The importance of over-the-counter-sales and product format in the environmental exposure assessment of active pharmaceutical ingredients

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Abstract

When assessing the environmental exposure of active pharmaceutical ingredients (APIs), the mass contributed from over the counter (OTC) sales and topical formats are typically not included. A data gathering exercise was performed to obtain UK per capita API usage for ibuprofen, diclofenac and ranitidine, combining all relevant sources to assess their relative importance as inputs. The calculated releases to wastewater compared well with influent concentrations measured at several UK wastewater treatment plants (WWTPs), although consistent overestimation was observed, attributed to a number of factors, including in-sewer removal. OTC sales were found to make up a large proportion of the mass of ibuprofen (76%) and diclofenac (35%) consumed and are important to include in exposure assessment. Product format should also be considered, as compared to oral applications, topical applications of ibuprofen and diclofenac contribute disproportionately to wastewater loadings per unit mass

used (43% and 99% of the total mass released, respectively). Options to reduce releases from these sources are highlighted. Releases of all three APIs did not vary significantly over time, but variation in releases from different regions in the UK were significant. The importance of several under-addressed aspects of API exposure assessment are therefore highlighted.

1. INTRODUCTION

Active pharmaceutical ingredients (APIs) are vital in the treatment of many ailments in a medical setting and are a cornerstone of modern-day life. Increasingly, the use of pharmaceuticals has been put in the hands of the consumer, allowing easier access to relief from common ailments via self-care.[1] Over the counter (OTC) products containing pharmaceuticals aiding in the relief of cold or flu-like symptoms, pain or heartburn are particularly commonplace and are a significant portion of the market. Along with the benefits to consumers of immediate access to symptom relief, the burden on healthcare systems is reduced and the OTC market has and continues to grow.[2] An inevitable downside to the improved access to self-care is the uncontrolled consumption and excretion of pharmaceuticals to wastewater and the environment, with APIs being detected around the globe.[3] Within Europe, in acknowledgement of this, and in addition to other water quality issues, the European Union produced the Water Framework Directive (WFD)[4] and Priority Substance Directives.[5,6] Combined, these directives provide a framework to identify substances that potentially pose a risk to surface waters, to define environmental quality standards (EQSs) for those deemed to, and to provide a legal basis with which member state compliance with these EQSs can be ensured. Member states, where concentrations in surface waters exceed EQSs, may take a number of different actions to reduce the concentrations of priority substances in surface waters. These actions depend on various factors, including the socioeconomic value of the substance.

Waste water treatment plants (WWTPs) have been identified as important sources of used substances, with increasing pressure put on owners to identify source inputs and to reduce effluent concentrations.[7] The Chemicals Investigation Programme (CIP) is a project being undertaken by UK Water Utility providers, coordinated by United Kingdom Water Industry Research (UKWIR) in response to these pressures.[8] The implementation of this project, including the substance selection criteria, and some of its results, have been described in

previous publications.[9–12] The project consists of three parts, CIP1-C1 – investigations to assess risk from chemicals discharged to receiving waters, CIP1-C2 – Investigations to assess WWTPs performance, CIP1-C3 – Urban sources of chemicals to sewer investigations.[9] As part of the CIP2 project, influent concentrations for ibuprofen, diclofenac and ranitidine were recorded alongside 16 other APIs across 45 WWTPs between 2015-2017.

The investigation of sources of APIs release to the environment is an important facet in ensuring no environmental harm comes from their use. Assessing the risk these sources are likely to have on their surrounding environments requires the determination of their subsequent concentration in surface waters and other environmental compartments. In this vein, models such as ePiE (exposure to Pharmaceuticals in the Environment) have been developed as part of the wider Innovative Medicines Initiative iPiE work scheme for the intelligent assessment of pharmaceuticals in the environment.[13] Whilst not necessarily developed for assessing pharmaceuticals specifically, other exposure models exist such as PhATE, iSTREEM, GWAVA, GREAT-ER and LF2000-WQX.[14–19]

As summarised by Kapo *et al.* (2017),[20] various studies have highlighted the importance of considering the pre-WWTP sewer system when estimating chemical exposure to the environment (including for APIs)[21], failure to do so leading to the overestimation of WWTP influent concentrations for certain chemicals. GREAT-ER and LF2000-WQX both consider the removal of substances during sewer transport.[14–16] However, currently, ePiE, PhATE, iSTREEM and GWAVA do not explicitly consider in-sewer removal.[13,17–19] It is important to consider the impact, or lack-thereof, that in-sewer removal might have on the inputs to these models when performing an exposure assessment.

OTC sales are a significant route by which certain APIs might be purchased and consumed. Burns *et al.* (2017)[22] highlighted the need for new approaches that incorporate OTC sales. The

lack of consideration of all routes of consumption identified as the reason that predicted environmental concentrations (PECs) underpredict measured environmental concentrations (MECs) in their own study And other studies such as Carballa et al. (2008)[23] and Oosterhuis et al. (2013)[24] only considering prescription data. A running theme is that OTC data is less accessible than prescription data.[25–30] Indeed, a few studies have incorporated aspects of OTC data into the prediction of environmental releases, however, the methods to obtain and use these data are country specific and no study that has considered OTC sales has also considered the topical applications of the APIs being investigated.[24,31–33] For example, He et al. (2020)[31] analysed data on OTC sales in Japan using data gathered by the ministry of Health Labour and Welfare, however only calculated emissions using the excretion factor of orally taken ibuprofen and diclofenac, not considering unabsorbed topically applied product. Azuma et al. (2015)[32] used a handbook detailing pharmaceutical sales in Japan to include OTC sales of diclofenac (although the other APIs investigated were prescription usage only), however this data was limited to pharmaceuticals sold by major pharmaceutical companies only and did not account for the volume of pharmaceuticals sold as generics by smaller companies. In addition, the use of topical products and the variation in absorption does not appear to have been considered in their methods either. Unfortunately, the methods to incorporate OTC data used are not applicable outside of Japan and in many countries, for example the UK, government agencies do not track data on over the counter sales.

Whilst not applicable for all APIs, topical formulations are also overlooked and the consideration of their different pathway to wastewater missed. There are a number of examples of this in the recent literature [23,24,31–33] despite the fact that a large proportion of topical application is not absorbed and metabolised by the human body.[34]

This study presents a holistic approach, investigating the significance of OTC and topical applications in addition to temporal and subnational variation in use. To the authors knowledge,

no studies in the existing literature have investigated all these aspects together, and consider topical applications. In the present study, we assess the importance of including OTC sales and topical applications, as well as any potential removal en route to WWTPs, when performing environmental exposure assessment. Due to practical time limitations, and the labour-intensive process involved in making use of the OTC dataset, a subset of pharmaceuticals was chosen as a proof of concept for this study, covering the main routes of emission and acquisition in the UK, namely, ibuprofen (available via prescription, OTC, both oral and topical), diclofenac (prescription, oral and topical, OTC topical), and ranitidine (prescription and OTC, oral only). All three APIs were identified by Comber et al. (2018)[11] as APIs having a high potential to be considered as candidate priority substances under the WFD. Since that publication, both diclofenac and ibuprofen are currently being considered by the EU commission as candidates for the priority substances list under the WFD [35]. The mass released to individual WWTPs based on these data is calculated and compared with influent concentrations measured during the CIP1-C2 project to validate the approach taken. Differences in regional and temporal releases are assessed, as well as whether high temporal or regional resolution is required given the extra effort to attain information to that level. The data sources and methods to use OTC sales data identified in this paper can be used in many countries globally, including countries where OTC sales data are not tracked by government agencies and could be used as an alternative data source to government data in countries in which it is tracked. In addition, two of the substances investigated are currently of high relevance to the EU commission.

2. METHODS

Monthly prescription data for ibuprofen, diclofenac and ranitidine were obtained via subscription, covering a 12-month period from April 2016 – March 2017, from the IQVIA Prescription Service. IQVIA are an American multinational company serving industries of health information technologies and clinical research. In the UK, they work with pharmaceutical companies and the majority of NHS Trusts.[36] Weekly OTC sales for all products in the UK containing ibuprofen, diclofenac and ranitidine covering the same period were obtained via subscription from Nielsen Holdings, an American global information data and measurements company who specialises in providing data on consumer goods.[37]

2.1 IMS (IQVIA) Prescription Data

The data obtained from IQVIA contained monthly post code level information on the number of 'sales' of an individual product per postcode in the UK (excluding Ireland). In some cases, only the National Health Service (NHS) authority area was given. In these cases, a Google search of the entire authority name + post code gave a list of postcodes within that authorities' area. An online document was provided with the data providing the definitions of the nomenclature (Health and Social Care Information Centre (HSCIC)).[38] The British National Formulary (BNF)[39] name of each product gave information on the active ingredient and the mass of the API per tablet or per dose in millilitres (this was converted to $mg.ml^{-1}$). The milligram per tablet and milligram per millilitre values were multiplied by the 'quantity' value given in the data. The quantity value given was equal to the number of tablets or millilitres sold (as defined by HSCIC). The resultant value was divided by 1,000,000 to give the amount of API in kilograms per month per postcode.

In a number of cases the BNF name contained a brand instead of the name of the API. To identify the products containing the APIs of interest (ibuprofen, diclofenac or ranitidine), a

search of each product was performed using the electronic Medicines Compendium (eMC)[40] website which contains up to date, easily accessible information about medicines licensed for use in the UK. Products not containing one of the three APIs were removed from the data.

2.2 Nielsen Over the Counter Sales

The data obtained from Nielsen were treated in a similar fashion to the prescription data. The same method as above was repeated to isolate products containing APIs of interest (ibuprofen, diclofenac or ranitidine). As well as identifying the API, a search of the eMC database was necessary to identify the mass of API in the specific products as this information was not given in the dataset. Only some of the products were present within the eMC database, a combination of other checks was used to confirm the amount of API per sale. Firstly, manufacturer's websites product information pages were checked to confirm dosage. In some cases, products were not present on manufacturer's current product range pages, presumably because that particular product had been discontinued. In these cases, a Google search of the product name or barcode given in the Nielsen dataset was performed and the API strength for products appearing for sale within the UK with an exact name or barcode match were added to the Nielsen data. On occasion bar codes were essential, for example, one brand of product containing ibuprofen had the same range of pack sizes for both 200 mg and 400 mg strength tablets, it was not clear from the name which strength tablets corresponded to which sales data. In this case the bar code information allowed confirmation and correct matching of API strength with sales data.

The product strength was multiplied by the pack size (number of tablets, mls or grams). The total API per pack was converted to kg and multiplied by the unit sales per week per product to get the mass of API sold that week.

The Nielsen data are comprehensive, although there are some limitations. Nielsen obtain sales data from collaborators and non-collaborators. Larger collaborators (86% of total coverage), provide census information on sales, providing every sale, every week for every store. Smaller collaborators provide every sale, every week for some stores, this representative sample is extrapolated for non-contributing stores appropriately. Smaller collaborators and non-collaborators (for which data are projected from larger collaborators) make up 14% of total coverage. This introduces some error into the OTC data which is not easily quantified.

2.3 Combining Mass Data for comparison with CIP2 data

The OTC and prescription data sets differed in their granularity with respect to time and location. The Nielsen data were recorded weekly compared with the prescription data being monthly. For location, the prescription data were recorded to post code level, whereas Nielsen data were available for larger defined regions: England & Wales, Central, East of England, Lancashire and English Border, London, North East, South & South East, South West, Wales & West, and Yorkshire. To combine the data spatially, the postcodes making up each region as defined by Nielsen were obtained with the rest of the Nielsen data. The relevant prescription data for those postcodes was pulled from the larger prescription datasets for each region investigated and the total kg per region was calculated.

Prescription, OTC and CIP data were also not temporally aligned. For instance, the prescription data were measured from the 1st to the last of each month, the OTC data were given at seven-day intervals, which did not align with the beginning and end of each month, the CIP data were obtained at irregular time points across the months. To allow the combining of the OTC and prescription data and subsequent comparison with the CIP data, totals were obtained for each time period, per month for prescription and per week for OTC. The weekly totals for the OTC data were then divided by seven allowing this data to then be matched with each month of the

prescription data i.e. weeks that crossed monthly boundaries were split and added to the relevant month.

Data were totalled before and after being transformed by absorption and metabolism data. This exercise resulted in totals for each API for each region per month and per year in addition to England and Wales. Subdivisions of the totals were calculated so the contribution of each sub-type could be accounted for e.g. OTC topical vs prescription topical.

2.4 Calculating per person usage and release

To calculate region-specific per capita prescription and OTC consumption, we obtained population data from the UK Office for National Statistics website.[41] We aggregated these population counts to the level of Nielsen regions, based on the main post code areas included in them, as defined by the first two letters and number.[42] Because population data were not available at the same resolution, some minor errors might have been introduced. For example, Breckland is made up of postcodes IP24, IP25 and IP26. IP24 and IP25 are included in the 'East of England' Nielsen region, however IP26 falls within the 'Yorkshire' Nielsen region. Since the population information for these specific areas was not broken out these were simply included in the prevailing region, in this case 'East of England'. There were six of these incidences overall and the error contribution was not found to be large, for example, the total population of Breckland is 137,032, assuming equal distribution across post codes, approximately one third is assigned to the incorrect region (<0.08 % of the UK population). Monthly and yearly per person release rates were calculated for each region and England and Wales and temporal and regional release patterns were statistically compared.

2.5 Calculating actual masses released after adsorption, metabolism and excretion

Once the total amounts of prescription and sales data had been tallied, we accounted for the amount of parent API excreted. The amount of API excreted after metabolism was the key factor for products taken orally and was relevant for ibuprofen, diclofenac and ranitidine. Ibuprofen and diclofenac were also found in many topically applied products, here there were two pathways to wastewater to consider. First, API absorbed through the skin, metabolised and excreted like the orally taken form and second, API not absorbed or metabolised (as shown in eq 1).

$$E_t = M_t . f_a . f_{met} + M_t . (1 - f_a) \quad (1)$$

where E_t is the emission to wastewater for a topical product; M_t is the mass of API in the topical product; f_a is the absorption of the topical product and f_{met} is the fraction of the parent API released after metabolism.

We assumed that 100% of the product that is not absorbed is released to wastewater. After product use, we assumed that consumers will wash the remaining product off using water in a sink as per the usage instructions. Product not fully absorbed into the skin will be transferred to clothes or bedding and will be subsequently washed. Whilst it is possible a consumer may use tissue paper to remove excess product and dispose via solid waste streams, we anticipated that most will wash hands due to the medicinal nature of the product and attempt to avoid applying gel to other parts of the body accidentally (as per the usage instructions). Some of the applied product may enter the environment via skin cell turnover, and we assumed that the majority of skin cells with product on or in them will be lost either whilst wearing clothes, washing or sleeping (with subsequent washing of clothes and bedding). Additionally, any remaining on the skin at the site of application that is not adsorbed into clothing or bedding is likely to be lost when bathing or showering.[34]

Ibuprofen undergoes significant metabolism in humans and is predominantly excreted via urine (~99%).[43,44] Data identified for the excretion of ibuprofen from human urine, as conjugate and free, is presented in the supplementary information (SI table 1). Due to the wide range of values found in the literature, we used the median value of 10.7% as the fraction of free and conjugated ibuprofen excreted. A number of studies in the literature show that it is necessary to consider releases of the conjugates as it appears that these may be readily converted back to the parent molecule in the environment or waste water treatment process via hydrolysation or enzymes present in treatment plants.[22,45–47]

A number of studies have investigated the bioavailability of topically applied ibuprofen compared with the orally taken drug, both *in vivo* and *in vitro*. Most studies performed in this area were not focussed on skin kinetics and do not provide clarity on the total mass of the active ingredient entering the body. Instead, the focus was on the amount of ibuprofen systemically bioavailable in the blood plasma as a percentage of what is available via the oral route. These studies do not factor in the importance of skin pharmacokinetics, including the ability of skin metabolism to affect how topically applied drugs enter the body as discussed by Nair *et al.* (2013).[43,48–50] Hadgraft, Whitefield, and Rosher (2003)[51] provide values more suitable for use in this work; they performed *in vitro* testing on six different types of formulations including gels, providing percentage values for the amount of applied active ingredient passing into and through the skin. The data are summarised in the supplementary information in SI Table 2 and show that the form of delivery is a key factor in the total absorption. We found that there were only three variations of gel formulation in the data sold under different brands. Absorption percentages (4.27-25.22%) were assigned based on the Hadgraft, Whitefield, and Rosher (2003)[51] data.

Diclofenac is metabolised to a large extent before excretion. According to Davies and Anderson (1997)[52], approximately 2% is excreted unchanged in urine, whilst diclofenac only

leaves the body via the faeces after it has been metabolised. We assumed that anything in faeces does not contribute to the influent concentrations measured during the CIP project (samples were filtered and only the dissolved fraction measured). Thus, the value for urine excretion is used, along with the percentage absorbed topically, to calculate the total diclofenac being excreted into the environment. Two recently published studies give conflicting results on the absorption of different diclofenac formulations through the skin *ex vivo*. Haltner-Ukomadu *et al.* (2019)[53] give absorptions between 12.5 to 35.1% using parafilm occlusion, known to enhance absorption. Pradal *et al.* (2019)[54] found relatively low values in comparison, with absorption fractions between 0.077% and 0.54% for two of the same formulations with no occlusion, but over a shorter time period. Both studies compared the rate of absorption between emulsion and hydrogel diclofenac formulations. The eMC website contains regulated and approved information on medicines available in the UK[40], information on pharmacokinetics is given by pharmaceutical companies in 'Summaries of Product Characteristics'. The total absorption value given for the most representative diclofenac formulation is 6%, which appears to be based on Reiss *et al.* (1986)[55–57]. This value is used for the absorption of topical diclofenac in this study due to both the extreme variation in the more recent studies, and its publication by eMC.

Ranitidine is an orally taken drug, therefore only the excretion of unchanged drug is of interest in this study. Kortejärvi *et al.* (2005)[58] summarise the literature on the pharmacokinetics of ranitidine, concluding between 25 - 30% can be excreted as unchanged drug. A conservative value of 30% has been used in calculating the release to wastewater of the total mass of ranitidine used.

2.6 Chemical Investigations Programme (CIP1-C2) Data

Comber et al. (2018)[11] provides great detail on the methods and their reliability pertaining to the data generated during the CIP 2 project. Briefly, samples were collected by stratified/random spot sampling with sampling at approximately monthly intervals. A minimum of 15% of samples were taken during non-working hours (evenings and weekends) to ensure coverage of variation occurring during the day. The samples were filtered, collected in stainless steel samplers, stored in glass containers and transported at 4 °C to the analysis laboratories. The samples were stored a maximum of 5 days prior to analysis. All analysis was by laboratories with ISO17025 accreditation. Methods used for the determination of pharmaceuticals were all based on variants of High Performance Liquid Chromatograph–Mass Spectrometry or Gas Chromatography-Mass Spectrometry.[11]

Under the CIP scheme, not all WWTPs were measured over the same time period. OTC sales data could only be obtained back to the beginning of 2016, therefore, WWTPs with influent measurements taken throughout 2016-2017 were selected for this study. A range of plant sizes were selected with generated loads ranging from 7,901 to 168,863 population equivalent (PE). For confidentiality purposes, the names of the plants are not given. However, relevant details are provided in the results section.

Measurements of influent concentrations were taken throughout the year, in some cases multiple measurements were taken in a month, whilst others may have had one or none. Multiple values were taken in 63% of the months measured. To allow comparison with the monthly API mass data, means and standard deviations were calculated for months with multiple measurements and used in the comparisons for each plant. For comparison with yearly totals, the mean concentration and standard deviation across the year was calculated for each plant. Using Tukey's IQR method a number of extreme outliers were removed from the influent measurements, detailed information on this process and values removed can be found in the supplementary information under 'Anomaly removal'.

316 *2.7 Comparing total mass released with influent data*

317 Within the EU, a per capita wastewater contribution of 200 $l.d^{-1}$ is recommended in ECHA
318 guidance[59,60]. Greater amounts of water entering WWTPs will result in lower API
319 concentrations, which will be further diluted in surface waters. The default of 200 $l.d^{-1}$ is likely
320 on the high side for the UK, a lower value of 150 $l.d^{-1}$ has been previously suggested as an
321 average per capita usage[7]. A more recent in depth analysis of water usage was conducted across
322 the UK by DiscoverWater.co.uk, a grouping together of multiple bodies concerned with water
323 management within the UK including amongst others, Water UK, Ofwat, and the Environment
324 agency[61]. This website shows up to date information on UK water usage, however data for
325 previous years is better presented elsewhere. Love2Laundry.com has linked to and displays
326 more detailed information from the Discoverwater dataset, including historic data from
327 previous years. Data include water usage across the different regions as well as the average
328 yearly per capita water usage across the whole UK which was 141 $l.d^{-1}$ in 2016-17[62]. This value
329 is significantly lower than defaults assumed in EU guidance. Influent water flows may contain
330 contributions from runoff and industry, however it was difficult to account for these in a
331 meaningful way based on the data available. In an effort to highlight or make visible how any
332 industry contribution might affect the data, WWTPs were selected from urban (presumed to
333 have industrial inputs), suburban and rural (presumed to have low or no industrial inputs)
334 settings. The assumption that those in suburban and rural settings would have minimal
335 industrial input (if any) was deemed reasonable based on inspection of these areas using
336 Google™ Maps. It was assumed that there is no API in runoff or manufactured in industry near
337 the plants selected although it is acknowledged that the dilution is a significant source of
338 variability in this work.

339 To allow a comparison of the mass of each API released with the influent data, we performed
340 the following actions. To obtain an expected mass heading to a specific WWTP, the regional

per person per month mass was multiplied by the PE (as a proxy for the population served) of the respective WWTP. The influent concentration data was transformed to a mass by multiplying the average UK water usage per person per day by the PE to account for dilution, the previously discussed value of 141 $l.p^{-1}.d^{-1}$ was used in this calculation. The use of a constant dilution is a significant source of error, however data on flow that coincide with the measured influent concentrations were not available. Regression analysis was performed on monthly predictions to assess how well the expected mass released predicted the actual mass in the influent.

2.8 Statistical Analysis

Using Tukey's IQR method a number of extreme outliers were removed from the influent measurements, detailed information on this process and values removed can be found in the supplementary information under 'Anomaly removal'.

One-way ANOVA was performed to look for statistical differences across the months and across the regions for each the per capita release of each API. Where a statistical difference was found a *post hoc* Tukey test was performed.

Data processing was performed in Microsoft Excel 2016 with more detailed statistical analysis being performed in JASP (version 0.11.1).

3. RESULTS AND DISCUSSION

3.1 Contribution of prescription, OTC, oral and topical consumption to regional use

The total mass of each API sold or prescribed in 2016-17 can be found in Table 1. For ibuprofen and diclofenac, OTC sales make up a significant portion of the total mass of API used by the populace per year. This is most significant for ibuprofen, where OTC sales make up 76.16% of the total mass. Prescriptions are more important for ranitidine, with just 4.88% of the total mass coming from OTC sales. With regards to OTC sales, orally taken forms of ibuprofen made up a significantly higher portion of the total mass in 2016 at 98.13%. This was in contrast to diclofenac where the mass contributed from topical OTC sales was nearly 99.99%. The sale of oral diclofenac OTC was actually banned in the UK in January 2015[63], the small amount of sales data showing oral OTC sales is therefore likely an artefact introduced by the information gathering techniques used by Nielsen described in the methods section. Combining prescription and OTC data, topical applications of ibuprofen made up 7.9% of the total mass in 2016. Diclofenac topical applications were more significant with 63.1% of the mass contribution, when considering prescription and OTC uses.

Overall, 409.5 tonnes of ibuprofen, 44 tonnes of ranitidine and 8.5 tonnes of diclofenac were released to the UK public through prescriptions and OTC sales in 2016. SI Table 3 shows the mass of API used per capita in each region across England and Wales in detail. The data demonstrate that regional preferences for self-medication (with respect to pain relief and heart burn) vary. For example, the OTC per person usage of ibuprofen is higher in the 'London' and 'South & South East' regions when compared with the average across England and Wales. However, the amount prescribed is lower than the average across England and Wales. This is in contrast to the 'North East' region, where total usage is fairly representative of England and Wales as a whole. However, in this region the prescription rates per person are higher than the

382 average across England and Wales with OTC sales being lower than average when compared
383 with England and Wales. Similar patterns can be observed across the data for both diclofenac
384 and ranitidine.

385 Table 1. Total mass of each API sold OTC or prescribed from 01/04/2016 to 31/03/2017 in
386 England and Wales

387 *3.2 Wastewater releases of prescription, OTC, oral and topical APIs*

388 Table 2 displays the totals for each API released to wastewater, calculated after topical
389 absorption (where applicable) and metabolism. For both diclofenac and ibuprofen, OTC
390 contributions make up over 50% of the API mass released. As can be seen from these data, a
391 significant proportion of API mass comes from OTC sales. In agreement with previous work,
392 depending on the API, not accounting for contributions from OTC sales could lead to
393 significant underprediction of exposure when comparing with MECs.[22]

394 The large releases from OTC diclofenac (where prescription usage accounts for a larger portion
395 of the mass being used) is explained by the relative contributions of topical and oral
396 applications. OTC sales for diclofenac are nearly all attributable to topical application. Based
397 on absorption and release percentages, 1.99% of the oral mass of diclofenac used is released to
398 wastewater compared with 94.1% of the topical mass used. It is a similar story for ibuprofen,
399 94.4% of the total topical mass used is released to wastewater compared with 10.7% of the
400 orally taken drug. This means that despite the use of orally taken ibuprofen being over 10-fold
401 greater (376,996 vs 32,465 kg $year^{-1}$), the amount released to the environment is less than 1.5-
402 fold greater (40,338 vs 30,643 kg $year^{-1}$). These values are of course subject to the assumptions
403 that any unabsorbed API is emitted to wastewater for topical applications. This assumption is
404 discussed in the methods section and is based on previous work on so-called secondary routes
405 of environmental exposure in Daughton et al. (2009).[34] Here it is shown that topical

applications contribute a disproportionally high environmental loading and are clearly an important source of releases to wastewater for certain APIs. Depending on skin absorption, topical applications have the potential to contribute much greater quantities per unit mass used compared with oral because the unabsorbed fraction is not metabolised. Steps to mitigate environmental loadings of topically applied APIs have previously been discussed by Daughton and Ruhoy (2009),[34] who suggest a number of pollution reducing measures for topical applications, including providing absorbent wipes to remove excess product after application, or the development of more accurate dispensers preventing wastage. Recent trends for ibuprofen products include topical patches, with any remaining unabsorbed API left in the patch to be discarded in the solid waste stream. These might be a more environmentally friendly alternative to topical gels for similar reasons. It is clear that exposure estimates of APIs can be improved by incorporating OTC consumption but that it is equally important to consider product format and all routes of exposure beyond oral prescription when assessing the environmental exposure of APIs. The contribution of each route of exposure and acquisition is key in a regulatory context. Where APIs become priority substances under the WFD, EU member states have a legal obligation to comply with set EQS values and where these are not met, must take action to reduce environmental concentrations. Identifying contributing factors and balancing them with human benefits is a key consideration.

Table 2. Total mass of API released to the environment after absorption and metabolism from 01/04/2016 to 31/03/2017

3.3 Variation in regional and temporal releases

Monthly and annual per capita release rates after absorption and metabolism are shown in SI Table 4, for each API at both the national level (England & Wales) and at the level of individual regions. The per capita usage for England and Wales was calculated by dividing up the total

mass by population, rather than being a mean of the other per capita values. One-way ANOVA was performed to look for statistical differences across the months and across the regions for each API. No statistical differences were found between the monthly release rates. A statistical difference was found between the regional releases so a *post hoc* Tukey test was performed. Most regions were statistically different from each other (statistically different regions can be viewed in SI table 4). A large variation was found between regions, the range in yearly per capita usage, as a percentage of the national per capita use, was 43% for ibuprofen, 50% for diclofenac and 76% for ranitidine. For ibuprofen, the 'North East', 'South West', 'Wales & West' and 'Yorkshire' were all significantly different to the national per capita usage of 'England and Wales'. A lower number of regions were considered statistically similar to the national region for the other two APIs. Only the 'Central', 'London', 'South and South East' and 'South West' were statistically similar to national usage for diclofenac, and only 'South and South East' and 'South West' regions were similar for ranitidine.

It is difficult to explain or postulate the reasons for the large differences between regions in the context of this study alone. These numbers could be indicative of the overall health of a region, linked to age demographics or could be down to differences in the culture relating to self-care or medicine use. An analysis of the data against other epidemiological data might help to shed light on these differences. For the purposes of this study, it can be concluded that using a per capita use rate for a whole country in a region or site-specific exposure assessment could introduce significant error in any modelling exercise as suggested by He et al. (2020).[31] There is a clear benefit to using region-specific use data where possible as shown by the statistically significant differences between a number of regions when compared with the total per capita usage for the 'England and Wales' national region.

3.4 Comparison of mass released with mass in influent

454 The influent masses of all three APIs, back-calculated from the influent concentrations
455 measured, are predicted reasonably well by the mass released, as calculated from sales and
456 prescription data (Figure 1). However, there is a consistent overestimation of the mass in
457 influent for all three APIs. This overestimation is greater for diclofenac, for which a larger
458 proportion of values fall outside of the two-fold and five-fold lines. The factor differences
459 between the expected mass and the mass in influent for each API can be seen in the
460 supplementary information. For ibuprofen, the median factor difference was 1.46 with a 95th
461 percentile value of 3.63. The median factor difference for diclofenac was 3.16 with a 95th
462 percentile of 12.14, and for ranitidine the values were 2.03 and 5.69 respectively.

463 Whilst there might be multiple factors leading to the overestimation of the influent mass, it is
464 common to all three APIs and appears to be independent of API format or route of acquisition
465 and the size or location type of the WWTPs. It was expected that the urban WWTPs included
466 in the study might have significant industrial wastewater contributions which would lead to a
467 greater overestimation of influent mass relative to the suburban and rural WWTPs, however no
468 clear patterns are visible across the data suggesting that the industrial inputs are either not as
469 high as anticipated for the urban WWTPs, or contribute wastewater that is of similar structure
470 to that produced by resident populations and is therefore taken into account in the PE capacity
471 of each WWTP (which is calculated based on an assumed BOD load per person). Overall this
472 suggests an additional factor needs to be considered when predicting influent concentrations.
473 Multiple studies have identified that a significant amount of removal via biodegradation and
474 other processes can occur during sewer transport.[20,21] To assess whether in-sewer removal
475 could reasonably explain the overestimation for each API, the mean overestimation of the
476 influent mass was divided by a range of sewer retention times (one to six hours) to give a range
477 of hypothetical in-sewer removal rates. These removal rates were compared to WWTP removal
478 rates identified in recent literature.[12,13] Theoretical removal rates appear within reason for

ibuprofen (0.05 - 0.32 h^{-1} compared to 0.15 – 1.5 h^{-1}), however the theoretical levels of in-sewer removal for diclofenac (0.1 – 0.62 h^{-1} compared to 0 – 0.1 h^{-1}) and ranitidine (0.08 – 0.49 h^{-1} compared to 0.09 h^{-1}) were only realistic for the longest theoretical sewer residence time of six hours.

Whilst the literature supports the hypothesis that in-sewer removal is contributing to the over estimation of influent mass, other factors appear to be playing a role, particularly for diclofenac and ranitidine. Bound et al. (2005)[64] performed a survey in England finding that just over 50% of respondents finished their medication, a third kept their pharmaceuticals until the expiration date (disposing of the left-overs at that point), with the remainder disposing of their pharmaceuticals once treatment was complete. Approximately 70% of respondents disposed of used pharmaceuticals via the solid waste stream. Some of the variation could be accounted for by differences in how consumers use OTC vs prescription drugs with presumably less variation in the correct amount of drug being prescribed by doctors, and patient conformity to taking the full course of treatment. Another factor might be the method of delivery, for example, there are less variety in pack sizes for topical applications compared with oral, potentially leading to more frequent over-prescribing or purchasing. Topical application makes up a larger proportion of use for diclofenac, therefore an over assumption in the amount of API washed off might cause a larger overestimation of API release compared to ibuprofen. Repeating this exercise with oral and prescription only APIs measured in the CIP influent data might eliminate a significant proportion of the variability and could allow reasonably accurate sewer removal rates for APIs to be derived. However, Johnson et al. (2004)[15] have demonstrated that accounting for the in-sewer removal of different API metabolites is complex. There is limited data collected on APIs or other chemicals in this regard.

Figure 1. Scatter plot with a logarithmic scale (base 10) comparing absolute values of the total daily mass of ibuprofen, diclofenac and ranitidine released to the sewer (x-axis) with the

back calculated mass measured in influent (y-axis) across all WWTPs. Lines show 0, 2- and 5-fold differences. Each point represents the comparison of a measured and predicted influent value.

3.5 Influence of sewer retention time

As the mass calculation for release is the per capita use rate multiplied by the PE of each WWTP and the influent mass is calculated using the per capita dilution, normalised per capita residual plots were made to identify any trends in the overestimation of the influent mass as plant size increases (residual plots can be found in the supplementary information SI figures 1-6). Figure 1 (in addition to SI Figure 1-3) shows that for each API, there is no increasing over estimation, and therefore in-sewer removal, as plant size increases. This is in contrast to Kapo et al. (2017)[20] who suggest median sewer residence times differ based on treatment facility size in the USA. Other data in the literature indicate that sewer retention time does not necessarily follow a predictable pattern. Holt *et al.* (1998)[65] quote a mean measured sewer retention time of two hours based on six WWTPs in Yorkshire (UK), although no explanation is given on where this value came from (e.g. whether it was obtained by company survey). A survey of wastewater treatment plant operators across Europe by Ort *et al.* (2014)[66] gives a median sewer retention time of approximately four hours.[20] The residence times were provided in response to a questionnaire given to WWTP managers, the approaches with which the surveyed treatment plants determined their sewer residence time in each case are unfortunately not stated.[66] During the work performed here a short exercise was performed to assess whether the median sewer residence times defined in Kapo *et al.* (2017) were able to predict the sewer residence times given in Ort *et al.* (2014)[66] based on the design capacity and population served census data given in their supplementary information. Residence times were assigned based on

528 the plant capacity and plotted against the residence times given in the survey, a poor
529 relationship was observed (R^2 = 0.057). The census population and design capacity were also
530 plotted against the residence times, however poor relationships (R^2 = 0.059 and 0.06
531 respectively) were observed here too. These data indicate that it may be necessary to assess
532 sewer retention time on an individual site basis, or that other factors may need consideration,
533 such as when and how the sewer system was designed and built. Whilst sewer retention time
534 may not vary in a predictable way, the data here appear to agree with recent literature
535 suggesting that in-sewer removal should be considered in exposure modelling exercises,
536 however further study is required to separate the amount of in-sewer removal from other
537 sources of overestimation.

538 *3.6 Conclusions*

539 The results show that OTC sales and topical product formats can contribute significantly to the
540 mass of APIs released to wastewater with topical formats contributing more per unit mass used
541 than oral formats (for the APIs included here). This is of great significance to the current
542 science surrounding the environmental risk assessment of pharmaceuticals given the lack of
543 consideration previously given to topical formats and their emissions. Exposure estimates of
544 APIs clearly need to incorporate all routes of acquisition and product format types to be truly
545 representative of the API under consideration. In addition to improving exposure science, these
546 findings are of regulatory importance with regards to the future assessment of APIs which end
547 up being regulated under the WFD and the subsequent legal obligation EU member states will
548 have in complying with EQS values.

549 Significant regional differences in API per capita usage were found, although no significant
550 month to month temporal variation was observed. It is therefore concluded that assessing the
551 exposure of an API using a per capita use rate for a whole country could introduce significant

552 error at the region or site-specific level and there is a clear benefit to using region-specific use
553 data where possible.

554 Mass to wastewater releases were predicted well when compared with the mass in influent back
555 calculated from the CIP data. A consistent overestimation of the mass in influent was observed,
556 however. The overestimation was attributed to a number of potential factors, including
557 consumer habits e.g. not using all of the medication purchased, assumptions made in mass
558 calculations and in-sewer removal, however further work to assess the importance of each
559 factor is recommended and is required to increase the accuracy of environmental exposure
560 assessments for APIs.

561 The study provides methods for incorporating OTC API data into environmental exposure
562 assessments that can be used in a wide range of countries. Nielsen gather data globally, in 100+
563 countries, the methods used herein are therefore applicable to any country where government
564 agencies do not gather data on OTC sales (such as the UK and many others) and could allow
565 for the incorporation of OTC data more widely. The authors encourage the use of the methods
566 detailed herein to investigate the OTC contribution of other APIs where this data is available.

567

568 **Supporting information**. One excel file is provided as supplementary information containing;
569 SI tables 1-4, anomaly removal method description, volume data on ibuprofen, diclofenac and
570 ranitidine.

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