

2021-01-15

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<http://hdl.handle.net/10026.1/16268>

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10.1016/j.scitotenv.2020.141624

Science of The Total Environment

Elsevier BV

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

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## 16 **Abstract**

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

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

## 32 1. INTRODUCTION

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

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

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

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

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

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

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

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

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

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

126

127 **2. METHODS**

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

136 *2.1 IMS (IQVIA) Prescription Data*

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

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



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

## 154 *2.2 Nielsen Over the Counter Sales*

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

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

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

### 181 *2.3 Combining Mass Data for comparison with CIP2 data*

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

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

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

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

#### 204 *2.4 Calculating per person usage and release*

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

#### 219 *2.5 Calculating actual masses released after adsorption, metabolism and excretion*

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

227 (1) 
$$E_t = M_t \cdot f_a \cdot f_{met} + M_t \cdot (1 - f_a)$$

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

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

243 Ibuprofen undergoes significant metabolism in humans and is predominantly excreted via urine  
244 (~99%).<sup>43,44</sup> Data identified for the excretion of ibuprofen from human urine, as conjugate and  
245 free, is presented in the supplementary information (SI table 1). Due to the wide range of values  
246 found in the literature, we used the median value of 10.7% as the fraction of free and conjugated  
247 ibuprofen excreted. A number of studies in the literature show that it is necessary to consider  
248 releases of the conjugates as it appears that these may be readily converted back to the parent  
249 molecule in the environment or waste water treatment process via hydrolysis or enzymes  
250 present in treatment plants.<sup>22,45-47</sup>

251 A number of studies have investigated the bioavailability of topically applied ibuprofen  
252 compared with the orally taken drug, both *in vivo* and *in vitro*. Most studies performed in this  
253 area were not focussed on skin kinetics and do not provide clarity on the total mass of the active  
254 ingredient entering the body. Instead, the focus was on the amount of ibuprofen systemically  
255 bioavailable in the blood plasma as a percentage of what is available via the oral route. These  
256 studies do not factor in the importance of skin pharmacokinetics, including the ability of skin  
257 metabolism to affect how topically applied drugs enter the body as discussed by Nair *et al.*  
258 (2013).<sup>43,48-50</sup> Hadgraft, Whitefield, and Rosher (2003)<sup>51</sup> provide values more suitable for use  
259 in this work; they performed *in vitro* testing on six different types of formulations including  
260 gels, providing percentage values for the amount of applied active ingredient passing into and  
261 through the skin. The data are summarised in the supplementary information in SI Table 2 and  
262 show that the form of delivery is a key factor in the total absorption. We found that there were  
263 only three variations of gel formulation in the data sold under different brands. Absorption  
264 percentages (4.27-25.22%) were assigned based on the Hadgraft, Whitefield, and Rosher  
265 (2003)<sup>51</sup> data.

266 Diclofenac is metabolised to a large extent before excretion. According to Davies and  
267 Anderson (1997)<sup>52</sup>, approximately 2% is excreted unchanged in urine, whilst diclofenac only

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

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

## 290 2.6 Chemical Investigations Programme (CIP1-C2) Data

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

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

307 Measurements of influent concentrations were taken throughout the year, in some cases  
308 multiple measurements were taken in a month, whilst others may have had one or none.  
309 Multiple values were taken in 63% of the months measured. To allow comparison with the  
310 monthly API mass data, means and standard deviations were calculated for months with  
311 multiple measurements and used in the comparisons for each plant. For comparison with yearly  
312 totals, the mean concentration and standard deviation across the year was calculated for each  
313 plant. Using Tukey’s IQR method a number of extreme outliers were removed from the influent  
314 measurements, detailed information on this process and values removed can be found in the  
315 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<sup>-1</sup> is recommended in ECHA  
318 guidance<sup>59,60</sup>. 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<sup>-1</sup> is likely  
320 on the high side for the UK, a lower value of 150 l.d<sup>-1</sup> has been previously suggested as an  
321 average per capita usage<sup>7</sup>. 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<sup>61</sup>. 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<sup>-1</sup> in 2016-17<sup>62</sup>. 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<sup>TM</sup> 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



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

### 349 *2.8 Statistical Analysis*

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

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

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

358 **3. RESULTS AND DISCUSSION**

359 *3.1 Contribution of prescription, OTC, oral and topical consumption to regional use*

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

373 Overall, 409.5 tonnes of ibuprofen, 44 tonnes of ranitidine and 8.5 tonnes of diclofenac were  
374 released to the UK public through prescriptions and OTC sales in 2016. SI Table 3 shows the  
375 mass of API used per capita in each region across England and Wales in detail. The data  
376 demonstrate that regional preferences for self-medication (with respect to pain relief and heart  
377 burn) vary. For example, the OTC per person usage of ibuprofen is higher in the 'London' and  
378 'South & South East' regions when compared with the average across England and Wales.  
379 However, the amount prescribed is lower than the average across England and Wales. This is  
380 in contrast to the 'North East' region, where total usage is fairly representative of England and  
381 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.<sup>22</sup>

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<sup>-1</sup>), the amount released to the environment is less than 1.5-  
402 fold greater (40,338 vs 30,643 kg year<sup>-1</sup>). 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).<sup>34</sup> Here it is shown that topical

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

424 Table 2. Total mass of API released to the environment after absorption and metabolism from  
425 01/04/2016 to 31/03/2017

### 426 *3.3 Variation in regional and temporal releases*

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

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

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

### 453 *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 95<sup>th</sup>  
461 percentile value of 3.63. The median factor difference for diclofenac was 3.16 with a 95<sup>th</sup>  
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.<sup>20,21</sup> 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.<sup>12,13</sup> Theoretical removal rates appear within reason for

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

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

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

504 back calculated mass measured in influent (y-axis) across all WWTPs. Lines show 0, 2- and  
505 5-fold differences. Each point represents the comparison of a measured and predicted influent  
506 value.

507

### 508 *3.5 Influence of sewer retention time*

509 As the mass calculation for release is the per capita use rate multiplied by the PE of each  
510 WWTP and the influent mass is calculated using the per capita dilution, normalised per capita  
511 residual plots were made to identify any trends in the overestimation of the influent mass as  
512 plant size increases (residual plots can be found in the supplementary information SI figures 1-  
513 6). Figure 1 (in addition to SI Figure 1-3) shows that for each API, there is no increasing over  
514 estimation, and therefore in-sewer removal, as plant size increases. This is in contrast to Kapo  
515 et al. (2017)<sup>20</sup> who suggest median sewer residence times differ based on treatment facility size  
516 in the USA. Other data in the literature indicate that sewer retention time does not necessarily  
517 follow a predictable pattern. Holt *et al.* (1998)<sup>65</sup> quote a mean measured sewer retention time  
518 of two hours based on six WWTPs in Yorkshire (UK), although no explanation is given on  
519 where this value came from (e.g. whether it was obtained by company survey). A survey of  
520 wastewater treatment plant operators across Europe by Ort *et al.* (2014)<sup>66</sup> gives a median sewer  
521 retention time of approximately four hours.<sup>20</sup> The residence times were provided in response  
522 to a questionnaire given to WWTP managers, the approaches with which the surveyed  
523 treatment plants determined their sewer residence time in each case are unfortunately not  
524 stated.<sup>66</sup> During the work performed here a short exercise was performed to assess whether the  
525 median sewer residence times defined in Kapo *et al.* (2017) were able to predict the sewer  
526 residence times given in Ort *et al.* (2014)<sup>66</sup> based on the design capacity and population served  
527 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.

571 Acknowledgments

572 The authors wish to thank the Annette Blackman of IQVIA and Ryan Milburn of Nielsen, for  
573 their patience and help in responding to requests for prescription and OTC datasets, the  
574 coordinator of the CIP programme UK Water Industry Research (UKWIR) for authorising the

575 use of the information reported here, and the UK Water Utility companies Anglian, Dwr Cymru,  
576 Northumbrian, Scottish, Severn Trent, Southern, South West, Thames, United Utilities,  
577 Wessex and Yorkshire Water for their considerable efforts in generating it.

578

579 Funding:

580 This research did not receive any specific grant from funding agencies in the public,  
581 commercial, or not-for-profit sectors.

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