD). In addition, studies publishing monitoring data are relatively few in number, and generally cover specific basins and time periods making this source of information unsuitable for assessing the impacts of measures taken to reduce pharmaceutical exposure. A recent review of the fitness of the WFD concluded that further efforts are required to have monitoring networks reach sufficient spatial coverage (Vermeulen et al., 2014).

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in detail in Oldenkamp et al. (2018), it was designed to generate predictions that are capable of predicting API concentrations in waterways to a resolution of 1 km across Europe. As described in Oldenkamp et al. (2018), Oldenkamp et al. (2018) have previously performed a validation exercise, comparing ePiE predicted values with measured values for the river Ouse (UK) and the Rhine. The model performed relatively well, however the extrapolation of consumption data both temporally and between countries was identified as a key factor influencing the results, particularly for the Rhine where consumption data were only available as greater than values, did not match the measured data temporally (consumption from 2009 was extrapolated to 2011–2014) and did not cover all of the countries required. In the validation exercise for the UK, only prescription data were included in the consumption data, however a number of APIs that are sold to consumers over-the-counter (OTC) were compared, likely contributing to the underestimation that was identified. In addition, no consideration was given to the topical pathway, either through consumption data or within the model itself. In a recently published study, we showed that OTC consumption and topical formats can contribute significantly in the UK, showing OTC sales made up over 50% of the mass used for ibuprofen and diclofenac and that topical formats contribute disproportionately to the mass released when compared with orally taken products (Austin et al., 2021). More recently, van Gils et al. (2020) extrapolated consumption data to an even greater degree, to the rest of Europe, and found lower accuracy predictions for pharmaceutical concentrations with their Computational Material Flow Analysis approach when compared to Oldenkamp et al. (2018). The availability and accuracy of the consumption data was explicitly identified as the key factor in determining the accuracy of their predictions, with excretion rates and fate in treatment plants being ruled out.

Establishing the reliability of exposure models is important to allow EU regulators to fill data gaps left by monitoring campaigns, to assess the exposure and risk of substances that have not yet been subject to monitoring campaigns and to predict the outcome and magnitude of the effect of actions they take to reduce risks pertaining to priority chemicals. It is clear that using appropriate consumption data is key in establishing the validity and reliability of an exposure model. Here, we aim to validate the ePiE model by comparing predictions made using the best possible consumption data with measured river concentrations in Croatia, Germany, Slovenia, Spain and the UK. In addition we assess modifications to the model to include the topical pathway and real WWTP removal data. This study focuses on ibuprofen which is currently being considered by the EU commission as a candidate for the priority substances list under the WFD and is currently of high relevance to the EU commission and member state authorities (DG Env, 2020).

2. Methods

2.1. Modelling with ePiE

ePiE is a spatially explicit model capable of predicting API concentrations in waterways to a resolution of 1 km across Europe. As described in detail in Oldenkamp et al. (2018), it was designed to generate predictions to this resolution with limited computational and input data requirements using FLO1K for its hydrology, a global geographic data set with annual predictions of streamflow metrics (annual mean flow, highest and lowest monthly mean flow) spatially distributed at 30 arc seconds (~1 km) resolution (Barbarossa et al., 2018).

ePiE considers the mass of each API released to wastewater per wastewater treatment plant (WWTP) in kg/year ($E_{wwtp}$) via Equation (1) (equation and definitions taken from Oldenkamp et al. (2018)). As suggested by Austin et al. (2021), an extra component was added to Equation (1) to account for topical product formats, resulting in Equation (2).

$$E_{wwtp} = \left( M \cdot f_{pc} + M_{pd} \cdot f_{met} \right) \cdot \sum_{j=1}^{n} \frac{\left( V_{ww,j} \cdot f_{conc,j} \right)}{V_{w,ww}} \cdot \left( 1 - f_{rem} \right)$$

$$E_{wwtp} = \left( M \cdot f_{pc} + M_{pd} \cdot (1 - f_{pc}) \right) \cdot \sum_{j=1}^{n} \frac{\left( V_{ww,j} \cdot f_{conc,j} \right)}{V_{w,ww}} \cdot \left( 1 - f_{con} \right)$$

where $M_r$ is the yearly consumption of API in topical products; $f_{pc}$ is the absorption of the topical product; $M_l$ (Equation (1)), $M_l$ (Equation (2)) and $M_{pd}$ are the yearly consumption of the API and its produg (if applicable) in orally administered products; $f_{met}$ is the fraction of the administered parent compound excreted/egested unchanged or as reversible conjugates via urine and faeces ($\cdot$); $f_{rem}$ is the fraction of produrg metabolized to the API of interest, and subsequently excreted/egested via urine and faeces ($\cdot$); $n$ is the number of agglomerations (partially) connected to the WWTP ($\cdot$); $f_{conc,j}$ is the level of WWTP-connectivity per agglomeration $j$; $f_{rem}$ is the API-specific removal efficiency per WWTP ($\cdot$); and $V_{ww,j}$ are the wastewater loads generated per agglomeration $j$ and the total in the relevant country, respectively (in population equivalents; p.e.). The values corresponding to each expression in equation (2) are shown in Table 1, with values for individual terms being given where possible. The derivation of these values is detailed further in the following methods. The consumption data could not be shown to a greater level of detail due to the proprietary nature of the data however further information is shown in SI sheet ‘Consumption data’.

2.2. Monitoring data

To gather monitoring data on ibuprofen, the scientific literature was searched using Web of Science and Google Scholar with the following search terms: API, pharmaceutical, ibuprofen, environmental monitoring, monitoring, surface water, wastewater, contaminant, contamination, effluent, environmental risk assessment, environmental exposure, water quality, water framework directive. ePiE does not predict groundwater concentrations, these data were therefore not considered relevant for this study. The search was performed using the topic field. The search was performed between the years of 2014–2020, although in the end only the data for the years that matched the consumption data available were used. Other sources were also searched including EIONET (European Environment Agency, no date.) and the websites of national and sub-national water management authorities in EU member states.

A number of papers that contained ibuprofen monitoring data were identified in the literature. In addition, data were available from the Ministry for Environment, Agriculture, Conservation and Consumer Protection of the State of North Rhine-Westphalia, a regional authority in Germany (MULNV - Ministerium für Umwelt Landwirtschaft Natur-und Verbraucherschutz des Landes Nordrhein-Westfalen, 2021). Consumption data were only available for three years prior to the time of this study (gathered October 2020), therefore a sub selection of the monitoring studies was made which temporally aligned with the sales data available. The studies included had detected ibuprofen in the waterbody of interest above limits of detection and quantification, and had coordinate information for sampling sites.

Fig. 1 shows the river basins and the positions of the sampling sites studied. Data were available for the Danube (Slovenia and Croatia) (Česen et al., 2018, 2019), Tagus (Spain) (Arenas-Sánchez et al., 2019; Rico et al., 2019), Rhine (Germany) (MULNV - Ministerium für Umwelt Landwirtschaft Natur- und Verbraucherschutz des Landes Nordrhein-Westfalen, 2021).
The outlets through which ibuprofen products are available varies across Europe (Oleszkiewicz et al., 2021). For Belgium, Croatia, France, Germany, Slovenia and Spain where ibuprofen is available within pharmacies or 'specialist stores' only, data were obtained from IQVIA. IQVIA are an American multinational company serving industries of health information technologies and clinical research. IQVIA (IQVIA, no date.) provide information on sales made through pharmacies or through wholesalers to pharmacies (or similar). Data from IQVIA included information on strength, pack size and number of units sold or dispensed per month. This information was used to ascertain the yearly mass used and released per country. Within the dataset we had access to, data for Switzerland were not available to product level, instead only the total number of units of products containing ibuprofen sold was obtained, i.e. it was necessary to assume the mass contribution of each unit. The total mass consumed and released in Switzerland was therefore calculated by taking the mean mass released per unit in countries with data for matching years and ibuprofen availability, namely, Belgium, France, Germany and Spain for 2018, 2019 and 2020, and multiplying by the total units consumed in Switzerland to obtain the total yearly mass released. The mean and SD of the mass released per year is given in the ‘Consumption data’ worksheet within the supplementary information. This usage information can be assumed to have larger error than the data for countries with per product sales, however a reasonable estimate on usage was made. For Luxembourg and Austria, no data were obtained on usage, the yearly usage and release of these countries was therefore made for the Rhine basin, since the WWTP contributions from these countries is much smaller than that of Germany, Switzerland and France (Table 2).

Equation (2) is a slight simplification of the mass calculation for topical products for ibuprofen. As discussed in Austin et al. (2021), (Table 2).

\[ M_{\text{total released}} = M_{\text{oral}} + M_{\text{topical}} \]

\[ = f_o \cdot M_{\text{oral}} + f_t \cdot M_{\text{topical}} \]

Where \( f_o \) is the oral fraction, \( f_t \) is the topical fraction, \( M_{\text{oral}} \) is the mass of ibuprofen released orally, and \( M_{\text{topical}} \) is the mass of ibuprofen released topically.

### Table 1

| Country | Data timespan | Total mass used (kg) | Mass used orally (kg) | Mass used topically (kg) | Total mass released to wastewater (kg) | Mass released (oral) (kg) | Mass released (topical) (kg) |
|---------|---------------|----------------------|-----------------------|-------------------------|---------------------------------------|--------------------------|---------------------------|
| Croatia | 2017          | 53,585               | 52,830                | 756                     | 6351                                  | 5653                     | 698                       |
| Slovenia| 2016          | 4819                 | 4819                  | 0                       | 516                                   | 516                      | 0                         |
|         | 2017          | 4995                 | 4995                  | 0                       | 534                                   | 534                      | 0                         |
| Spain   | Aug 2017–July 2018 | 684,295             | 682,127               | 2168                    | 75,025                                | 72,991                   | 2033                      |
| UK      | Oct 2016–Sep 2017 | 410,393             | 373,738               | 36,655                  | 74,637                                | 39,990                   | 34,647                    |
| Germany | Nov 2017–Oct 2018 | 458,171             | 449,097               | 9073                    | 56,286                                | 48,053                   | 8233                      |
|         | Nov 2018–Oct 2019 | 493,303             | 485,061               | 8242                    | 59,338                                | 51,902                   | 7437                      |
|         | Nov 2019–Oct 2020 | 494,068             | 485,825               | 8244                    | 59,279                                | 51,983                   | 7296                      |
| France  | Nov 2017–Oct 2018 | 128,522             | 128,522               | 0                       | 13,752                                | 13,752                   | 0                         |
|         | Nov 2018–Oct 2019 | 121,574             | 121,574               | 0                       | 13,008                                | 13,008                   | 0                         |
|         | Nov 2019–Oct 2020 | 88,067              | 88,067                | 0                       | 9423                                  | 9423                     | 0                         |
| Belgium | Nov 2017–Oct 2018 | 48,281              | 47,973                | 308                     | 5380                                  | 5133                     | 247                       |
|         | Nov 2018–Oct 2019 | 48,772              | 48,459                | 313                     | 5434                                  | 5185                     | 249                       |
|         | Nov 2019–Oct 2020 | 43,157              | 42,876                | 281                     | 4813                                  | 4588                     | 226                       |
| Switzerland | 2018           | 19,385              | NA                    | NA                      | 2212                                  | NA                      | NA                        |
|         | 2019           | 21,200              | NA                    | NA                      | 2360                                  | NA                      | NA                        |
|         | 2020           | 16,500              | NA                    | NA                      | 1903                                  | NA                      | NA                        |
information on strength and pack size were found in the list of products registered with the European Medicines Agency if a product name was given (EMA, no date.).

Unfortunately, it was not possible to identify some of the product pack sizes or strengths, with only the company name given and product type e.g. suspension, tablet or gel. In these cases, the mean pack size and strength of the products available in each country for each product type were used in the mass calculation. Overall, these products made up <1% in Belgium, <3% in France, 15% in Germany, 20% in Italy and 40% of the total mass used in Spain. Within a product type, there are only a limited number of strengths, for example tablets are most commonly available in 200 mg or 400 mg, or liquid suspensions are most commonly available in 20 mg/ml or 40 mg/ml strengths. The total mass calculations for these countries is anticipated to be slightly less accurate than countries with the full strength and pack size information.

In the UK, ibuprofen products are available in pharmacies but also more widely. It was therefore necessary to gather data for products sold through ‘general’ sales, through outlets such as supermarkets or ‘outside of pharmacies’. This data was obtained through Nielsen Holdings, an American global information data and measurements company who specialises in providing data on consumer goods (Nielsen Company, no date.). Additional data that were gathered but not used in our previous study (Austin et al., 2021) were processed for use following the methods detailed in Austin et al. (2021), specific details on this process are available there and in the supplementary information in worksheet ‘UK consumption data methods’.

These data were combined with pharmacy data from IQVIA to obtain a total mass of ibuprofen used in England and Wales and within sub regions. The data gathered for the previous work did not include Scotland or Northern Ireland, therefore to obtain a total UK usage, necessary to run the ePiE model, the per capita usage for

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**Table 2**

| Country | Country code | Number of WWTPs | Percentage of WWTPs | Population served | Percentage of Rhine population | Consumption data used |
|---------|--------------|----------------|---------------------|--------------------|-------------------------------|----------------------|
| Germany | DE           | 1736           | 64.1                | 38,412,708         | 71.8                          | Per product sales     |
| Switzerland | CH | 613           | 22.6                | 6,293,308          | 11.8                          | Total unit sales multiplied by mean ibuprofen per unit in Belgium, France, Germany and Spain |
| France | FR           | 231            | 8.5                 | 4,355,079          | 8.1                           | Per product sales     |
| Netherlands | NL | 69            | 2.5                 | 3,299,637          | 6.1                           | Not included (predictions upstream) |
| Luxembourg | LU | 31            | 1.1                 | 540,605.4          | 1.0                           | Extrapolation of mean per capita usage from Belgium, France, Germany and Spain |
| Austria | AT           | 23             | 0.8                 | 594,893.7          | 1.1                           | Extrapolation of mean per capita usage from Belgium, France, Germany and Spain |
| Belgium | BE           | 4              | 0.1                 | 37,689.9           | 0.1                           | Per product sales     |
| Total   |              | 2707           |                     | 53,473,921         |                               |                      |

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**Fig. 1.** Map of Europe including larger countries showing the river basins considered in this study (blue lines), namely, Ouse and Tyne (UK; top left), Rhine (German; top right), Tagus (Spain; bottom left) and Sava (Slovenia and Croatia; bottom right) with locations of sampling sites (yellow dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
England and Wales was calculated using the population of England and Wales (58, 381, 300) and multiplied by the total population of the UK (65, 648, 000) (Office for National Statistics, 2017).

Whilst the per capita usage in Scotland and Northern Island may not be exactly the same as in Wales and England, ePiE essentially calculates a per capita consumption, dividing the total mass of a country by the total P.E assigned across all the WWTPs in said country. Therefore this small extrapolation was not anticipated to introduce significant error.

### 2.4. Model validation

The model output includes predicted mean annual concentrations for high, average and low flow conditions as predicted by FLO1K. European data for representative rivers shows flow varies greatly throughout the year (EC, no date.). This is an important consideration when comparing predicted values with measurements made at specific times of the year. The measurements considered in this study were taken at varying time points throughout the year and it was therefore expected that annual mean predictions based on predicted mean flow would be more accurate when measurements were taken at times of year where the river flow of the sampling sites were closest to the annual mean flow. Predictions were quantitatively compared with measured values in two ways. The first method (referred to as assessment I from here on) was to compare the average site measurements within a year period with ePiE predictions. Measured values < LOQ were replaced by LOQ/√2. It has been demonstrated that using this value as a replacement introduces the least error for data that are both normally and log normally distributed with data censorship of up to 50% and is also in line with previous ePiE assessments (Oldenkamp et al., 2018; Verbovsek, 2011). This substitution approach is less than ideal but was deemed necessary due to the large number of non-detects and the low number of detects at each site, preventing more advanced methods of estimating concentrations below the LOQ such as maximum likelihood estimation (MLE) as suggested and analysed recently (George et al., 2021; Shoari and Dubé, 2018).

Sites where 50% of the values were < LOQ were not included in the mean measured vs predicted comparisons for assessment I. This approach is arguably more statistically appropriate for a quantitative assessment, however it does not necessarily assess the real-world performance of the model, for example, when predicting average yearly concentrations in areas with no monitoring data, to be used for risk assessment in a regulatory context. For this reason, a second method was used (referred to as assessment II from here on), whereby the same measurement vs predicted values was made, however this time all sites downstream of a WWTP were kept in the assessment, even those where all measurements were < LOQ and therefore all replaced by LOQ/√2.

Two of the monitoring studies presented measured flow data for their sampling sites (Camacho-Muñoz et al., 2019; Cesen et al., 2019). For these sites, a comparison was made between the mean annual measured flow and the mean annual flow predicted by FLO1K to assess the reasonableness of the FLO1K predictions.

API removal ($\xi_{rem}$) is currently predicted within ePiE by SimpleTreat 4.0 (Struijs, 2014). A number of parameters can be input to describe the chemical being processed, including the molecular weight, $K_w$, $pKa$, vapour pressure, solubility and partition coefficients for organic carbon, raw sewage and activated sludge. The values used to parameterise ePiE for ibuprofen are detailed in the supplementary information in worksheet ‘ibuprofen parameterisation’. The majority were taken from the literature detailed in Oldenkamp et al. (2018), with some minor alterations and inclusions from literature included in EPISUITE’s PHYS/PROP database and other publicly available sources. With the parameters input, SimpleTreat 4.0 predicts ibuprofen removal will be 84% for municipal plants with a primary settler and secondary treatment or 89% without a primary settler with 16% and 11% respectively being released in effluent. The reason removal is higher without a primary clarifier is well described in the SimpleTreat 4.0 model description and is because ibuprofen is removed via biodegradation and is considered non-sorptive (Struijs, 2014). These values are conservative in comparison to recent literature which show higher ibuprofen removal in WWTPs. Comber et al. (2019) analysed the removal of a number of chemicals from a large WWTP sampling campaign across the UK. The median fraction of ibuprofen remaining after each treatment step was found to be 0.83 after the primary process, 0.04 after secondary treatment (either activated sludge or trickling filter) and 0.01 after tertiary treatment. This is supported by a study in Slovenia which shows close to 100% removal of ibuprofen at several WWTPs using different treatment processes in the Sava basin, although higher variation was observed in winter during lower temperatures (Cesen et al., 2018). The removal after secondary treatment is at least 12% higher than predicted by SimpleTreat 4.0. To ascertain the impact using real world removal values would have on the predicted concentrations, the ePiE model was run both using the default SimpleTreat 4.0 implementation and with an override with ibuprofen removal in WWTPs ($\xi_{rem}$) set to 96%, as found in Comber et al. (2019).

By default, no consideration is given to API removal in sewer systems before entry to the WWTP. As summarised in Austin et al. (2021), various studies have highlighted the importance of considering the sewer system when estimating exposure to the environment, failure to do so leading to overestimation of WWTP influent concentrations. In Austin et al. (2021), the mean over prediction of the mass of ibuprofen entering WWTPs was 32.4% (SD ± 32.8). An additional set of predictions were made by reducing the mass released to wastewater by this value to ascertain the impact on predictions and whether applying a factor of this kind increases prediction accuracy.

Where the coordinates of sampling stations on the Rhine were not quite on the rivers defined within ePiE, the nearest node was taken for comparison. In some situations, it was unclear which river the monitoring station was on i.e. it was equidistant between two or three rivers. In these situations, no comparison was made.

### 3. Statistical analysis

As in Oldenkamp et al. (2018), the predictive accuracy of ePiE was calculated using the median symmetric accuracy ($\xi$) and the symmetric signed percentage bias (SSPB), both derived and discussed thoroughly in Morley et al. (2018). The $\xi$ is an order-dependent assessment of relative error. This metric avoids the pitfalls of scale-dependent metrics such as the root mean square error (RMSE) that place equal importance on errors of the same magnitude, independent of the magnitude of the base quantity. For example, a predictive error of 100 ng.L$^{-1}$ where the prediction is 200 ng.L$^{-1}$ and the measurement is 100 ng.L$^{-1}$ is an overprediction by a factor of 2, however when the prediction is 101 ng.L$^{-1}$ and the measurement is 1 ng.L$^{-1}$ the overprediction is by a factor of 101. The magnitude is the same however the implications and importance of each error are not equal. Additionally, this metric avoids the pitfalls of other order-dependent metrics such as the mean absolute percentage error (MAPE), which penalise overprediction more than underpredictions, for example, a prediction of 100 ng.L$^{-1}$ where the measurement is 50 ng.L$^{-1}$ gives 100% error, whereas a prediction of 50 ng.L$^{-1}$ where the measurement is 100 ng.L$^{-1}$ gives a 50% error. The SSPB is closely related to $\xi$ but estimates the central tendency of the error as a percentage, giving a negative value for underprediction and a positive value for overprediction.

### 4. Results and discussion

#### 4.1. Ibuprofen consumption

The ibuprofen sales data gathered are shown in the supplementary information in the worksheet ‘Consumption data’. The data indicate a large variation in ibuprofen usage across the European member states
included in the study, up to nearly a factor of 10. Spain and Croatia had the highest annual per capita usage at 14,666 and 12,901 mg, respectively. France had the lowest usage at 1809 mg (pre 2020), followed by Slovenia and Switzerland. In France, Belgium and Switzerland where data were gathered across multiple years, a notable decrease in ibuprofen consumption was observed in 2020. This pattern was not observed in the German consumption data. For Belgium, France and Germany, the mean mass consumed and released per unit sold were also calculated in order to calculate the mass consumed in Switzerland (only units sold were obtained for this country). Interestingly, the mass consumed per unit in each of these countries varied following the same pattern of the overall per capita consumption and release, i.e. Germany which has the highest per capita consumption of these three countries also had the highest mass per unit sold and vice versa, with France having the lowest, indicating either larger average pack sizes or a tendency towards stronger products in Germany. The contribution of topical products was also calculated from the consumption data. The U. K had the highest topical product usage, contributing 46% to the mass of ibuprofen released. The topical contribution was lower in the other countries, contributing 12-15% in Germany, 11% in Croatia, 4.5% in Belgium and just 3% in Spain. In France and Slovenia no topical ibuprofen market appears to exist.

The large observed variation in usage across countries exemplifies the issues in extrapolating consumption data between countries and the potential error that can introduce into exposure modelling exercises. This finding was not a surprise based on our previous study where we found significant differences in ibuprofen consumption even between regions within the UK (Austin et al., 2021), however the size of the difference was not expected. Fortunately, as discussed in the methods, only a minimal extrapolation was performed to fill in the consumption data for Luxembourg and Austria which contributed only 2.5% of the consumption data used in the Rhine basin predictions. The differences in consumption between the countries studied did not appear to be influenced by the availability of ibuprofen outside of pharmacies, however, whilst not conclusive, the mass per unit, directly related to the average pack size and product strength, appears to be a contributing factor to the overall consumption in a country, whether that be through the selection and preferences of consumers in the respective country, or the availability and prevalence of larger pack sizes and stronger products. Topical products again were found to contribute disproportionately to releases based on estimated releases, despite fairly low consumption for some countries (Austin et al., 2021).

4.2. Sampling sites and ibuprofen exposure

Fig. 1 shows the basins studied, including the sampling sites where measurements were taken. A total of 142 sites were included in the study with the majority from the Rhine basin (109). Details of all of the sites included can be found in ‘Extra site details 1 and 2’ in the SI. As the Rhine basin measurements were taken from sampling stations, this meant some had values across multiple years. A total of 176 mean measurements were therefore available for comparison in this study. ePiE only predicts concentrations downstream of WWTPs with a capacity >2000 p.e. A total of 43 sites were removed where this criterion was not met, 38 from the Rhine (46 mean measurements), one from Slovenia and four from Spain. All of the measured values removed from the data for this reason were <LOQ except five sites in the Rhine and the four removed from the Tagus basin data. These measured values indicate upstream sources of ibuprofen emissions, such as from WWTPs smaller than <2000 p.e., a limitation previously discussed by Oldenkamp et al. (2018) which is a result of WWTP facilities serving <2000 p.e. not being included in the UWWTW-Waterbase which was used to develop the model (European Environment Agency, 2019). In the case of the Tagus, including smaller WWTPs may not have enabled predictions to be made for these sites. Rico et al. (2019) identified urban areas and small villages with no WWTPs as key point sources for the chemicals they studied. Within ePiE direct discharges from agglomerations which are not linked to treatment facilities are assigned as direct discharges, with the point source being the next downstream WWTP.

4.3. LOQ

As described in the methods, two assessment methodologies were used to compare predictions with measurements. Assessment I made comparison of predictions against determined measurements, minimizing the censored data included to assess prediction accuracy; assessment II aimed to better assess the real world use of the model, where predictions for pharmaceutical concentrations in rivers are made with no monitoring data for comparison.

Removing mean concentrations at sites where less than 50% of the data were <LOQ resulted in significant amounts of data being removed from the assessment, particularly for the Rhine. Detailed information on the measured and predicted values per site can be seen in the SI in ePiE predictions assessment 1 and 2. Overall, for the first assessment 3/3 sites were available for the U.K, 13/18 for the Sava, 12/12 for the Tagus and 27/143 for the Rhine.

The variety in the confidence of measurements < LOQ is generally attributable to two main factors, both the variation in the LOQ achieved in each of the studies included and low concentrations of ibuprofen found at certain sites. Details of the sampling methodology can be found in detail in the respective studies; however, the most relevant details are included here in the SI under ‘Sample analysis’. The LOQs achieved for the academic studies were very low, particularly for the Sava (0.0305 ng.L⁻¹) and Tagus basins (0.3 ng. L⁻¹). Based on these LOQs, non-detects in the Sava basin can be attributed to genuinely low concentrations of ibuprofen. The measurements taken in the Rhine had a higher LOQ of 25 ng. L⁻¹ and a significant number of non-detects on the Rhine are expected to be concentrations that would be detected concentrations if the LOQ were similar to the academic studies, as opposed to non-detects where ibuprofen is not present.

These non-detects in the Sava measured data align with the low consumption data for Slovenia, with all non-detects being found in the Slovenian section of the Sava and its tributaries. The higher consumption found in Croatia is reflected in the higher measured values, although these are still greatly overpredicted. The source of the larger overprediction specifically relating to the Cesen et al. (2019) study is unclear. This study took measurements in the main Sava river, whereas Cesen et al. (2018) focussed measurements around WWTPs on tributaries of the main river. One potential explanation is that the lower measured values in Slovenia due to lower consumption are having a knock-on effect downstream to the sites in Croatia. However, this does not explain the fact that the overprediction becomes much greater when the Slovenian sites are included in assessment II. This overprediction cannot be explained by differences between predicted and measured flow, which was given for each of these sites specifically on the dates the samples were taken (observable in ‘extra site details’ in the SI). A comparison of the predicted mass of ibuprofen entering the WWTP with values given in Cesen et al. (2018) revealed much lower than expected mass entering the WWTPs in Slovenia, in some cases, two orders of magnitude lower than predicted (observable in the SI ‘Slovenia influent comparison’). The low amounts detected were compared with studies in other countries by the authors who postulated the reason to be lower consumption in Slovenia. The consumption data gathered here confirm this. Based on the low per capita consumption, the disparity may be down to behaviours surrounding analgesic usage within Slovenia. It may be that there is a higher frequency of left-over medicine which may be disposed of via solid waste, held onto or even higher adherence to take back schemes, however further information would be required to ascertain the truth. In reality, when ensuring all consumption routes are accounted for i.e. OTC, prescription, oral, assimilated and non-assimilated, over prediction is somewhat expected. As shown and discussed in a number of studies, the assumption that 100% of the
pharmaceuticals purchased are consumed is not true, although it is also not easily quantifiable as a source of error (Boxall et al., 2014; Daughton and Ruhoy, 2009; Vatovec et al., 2017).

4.4. ePiE performance

Table 3 and Fig. 2 display the results of the comparison of predicted vs measured values for assessment I. Fig. 2 shows that the majority of the predictions fall within one order of magnitude of measured values. Where multiple measurements were made at sites within a year, the 95% CI was calculated. As shown by the horizontal bars, the measured values at each site potentially fall within a wide range, a combination of the low sample numbers and inherent variability in the grab samples. The vertical bars indicate predictions made at differing flows with the upper bar indicating low flow and lower bar indicating high flow. The median symmetric accuracy $\xi$ reflects the median percentage error of the predictions whereby 50% of the unsigned percentage errors of predicted vs measured comparisons are smaller than $\xi$. In assessment I, the $\xi$ for all studies combined was 191.52% which can be interpreted as predictions typically being 3-fold different to mean measured values. The vertical error bars indicate that this error is typically within the variability of the yearly flow and is much less than the large variation in yearly measurements indicated by the 95% CI of the mean (horizontal error bars), albeit calculated with a low number of measurements in most cases (observable in the SI). The large confidence intervals for the measurements (spanning multiple orders of magnitude in some cases) and the variation in predictions due to flow help to put the error in the predictions in context. The SSPB for all studies combined was 63.17% showing the error had a bias towards overprediction. A key component of the ePiE predictions are the predictions of flow. These results should therefore be considered within the context of these predictions. Fig. 3 shows a comparison of predicted vs measured flows where these data were available at some of the sites within the Sava and the Tagus. The $\xi$ and SSPB for the mean flow were 64.57%, and 50.45% respectively, indicating the mean flow was slightly overpredicted for these sites but within a factor of 2 in most cases. Notably, all predictions were well within an order of magnitude of the measurements with the majority being within a 5-fold difference (as observable in Fig. 3). As seen in Fig. 3, for some specific sites, high and low flow predictions better matched the measured data, indicating ibuprofen predictions would have been more accurate if predictions at high and low flow were selected in some cases. Nevertheless, the contribution of error from this source should be noted and the influence of the slight overprediction of flow potentially pushing predicted concentrations slightly lower overall, greater flow giving lower concentrations at a given mass of ibuprofen.

As can be observed in Table 3, there was a large variation in the value of $\xi$ and the SSPB between individual studies. Although having a low number of sites with one site at the very end of an estuary (with some measured salinity), ePiE predicted the measured values in the UK very closely. A much larger error and overprediction were observed for sites on the Tagus and Sava. Diagonal lines show 1:1 in addition to 2-,5- fold differences. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 3. Scatter plot with logarithmic scale (base 10) comparing measured (x-axis) vs mean flow predicted concentrations (y-axis) for assessment one for the Rhine (yellow crosses), Tagus (orange squares), Sava (Slovenia only, green triangles), Sava (Slovenia and Croatia, purple circles) and Ouse and Tyne (blue diamonds). Vertical error bars show ePiE predictions under max and min predicted flow conditions. Horizontal error bars show 95% CI of the mean where multiple measurements were taken. Diagonal lines show 1:1 in addition to 1,2- order of magnitude differences. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Fig. 4. The horizontal bars indicate 95% CI for the measured values. For visibility these are only included in scatter plot 4A. Like in Fig. 2, the horizontal bars indicate a large 95% CI spanning several orders of magnitude. Again, the vertical bars indicate predicted concentrations at low (upper bar) and high (lower bar) predicted flows. The overall error of prediction was slightly lower for this comparison, despite the inclusion of censored data. For the default predictions made in assessment 2, 4A. Within

### Table 3

| Study                  | Basin/River | Assessment 1 | Assessment 2 |
|------------------------|-------------|--------------|--------------|
|                        |             | No. comparisons | $\xi$  | SSPB | No. comparisons | $\xi$ | SSPB |
| All studies combined   |             | 55           | 191.52     | 63.17 | 176           | 190.37 | 176.38 |
| Letsinger et al. (2019) | Ouse, Tyne  | 3            | 21.05     | –21.05 | 3            | 21.05  | –21.05 |
| Cesen et al. (2018)    | Sava        | 9            | 349.78    | 349.78 | 11            | 655.19 | 655.19 |
| Comber et al. (2019)   | Sava        | 4            | 702.30    | 702.30 | 7             | 5545.04 | 5545.04 |
| Arenas-Sánchez et al., 2019 | Upper Tagus | 12           | 420.42    | 420.42 | 12            | 420.42 | 420.42 |
| ELWAS-WEB              | Rhine       | 27           | 156.30    | 24.54  | 143           | 183.04 | 156.30 |
the bias of the error towards overprediction was much greater than observed in assessment I. This is driven predominantly by the inclusion of censored data from both studies on the Sava and the measurements taken in the lower Rhine, where a large number of values < LOQ were included. The Rhine censored values are clearly observable in Fig. 4 as a column of yellow markers. Despite this, the majority of predicted values were still found within one order of magnitude of the measurements. This more realistic assessment indicates that ePiE has a tendency to overpredict measured concentrations of ibuprofen in a real use scenario.

The results for assessment II show the predictions made by ePiE were typically within a factor of 3 different to mean measurements with a tendency towards conservatism i.e. overprediction. These predictions can be considered useful, especially within the context of the observed variability found at each site where multiple sample measurements were taken and the variation in river flow. The performance of ePiE in this study is not directly comparable with the initial exercise performed in Oldenkamp et al. (2018) for a number of reasons, including the fact that here only one API was considered. In this study, up to date consumption data were obtained including data on OTC sales, online sales and topical consumption and release. In addition, predictions were not selected based on where predicted flows best matched measured flows as this data was not always available (and may not be available in a real-use scenario). Generally speaking, assessment I was most closely aligned with the previous validation exercise performed in terms of the method used. Statistical performance was comparable, with predictions for the Rhine and the Ouse being slightly improved here. The overall error was higher when including the comparisons made for the Sava and Tagus basins. The overall statistics of the predictions could have been improved if the prediction was taken where the predicted flow best matched the measured flow (as done previously in Oldenkamp et al. (2018)). However this was not applicable to all basins and data sources where flow data were not available, therefore it was concluded that error stats of those predictions would not be particularly applicable to a real world scenario where measured flow data did not exist. It is clear that predictions can be made even more accurate if river flows are available for prediction sites and high, mean or low flow predictions can be selected accordingly.

There is debate on the use of substitution when analysing datasets that contain censored values, including what to substitute with (George et al., 2021; Shoari and Dubé, 2018; Verbovsek, 2011). In this study, inclusion of all censored values in assessment II had a significant effect on the results of the predicted vs measured comparison with a clear tendency for ePiE to overpredict the mean measured values in this assessment. Given the ubiquitous use of ibuprofen, the inclusion of the censored values via substitution was considered the most realistic assessment approach as it was still detected in the countries with the lowest consumption included in this study. Censored values were substituted with LOQ/$\sqrt{2}$ meaning the overprediction by ePiE is most likely higher in reality than found in this study. If censored values were replaced with 0 or < LOQ/2, mean measured values would have been lower, leading to a greater observed over prediction.

4.5. Performance after modification

As part of assessment II, in addition to default ePiE predictions, two extra sets of predictions were made. One with a custom WWTP removal rate, replacing the SimpleTreat predicted removal and altering the value of $f_{rem}$ in Equation (2). The second incorporating the custom removal rate in addition to a pre-WWTP removal factor to take into factors such as potential in-sewer removal or non-use of purchased API products. A comparison of predicted vs measured for these two scenarios can be seen in Fig. 4, with the custom WWTP removal rate scenario displayed in scatter plot 4B and the scenario including the additional removal factor shown in scatter plot 4C. A comparison of the error observed in these scenarios can be seen in Table 4. As discussed in the methods, SimpleTreat underestimates the removal of ibuprofen in WWTPs by around 10% with at least 96% being removed in two recent studies in the UK and Slovenia (Cesen et al., 2018; Comber et al., 2019). Making predictions with a 96% override for WWTPs in the ePiE model resulted in an improvement in overall prediction accuracy with a 63% decrease in $\xi$ and a 146% decrease in the overprediction bias, leaving a small over prediction bias of 26.77% for all studies. This can be observed within Fig. 4 as a general shift of all plotted points down the y-axis in scatterplot 4B, as compared to 4A. This was an improvement in the prediction accuracy compared to default predictions with the median factor.
difference less than 2.5-fold different to mean measurements (compared to nearly 3-fold).. As shown summarised in Table 4 the error bias was altered across each individual study; this was an improvement in every case except for the UK data, where this alteration led to a large bias towards underprediction (with the other studies showing reduced overprediction). The $\xi$ was reduced for the Rhine, bringing the median error to below two-fold for this basin, with a very small underprediction bias. An increase in $\xi$ was observed for the Tagus and the UK data (despite the reduced overprediction in the Tagus).

Our previous work indicated an overprediction in the mass of ibuprofen in the influent of receiving WWTPs compared to measured amounts (mean 32.4%, SD ± 32.8), this was attributed to various aspects, including the purchasing and none-use of APIs, or potential insider removal processes (Austin et al., 2021). The factor of over-prediction was applied to the consumption data here before predictions were made, in addition to the custom SimpleTreat removal, with results viewable in Fig. 4 and Table 4. For all studies combined, there was a slight increase in $\xi$ compared with the custom SimpleTreat only predictions. The SSPB became negative, inferring a small underprediction, observable by a downward shift in the plotted points in Fig. 4C compared with 4B and 4A. In terms of individual studies, this alteration reduced the accuracy of predictions made for all studies except comparison with measured values from Cesen et al. (2019) and those made for the Tagus. In addition, predictions were on the whole under-estimating measured concentrations, except for the data measured in Slovenia and Croatia.

### 4.6. Using ePIE

Based on the results of this study, the addition of a custom WWTP removal factor can be recommended as this improved the overall accuracy of the predictions. The selection of the removal rate of 96% was based on recent literature (Cesen et al., 2018; Comber et al., 2019) and is supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies. Kasprzyk-Hordern et al. (2009) also noted 96% removal of ibuprofen via activated sludge, although indicated a slightly lower efficiency for trickling filter type WWTPs and a high but supported by older studies.

### Table 4

Statistical analysis of predicted vs measured per basin and overall for modified predictions for assessment 2.

| Study                  | Basin/ River | SimpleTreat mod | SimpleTreat mod and overestimation factor $\xi$ | SSPB | $\xi$ | SSPB |
|------------------------|--------------|-----------------|-----------------------------------------------|------|------|------|
| All studies combined   |              |                 |                                               |      |      |      |
| Letsinger et al. (2019)| Ouse, Tyne   | 128.31          | 128.31 – 16.69                                 |      |      |      |
| Cesen et al. 2019      | Sava, River  | 228.74          | 228.74 – 288.4                                 |      |      |      |
| Cesen et al. 2019      | Sava         | 419.24          | 419.24 – 552.39                                |      |      |      |
| Arenas-Sánchez et al.  | Upper        | 43.66           | 43.66 – 815.27                                 |      |      |      |
| Rico et al. (2019)     | Tagus        | 866.32          | 866.32 – 231.7                                 |      |      |      |
| ELWAS WEB              | Rhine        | 88.09           | 88.09 – 19.57                                  |      |      |      |

...as with any modelling exercise, some limitations should be considered, some more important than others depending on the API in question. Currently, ePIE does not include WWTPs smaller than <2000 p.e. as point sources, a limitation previously discussed by Oldenkamp et al. (2018). This is a limitation that arises from the fact that WWTP facilities serving <2000 p.e. are not included in the UWWTD-Waterbase which was used to develop the model (European Environment Agency, 2019). Any discharge from an agglomeration that is tied to one of these smaller plants (that do not exist in the model), will simply be added to the next WWTP point source. Due to the fact that smaller plants are more likely to occur in the upper reaches of river basins, on smaller waterways, a small loss of spatial resolution for discharges in these areas is expected. Indeed, if small agglomerations drain into further downstream WWTPs, it means that the PECs in head catchments may be underestimated or even zero. However, since head catchments are generally scarcely populated and a small percentage of the overall population along any river, the potential API load to streams is low and, consequently, actual mass loads are low.

ePIE does not include some potential sources of pharmaceutical input including point source discharges from pharmaceutical manufacturing facilities, sewage overflow during peak rainfall events or diffuse sources such as runoff or leaching resulting from the application of sludge from WWTP’s being applied to fields. Whilst consumption and exposure via municipal treatment plants is considered the main route of exposure to the environment, these aspects are something that may be worth considering to improve realism for certain APIs. In this exercise these limitations were not considered to be a concern based on the physical chemical properties of ibuprofen and the results obtained.

Other considerations include the static pH which does not account for the impact that the variable pH found in reality might have on the environmental fate of ionisable APIs. Additionally, for some APIs, there is the potential for metabolites excreted by humans to be back-transformed in the WWTP, this was not considered to have a major impact for ibuprofen. Based on the accuracy and conservatism of the predictions made here, neither of these limitations appears to have had a noticeable impact in this exercise.
5. Conclusions

This study shows that with up to date consumption data and the inclusion of all routes of API consumption, the ePiE model makes useful, conservative exposure predictions for ibuprofen. Predictions were found to typically be within a factor of 3 of mean measured values across a number of basins within Europe. Basins were representative of varying conditions, including ibuprofen consumption rates, population densities and climates. Incorporating specific information pertaining to the basin or country being assessed, as such custom WWTP removal rates, was found to improve the realism and accuracy of predictions (to within a factor of 2.5 of mean measured values). The consumption data gathered for this study indicate that the extrapolation of consumption data between years and countries should be kept to a minimum when modelling the exposure of pharmaceuticals, with the per capita consumption of ibuprofen varying by nearly a factor of 10.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Author Tom Austin was employed by Reckitt at the time of writing, a manufacturer of products containing Ibuprofen.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.112777.

References

Acúa, V., Bregoli, F., Font, C., Barceló, D., Corominas, L.L., Ginebreda, A., Petrovic, M., Rodríguez-Roda, I., Sabater, S., Maré, R., 2020. Management actions to mitigate the occurrence of pharmaceuticals in river networks in a global change context. Environ. Int. 143, 105993. https://doi.org/10.1016/j.envint.2020.105993.

Arenas-Sánchez, A., Rico, A., Rivas-Tabares, D., Blanco, A., García-Doncel, P., Romero-Salas, A., Nozal, L., Vighi, M., 2019. Identification of contaminants of concern in the Rhine. The extended ePiE model was developed as part of the Prioritisation and Risk Evaluation of Medicines in the Environment (PREMIER) project. PREMIER has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 875508. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

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annual streamflow at 1 km resolution from 1960 through 2015. Sci. Data 5, 1–11. https://doi.org/10.1038/sdata.2018.52.

Bennardi, D., 2014. Self-medication: a current challenge. J. Basic Clin. Pharm. 5, 19. https://doi.org/10.4103/0976-0105.128253.

Boxall, A.B.A., Keller, V.D.J., Straub, J.O., Monteiro, S.C., Fussell, R., Williams, R.J., 2014. Exploiting monitoring data in environmental exposure modelling and risk assessment of pharmaceuticals. Environ. Int. 73, 176-185. https://doi.org/10.1016/j.envint.2014.07.018.

Brack, W., Duilio, V., Ågerstrand, M., Allan, L., Altenburger, R., Brinkmann, M., Banke, D., Burgess, R.M., Cousins, I., Escher, B.I., Hernández, P.J., Hewitt, L.M., Hilscherova, K., Hollender, T., Koller, H., Kace, R., Klauer, B., Lindim, C., Rietz, D.L., Müge, C., Munthe, J., O’Toole, S., Posthuma, L., Rüdel, H., Schafer, R. B., Seng, M., Smedes, F., van de Meent, D., van den Brink, P.J., van Gils, J., van Wezel, A.P., Vetaah, A.D.K., Vermeirens, E., van der Ohe, P.C., Vranas, B., 2017. Towards the review of the European Union Water Framework management of chemical contamination in European surface water resources. Sci. Total Environ. 576, 720-737. https://doi.org/10.1016/j.scitotenv.2016.10.104.

Camacho-Muñoz, D., Petrie, B., Lepard, L., Proctor, K., Rice, J., Youndan, J., Barden, R., Kasprzyk-Hordern, B., 2019. Stereospecific profiling of chiral pharmaceutically active compounds in wastewaters and the receiving environment – a catchment-scale and a laboratory study. Environ. Int. 127, 558-572. https://doi.org/10.1016/j.envint.2019.02.050.

Cesen, M., Ahel, M., Terzic, S., Heath, D.J., Heath, E., 2019. The occurrence of contaminants of emerging concern in Slovenian and Croatian wastewaters and receiving Sava river. Sci. Total Environ. 650, 2446-2453. https://doi.org/10.1016/j.scitotenv.2018.09.236.

Cesen, M., Heath, D., Krivec, M., Kosmilj, J., Kosjek, T., Heath, E., 2018. Seasonal and spatial variations in the occurrence, mass loadings and removals of compounds of emerging concern in the Slovene aqueous environment and environmental risk assessment. Environ. Pollut. 242, 145-154. https://doi.org/10.1016/j.envpol.2018.06.052.

Comber, S., Gardner, M., Sorme, P., Ellor, B., 2019. The removal of pharmaceuticals during wastewater treatment: can it be predicted accurately? Sci. Total Environ. 676, 222–230. https://doi.org/10.1016/j.scitotenv.2018.11.213.

Daughton, C.G., Ruboy, I.S., 2009. Environmental footprint of pharmaceuticals: the significance of factors beyond direct excretion to sewers. Toxicol. Environ. Chem. https://doi.org/10.1897/08-382.1.

DG Env, 2020. Priority Substances Review—Next Steps. EC, 2013. European Commission, European Parliament Legislative Resolution of 2 July 2013 on the Proposal for a Directive of the European Parliament and of the Council Amending Directives 2000/60/EC and 2008/105/EC as Regards Priority Substances in the Field of Water Policy. https://eur-lex.europa.eu/ (accessed 6.10.21).

European Environment Agency, 2019. Urban Waste Water Treatment Map [WWW Document]. https://www.eea.europa.eu/en/medicines/national-r egers-authorised-medicines/ (accessed 4.12.21).

European Environment Agency, 2019. Urban Waste Water Treatment Map [WWW Document]. https://www.eea.europa.eu/themes/environmental-water-u se-and-environmental-pressures/wwwref/interactive-maps/urban-waste-water-treat ment-maps . accessed 9.21.19.

European Environment Agency, n.d. National registers of authorised medicines | European Medicines Agency [WWW Document]. URL https://www.ema.europa.eu/ (accessed 6.10.21).

European Environment Agency, n.d. European Information and Observation Network — Eionet Portal [WWW Document]. URL https://www.eionet. europa.eu/ (accessed 6.10.21).

George, B.J., Gains-Germain, L., Broms, K., Black, K., Furman, M., Hays, M.D., Thomas, K.W., Simmons, J.E., 2021. Censoring trace-level environmental data: Statistical analysis considerations to limit bias. Environ. Sci. Technol. 55, 5766–3795. https://doi.org/10.1021/acs.est.0c02256.

Hadgraft, J., Whitefield, M., Rosher, P.H., 2003. Skin penetration of topical formulations of ibuprofen 5%: an in vitro comparative study. Skin Pharmacol. Appl. Skin Physiol. 16, 137–142. https://doi.org/10.1159/000069759.

iPiE | IMI Innovative Medicines Initiative [WWW Document], n.d. https://www.imi.europa.eu/projects-results/project-factsheets/4.20.21.

IQVIA, 2019. The Global Use of Medicine in 2019 and Outlook to 2023, IQVIA, n.d. About IQVIA United Kingdom [WWW Document]. URL https://www.iqvia. com/ (accessed 9.4.18).

Kasprzyk-Hordern, B., Dinisale, R.M., Guve, A.J., 2009. The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. Water Res. 43, 363–380. https://doi.org/10.1016/j.watres.2008.10.047.

Kasprzyk-Hordern, B., Dinisale, D.L., Morig, S., Villagra, D., Barceló, D., Rotchell, J.M., 2019. Spatial and temporal occurrence of pharmaceuticals in UK estuaries. Sci. Total Environ. 679, 74–84. https://doi.org/10.1016/j.scitotenv.2019.04.182.

Morley, S.K., Britto, T.V., Welling, D.T., 2018. Measures of model performance based on the log accuracy ratio. Space Weather 16, 137–147. https://doi.org/10.1002/2018SW001669.

MULNV – Ministerium für Umwelt Landwirtschaft Natur- und Verbraucherschutz des Landes Nordrhein-Westfalen, 2021. ELWAS Web. The Ministry for Environment, Agriculture and Consumer Protection of the State of North Rhine-Westphalia.
Westphalia [WWW Document]. https://www.elwasweb.nrw.de/elwas-web/index.xhtml#textol-false#.
NielsonIQ, n.d. About Us, What Consumers Watch and Buy [WWW Document]. URL http://nielsen.com/global/en/ (accessed 12.8.21).
Office for National Statistics, 2017. Population Estimates for UK, England and Wales, Scotland and Northern Ireland: Mid-2016 - Office for National Statistics [WWW Document]. https://www.ons.gov.uk/releases/populationestimatesforukenglandandwales/Scotlandandnorthernirelandmid2016, accessed 9.21.19.
Oldenkamp, R., Hoeks, S., Greskowiak, J., Straub, J.O., Oldenkamp, R., Pfister, T., Hänner, A., 2019. Environmental risk assessment for the active pharmaceutical ingredient mycophenolic acid in European surface waters. Environ. Toxicol. Chem. 38, 2259–2278. https://doi.org/10.1002/etc.4524.
van Gils, J., Posthuma, L., Koarz, I.T., Brack, W., Altenburger, R., Baveco, H., Focks, A., Grekowski, J., Kühne, R., Kutsarova, S., Lindim, C., Markus, A., van de Meent, D., Munthe, J., Schueder, R., Schüürmann, G., Slobodnik, J., de Zwart, D., van Wezel, A., 2020. Computational material flow analysis for thousands of chemicals of emerging concern in European waters. J. Hazard Mater. 397, 122655. https://doi.org/10.1016/j.jhazmat.2020.122655.
Vatovec, C., Van Wagener, E., Evans, C., 2017. Investigating Sources of Pharmaceutical Pollution: Survey of Over-the-counter and Prescription Medication Purchasing, Use, and Disposal Practices Among University Students. https://doi.org/10.1016/j.jenvman.2017.04.101.
Verbovsek, T., 2011. A comparison of parameters below the limit of detection in geochemical analyses by substitution methods Primerjava ocenitev parametrov pod mejo določljivosti pri geokemi analiza z metodo nadomešcanja. RMZ Mater. Geoenvir 58, 393–404.
Vermeulen, J., Whiteoak, K., Nicholls, G., Gerber, F., Mcandrew, K., Cherrier, V., 2019. Fitness Check Evaluation of the Water Framework Directive and the Floods Directive Final Evaluation Report.