Hospital-use pharmaceuticals in Swiss waters modeled at high spatial resolution

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ABSTRACT

A model to predict the mass flows and concentrations of pharmaceuticals predominantly used in hospitals across a large number of sewage treatment plant (STP) effluents and river waters was developed at high spatial resolution. It comprised 427 geo-referenced hospitals and 742 STPs serving 98% of the general population in Switzerland. In the modeled base scenario, *domestic*, pharmaceutical use was geographically distributed according to the population size served by the respective STPs. Distinct *hospital* scenarios were set up to evaluate how the predicted results were modified when pharmaceutical use in hospitals was allocated differently; for example, in proportion to number of beds or number of treatments in hospitals. The *hospital* scenarios predicted the mass flows and concentrations up to 3.9 times greater than in the *domestic* scenario for iodinated X-ray contrast media (ICM) used in computed tomography (CT), and up to 6.7 times greater for gadolinium, a contrast medium used in magnetic resonance imaging (MRI). Field measurements showed that ICM and gadolinium were predicted best by the scenarios using number of beds or treatments in hospitals with the specific facilities (i.e., CT and/or MRI). Pharmaceuticals used both in hospitals and by the general population (e.g., cyclophosphamide, sulfamethoxazole, carbamazepine, diclofenac) were predicted best by the scenario using the number of beds in all hospitals, but the deviation from the *domestic* scenario values was only small. Our study demonstrated that the bed number-based *hospital* scenarios were effective in predicting the geographical distribution of a diverse range of pharmaceuticals in STP effluents and rivers, while the *domestic* scenario was similarly effective on the scale of large river-catchments.

KEYWORDS: benzotriazole; carbamazepine; catchment; cyclophosphamide; diatrizoate; diclofenac; fluconazole; furosemide; gabapentin; gadolinium; hospitals; iobitridol; iodinated X-ray contrast media (ICM); iohexol; iomeprol; iopamidol; iopromide; ioxitalamic acid;

43 modeling; oxazepam; ritonavir; river; sewage treatment plant (STP); sulfamethoxazole;
44 verapamil

45

46 1. INTRODUCTION

47 Hospitals are often discussed as potential point sources for the discharge of numerous
48 human-use pharmaceuticals into the environment, with major contributions to wastewater
49 loads.[1-4] Case studies have shown that the contribution of hospital wastewater to
50 pharmaceutical loads in sewage treatment plants (STPs) varies considerably, from less than
51 5% to more than 50%, depending on the specific hospital characteristics (location, type, size,
52 and number relative to the catchment population) and the target substance.[3,5-9] The number of
53 hospital beds per 1000 population is a general measure of inpatient services availability, and
54 varies among countries; for example, 0.3 (Bangladesh), 2.5 (China), 2.9 (world average), 3.2
55 (U.S.), 5.5 (Switzerland), 8.4 (Germany) and 14.1 (Japan), as of 2005.[10] The values found in
56 specific catchment studies on hospital wastewater were 0.5–4.4 (Australia),[5,7] 3.6–3.8
57 (Switzerland),[1,9] 4.4 (Oslo),[11] 6.5 (Italy),[12] and 12.1 (Berlin).[13] The environmental impact of
58 pharmaceutical residues in hospital wastewater has been studied.[6,9,14,15] Pharmaceuticals of
59 particular concern include iodinated X-ray contrast media (ICM), which are used for
60 computed tomography (CT) in large quantities;[16] cytostatics, which are often toxic;[17] and
61 antibiotics, which contribute to the spread of antibiotic resistance.[4,18] In conventional sewage
62 treatment processes, these pharmaceuticals are only partially eliminated, and their residues are
63 found in surface and groundwater.[19-21]
64 Thus far, two options have been proposed for reducing environmental discharge of
65 hospital-derived pharmaceuticals: (1) separate treatment of hospital wastewater at the
66 source,[22,23] and (2) upgrading municipal STPs to include post-treatments such as ozonation
67 and powdered activated carbon.[24-26] Several countries have already begun to consider the

latter; in Switzerland, for example, a general 80% reduction in organic micropollutants from raw sewage, evaluated by selected compounds, is envisaged for roughly 100 STPs by a new water protection act.[27,28]

Both options above naturally involve massive costs. Therefore, in deciding whether a given STP and/or hospital should be modified for the elimination of pharmaceuticals, it is essential to identify which catchments have high loads or high concentrations of pharmaceuticals in the receiving waters. In large geographical areas with multiple substances, such assessments can be very laborious when based on field monitoring; and in such cases, modeling approaches are more useful.[29,30] The discharge of domestically used compounds has been successfully modeled using catchment-scale water quality models, such as GREAT-ER,[31] LF2000-WQX,[32] or similar approaches.[29,33] In these models, however, hospitals are not included as emission sources. Recently, Al Aukidy et al.[8] proposed a framework for assessing the environmental risk posed by pharmaceuticals derived from hospital wastewater. They proposed to use pharmaceutical concentrations in hospital wastewater reported in various countries as reference concentrations, and use total hospital bed numbers in catchments to estimate the dilution of the hospital wastewater by domestic wastewater. In their study, the estimated risk quotient had an uncertainty of 2–3 orders of magnitude, owing to the large variation in pharmaceutical concentrations in hospital wastewater in the literature. This uncertainty increases in the case of pharmaceuticals not used in every hospital but only in specific types of hospital; here, the spatial distribution of such pharmaceuticals would differ from that of hospital beds, a case not addressed by Al Aukidy et al. However, assessments based on actual consumption of pharmaceuticals in the target area, with consideration of hospital types, would greatly reduce such uncertainty. In Australia and Switzerland, audit data of pharmaceutical consumption obtained from hospitals was used to successfully estimate the hospital-based contribution to pharmaceutical loads in one or a few STPs.[5,7,9] For assessment across a large

number of catchments, however, a model using more easily-available data (e.g., number of beds, hospital types) is more convenient in terms of data collection and modeling. In Germany, the mass flow of ICM in the urban water cycle of Berlin was predicted by a model comprising 12 STPs and hospitals, using estimated ICM consumption data.[34] Thus far, however, there has been no study on the modeling of different classes of hospital-use pharmaceuticals across a large number of catchments, with consideration of hospital type.

Here, we proposed and validated a model-based method using national consumption data to efficiently predict the geographical distribution of a diverse range of pharmaceuticals (including some specifically used in hospitals) in STP effluents and rivers, at high spatial resolution, incorporating multiple types of hospitals as geo-referenced point sources, across all of Switzerland. The model is based on a previously developed national substance flow model, which predicted the respective amounts of micropollutants discharged by the general population.[29] Our objectives were to (i) test and compare distinct scenarios with different levels of model complexity (i.e., pharmaceuticals were geographically distributed according to (a) population size served by respective STPs, (b) total number of hospital beds, (c) number of beds at specific hospitals, or (d) number of medical treatments related to specific pharmaceutical usage); (ii) test different cases for varying ratios of outpatients to total patients; (iii) validate the model through field measurements; and (iv) evaluate the applicability of the model in terms of spatial resolution, model complexity, data acquisition demands, and predictive uncertainty.

2. EXPERIMENTAL SECTION

2.1 **Model setup**

As a basis, we used a substance flow model for Switzerland.[29] The model incorporates a total of 742 STPs, covering more than 98% of the general population (7.31 million). The input data

are (i) national pharmaceutical consumption data, (ii) excretion rates of pharmaceuticals, (iii) elimination rates in municipal STPs, (iv) location and population of the catchments, and (v) dilution in the receiving waters. No elimination was assumed in the rivers, as the environmental half-lives of many pharmaceuticals are on the same order of magnitude or larger than the maximum residence time of Swiss rivers (1 d). The base flow conditions (Q_{347}) were used to account for minimum dilution in the rivers. Geographically, the total national pharmaceutical loads were allocated proportionally to the population size of the respective STP catchments, which ranged from 30–390,000 (average 9900, median 2700).

The national pharmaceutical consumption data for 2009 was purchased from IMS Health (Danbury, CT, USA), which collects data in many countries, which is used for scholarly research.[35] In Switzerland, data are available on the overall national distribution of all registered pharmaceuticals by manufacturers, importers, wholesalers and suppliers, divided into four distribution channels: (i) pharmacies, (ii) drug stores, (iii) doctors' offices, and (iv) hospitals. The sum of channels (i)–(iii), plus the amount dispensed through hospitals but excreted outside by outpatients, is considered as the total consumption by the general population (domestic consumption). Only the amount dispensed and excreted in hospitals (e.g., by inpatients) is assumed to be discharged from hospitals. This amount, as a fraction of total consumption, is thus referred to in this study as the *effective hospital fraction* (HF), which describes the allocation of pharmaceuticals between hospitals and households. HF was determined in the following manner. First, for each pharmaceutical, the ratio of the total amount dispensed through hospitals (i.e., channel (iv) above) to total consumption was termed the *hospital-dispensed fraction* (HF_{dis}). Based on HF_{dis}, HF was estimated as the fraction of the total amount of a given pharmaceutical dispensed through all hospitals, minus the portion of this amount excreted by outpatients outside the hospitals. Hence, the consumed amount

that was subsequently discharged from hospitals was expressed as (total consumption × HF), and that discharged from the general population as (total consumption × (1−HF)).

The hospital-allocated pharmaceutical consumption (i.e., total consumption × HF) was distributed to the respective hospitals according to the scenarios described in Section 2.3. The consumption by the general population (i.e. total consumption × (1−HF)) was distributed in proportion to the respective catchment populations. The respective consumption by hospitals and by the general population was assigned for each STP, and the resulting loads and concentrations of pharmaceuticals in STP effluents and rivers were predicted, taking excretion from the human body and elimination at STPs into account, as in the base model.[29] This allocation of pharmaceutical consumption to STP catchments is illustrated in Figure S1 of the Supporting Information (hereafter, SI).

2.2 **Hospital data**

Information on the hospitals' location, type and number of inpatient beds was derived from the official database of 2007 (Federal Office of Public Health), which included all the hospitals in Switzerland (427 hospitals, with 44,892 beds in total). In addition, for hospitals with radiology and/or oncology departments, information on the respective facilities, as well as the actual numbers of treatments related to CT, MRI and inpatient chemotherapies, was acquired. Further details of the data acquisition are described in S1 (SI). The number of in-use beds was determined based on the occupancy rate for each hospital (median 90%, Q1 84%, Q3 98%), and used for subsequent modeling and analysis, including the characteristic hospital bed density per 1000 population (hereafter, B_{1000}).

In Switzerland, hospitals and hospital beds are concentrated in the large cities (Figures S2 and S3a). In comparison, B_{1000} provides a different picture (Figure S3b): several suburban catchments had higher B_{1000} values of up to 118, which is 21 times the national average B_{1000}

for Switzerland (5.5). More details on the geographical distribution of hospitals and hospital beds, and the distribution of B_{1000} are described in S2.

2.3 **Scenarios**

Five distinct scenarios were developed for distributing pharmaceuticals (Table 1). Four of these were the *hospital* scenarios, in which hospital-allocated pharmaceutical consumption was distributed over the number of hospital beds or specific treatments. For contrast media and cytostatics, hospitals equipped with CT or MRI facilities, and hospitals with oncology departments, were distinguished in bed-specific and treatment-specific scenarios. Furthermore, for each pharmaceutical, the effect of HF variation was evaluated for two cases; in the average case (AC), HF_{ac} was set according to a realistic average proportion of expected inpatients; in the high case (HC), HF_{hc} was set at the same value as HF_{dis} or slightly lower, conservatively assuming a higher proportion of inpatients than the average case. The *domestic* scenario was evaluated in comparison with the *hospital* scenarios. In the *domestic* scenario, all the pharmaceutical consumption was allocated to the general population (i.e., HF = 0), as in the base model.

2.4 **Input data uncertainty**

For the base model, the maximum uncertainty in the predicted pharmaceutical load discharged from each STP, through variation of the model parameters, was evaluated as 64%.[29] In rivers, the uncertainty of Q_{347} added further uncertainty, ranging from 30–70%, to the predicted concentrations, depending on the river size. These uncertainties naturally applied to the *hospital* scenarios as well. In addition, the uncertainty of the hospital data *per se* must be accounted for. Briefly, the uncertainty was small (< 10%) for basic hospital data, pharmaceutical consumption, and HF_{dis}. In comparison, large uncertainty was found for

192 treatment numbers of MRI and chemotherapy. In 49% of hospitals equipped with MRI
193 facilities, and 74% of hospitals with an oncology department, treatment numbers were not
194 available, and thus had to be estimated. The actual treatment numbers (where available) did
195 not show a good correlation with the bed numbers (Figures S4b and S4c). Therefore, for each
196 hospital type (e.g., supply hospitals, primary care hospitals), the median of the actual
197 treatment numbers (SI, Table S1) was used, in order to avoid extreme over- or
198 underestimation. In contrast, the actual CT treatment numbers highly correlated with the bed
199 numbers (Pearson, $r = 0.92$, $P < 0.001$; Figure S4a). Therefore, in 54% of CT hospitals where
200 treatment numbers were not available, linear regression using the respective bed numbers was
201 employed, and thus the uncertainty was expected to be small. Further details on the
202 uncertainty regarding input data for the *hospital* scenarios are described in S3.
203
204 2.5 **Pharmaceuticals**
205 We modeled and measured 19 compounds, including 11 major pharmacological classes.
206 Escher et al.[6] provide a list of the top 100 pharmaceuticals used and excreted in the largest
207 amounts in a typical and regionally important general hospital in Switzerland. Based on this
208 list, we selected pharmaceuticals which were representative and poorly eliminated during
209 sewage treatment. We studied seven ICM used for CT (Table 2), representing the
210 pharmacological class which showed the highest consumption and was mainly dispensed in
211 hospitals ($HF_{dis} = 0.58$). The seven ICM were modeled altogether as 'iodine', which was the
212 sum of the iodine content of all the ICM. This was because the occurrence of ICM measured
213 in the STP effluents varied significantly among catchments (Figure S5), seemingly owing to
214 varying hospital preferences. Gadolinium complexes are used for MRI as contrast media, and
215 are dispensed only in hospitals ($HF_{dis} = 1$). Therefore, gadolinium (Gd) is most useful for
216 studying the discharge of hospital effluents to STPs.[5,36] Gadolinium complexes are designed

217 to be stable and non-reactive, and are quickly excreted from the human body, with a 1.3–2 h
218 half-life.[36,37] In addition, they are not removed during conventional sewage treatment.[38]
219 Cyclophosphamide was selected as a model cytostatic, because it is used only for
220 chemotherapy and has a large HF_{dis} (0.68). Sulfamethoxazole (HF_{dis} = 0.17) was selected
221 because of its broad use as an antibiotic in general hospitals. In addition, we selected eight
222 more pharmaceuticals with relatively small HF_{dis} (0.03–0.49). Benzotriazole, which is closely
223 related to domestic wastewater (i.e., HF_{dis} = 0), was selected as a reference compound.[39] The
224 modeled compounds included four of the five originally proposed indicator compounds used
225 to evaluate the removal of micropollutants in advanced wastewater treatment as envisaged in
226 the new Swiss water protection act.[27,28] Excretion rates and elimination in STP were based on
227 averages from literature data. The parameters and scenarios for the ICM, gadolinium,
228 cyclophosphamide and sulfamethoxazole are shown in Table 2; and those for the remaining
229 compounds, in Table S2.
230
231 **2.6 Field sampling and laboratory analyses**
232 Samples of 14 STP effluents and 7 river waters in Switzerland (Table S3; locations are
233 indicated in Figures 1 and S3b) were collected during June and October, 2010. The sampling
234 sites were selected based on meeting at least one of the following criteria: catchments with
235 large variation in predictions between the *hospital* scenarios and the *domestic* scenario;
236 catchments with hospitals equipped with CT or MRI facilities, or an oncology department;
237 locations with high predicted mass flows or concentrations. The STP catchments contained
238 varying combinations of general, psychiatric, and rehabilitation hospitals, with varying
239 proportions of hospital beds by hospital type (Table S4).
240 Details on the sampling methods, analytical procedures and quality control are described in
241 S4. Briefly, 24-h composite samples were taken over one week (STPs), and 1-, 2- or 4-week

242 composite samples over 1–8 weeks (rivers). The compounds, excluding gadolinium, were
243 analyzed by online SPE-HPLC-MS/MS.[40] Gadolinium was analyzed using ICP/HRMS.
244
245 **2.7 Methods for scenario evaluation and model validation by measurement**
246 Throughout this study, we evaluated the pharmaceutical discharge based on mass flow (load).
247 For rivers, pharmaceutical mass flow was evaluated at each STP discharge point by
248 aggregating the loads from the upstream STPs. To compare the model predictions among the
249 different *hospital* scenarios, with respect to the *domestic* scenario, the modeled
250 pharmaceutical mass flow was evaluated as the change relative to the *domestic* scenario (i.e.,
251 mass flow predicted by a *hospital* scenario/mass flow predicted by the *domestic* scenario).
252 This relative change remained the same for all pharmaceutical concentrations, as the assumed
253 flows are the same in all the scenarios.
254 The measured pharmaceutical mass flows were determined by multiplying the measured
255 concentrations by the actual discharge over the sampling period, for each STP and river
256 (Table S5). The agreement between the respective calculated and modeled average daily mass
257 flows was evaluated, following Ort et al.,[29] using the predictive accuracy factor
258 (prediction/observation; hereafter, PAF), its median value (MPAF), its relative standard
259 deviation (RSD), and the R^2 from the linear regression forced through 0.
260 The benzotriazole mass flow predicted by the *domestic* scenario agreed well with the
261 measured mass flow, both in the STP effluents and the rivers (Figure S6); and this showed
262 that the *domestic* scenario was valid for predicting compounds used domestically.
263 Throughout the paper, evaluations are mainly based on the results for ICM, gadolinium,
264 cyclophosphamide and sulfamethoxazole. The predicted mass flow and concentrations of
265 those four compounds in all the STP effluents and river waters, along with their relative
266 change, are shown in Table S6.

267

268 3. RESULTS

269 3.1 **Modeled pharmaceutical discharge**

270 3.1.1 **STP effluents**

271 ***Overall.*** Our results showed that the *hospital* scenarios predicted higher mass flows than the
272 *domestic* scenario only in a small number of catchments (Figures 1a, 2, S7–S9). In 76% of all
273 catchments with 30–100,000 population and no hospital beds, the change relative to the
274 *domestic* scenario was simply (1–HF) for all the *hospital* scenarios, because the catchments
275 had no hospital-allocated pharmaceutical consumption (see Figure S1 for the expected
276 relative change depending on catchment characteristics). Among all the scenarios, the relative
277 change exceeded 1 in 8–15% of catchments (Tables S7 and S8), where the number of hospital
278 beds or treatments per population were above the respective national average values (Table
279 S9). Large relative changes were found in a few percent of catchments, which were mostly
280 suburban or relatively remote, with 1000–10,000 population. These catchments differed
281 among scenarios and compounds, depending on the services provided by the hospitals. In
282 contrast, in catchments with more than 100,000 population, the predicted mass flows varied
283 less among scenarios and compounds, and the relative change mostly ranged from 1–3. This
284 indicated an abundance of hospitals of all types in these heavily populated catchments.
285 The *all beds* scenario had more catchments with large relative changes than the other
286 scenarios. This is because, in *all beds*, catchments containing any type of hospital are
287 assigned hospital-allocated pharmaceutical consumption. Therefore, a very large relative
288 change was found in catchments where the existence of hospitals of special types caused large
289 B_{1000} (e.g., suburban catchments). In such catchments, the *all beds* scenario can overestimate
290 the mass flow of specific pharmaceuticals. For example, the relative change for ICM and
291 gadolinium in *all beds* was the largest (e.g., around 7 for ICM, AC) in the two small

292 catchments of Rheinau and Schinznach-Bad (Figure 2), both of which have a population of
293 1300 and the highest B_{1000} values (118 and 108, respectively). However, this result is
294 unrealistic, because the catchments only contain a psychiatric hospital (Rheinau), and a
295 rehabilitation hospital (Schinznach-Bad), neither of which has a radiology department; and
296 the field measurements confirmed the overestimation of contrast media in these catchments
297 (Section 3.2.1).

298 ***Contrast media.*** The contrast media included ICM (HF_{ac} = 0.3, HF_{hc} = 0.5) and gadolinium
299 (HF_{ac} = 0.5, HF_{hc} = 0.8). In the *CT beds* scenario, the largest relative changes, of 3.9 (AC) and
300 5.8 (HC), were found in STP Saignelegier (2100 population) and STP Zurzach (7500).
301 Gadolinium showed the largest relative change because it has the largest HF value. In the *MRI*
302 *beds* scenario, the largest relative changes (3.7–6.7 in AC, 5.3–10.1 in HC) were found in six
303 catchments, with varying population ranging from 2100–52,000. In the *MRI treatments*
304 scenario, the maximum relative change was even larger, at 22.4 (STP Saignelegier, HC); note,
305 however, that the treatment number in this catchment was estimated.

306 ***Other pharmaceuticals.*** Various HF values (HF_{ac} = 0.01–0.1, HF_{hc} = 0.03–0.49) were applied
307 to the remaining ten pharmaceuticals. Among the latter, ritonavir had the largest relative
308 change (e.g., 3.1 in *all beds*, AC, STP Rheinau). In the case of cyclophosphamide (HF_{ac} =
309 0.05, HF_{hc} = 0.34), the relative change reached 1.5 in the *oncology beds* and *chemotherapy*
310 scenarios for AC, and 3.8 in *oncology beds* for HC. Regarding sulfamethoxazole (HF_{ac} = 0.03,
311 HF_{hc} = 0.17), the relative change reached 1.7 (AC) and 4.5 (HC) in *all beds*, and 1.4 (AC) and
312 3.2 (HC) in *general beds*.

313 ***Comparison between bed-specific scenarios and treatment-specific scenarios.*** The
314 respective predictions by the bed-specific and treatment-specific scenarios did not differ much
315 for ICM (Figure S10). In comparison, the difference was large for gadolinium (up to a factor
316 of 2) and cyclophosphamide (up to 4). This reflects the fact that bed and treatment numbers

317 did not correlate well in the case of MRI and chemotherapy (Figures S4b and S4c). However,
318 missing treatment numbers produced large uncertainties (Section 2.4); therefore, great care
319 should be taken in the case of treatment-specific scenarios in such catchments.
320
321 3.1.2 **Rivers**
322 Similarly to STP effluents, the relative changes were largest in catchments with 1000–10,000
323 upstream population (Figures 1b, S11–S13). The largest relative changes in rivers (e.g., 3.9
324 for ICM in *CT beds*, AC) were similar to those in STP effluents. However, large relative
325 changes were found in fewer river waters than STP effluents (Tables S10 and S11); for
326 example, relative changes of greater than 3 for gadolinium in *MRI beds* (AC) were noted in
327 effluents of six STPs but in only three river waters. All the scenarios predicted very similarly
328 in rivers where the upstream population exceeded 10,000. As the loads of all the upstream
329 STPs were aggregated, the respective differences from the *domestic* scenario were averaged
330 out.
331
332 3.2 **Model validation by measurement**
333 3.2.1 **Contrast media**
334 As explained above, the *all beds* scenario was inappropriate for modeling ICM and
335 gadolinium (e.g., MPAF 3.0, RSD 469% for ICM, AC; Figure 3, and Tables S12 and S13).
336 Especially in the STP catchments of Rheinau and Schinznach-Bad, the *all beds* scenario
337 considerably overestimated the contrast media (PAF 11–55), because the catchments did not
338 have CT or MRI facilities. In contrast, the facility-specific scenarios showed better agreement
339 with the measured values (e.g., PAF 1.2–3.6 in *MRI beds*, AC) in those catchments.
340 The *domestic*, *CT beds* and *CT treatments* scenarios somewhat overestimated ICM in the STP
341 effluents (MPAF 1.5–2.5, AC; Figure 3a), although the magnitude of overestimation was not

markedly higher than the base model uncertainty. The observed overestimation may have partly derived from the uncertainties of consumption numbers and/or the varying elimination rates of ICM in the STPs. The reported elimination of ICM varied largely (e.g., 0–90% for iopromide), possibly due to varying sludge age and/or degree of nitrification.[20,41-43] In our model, an average elimination rate of 40% was assumed (Table 2). Among the scenarios, *domestic* had an MPAF closest to 1, with the largest R^2 value (Figure 3a), but the deviation from the measured values was found to be large (PAF 0.27–7.7). In contrast, the *CT beds* and *CT treatments* scenarios in AC showed smaller RSD values, and deviated less from the measured values (PAF 0.48–5.8). Among the sampled STPs, four catchments showed relative changes of greater than 2 in *CT beds*, AC. The *domestic* scenario underestimated the measured values in two of these catchments (PAF 0.27 and 0.48 in *domestic*, against 0.82 and 1.1 in *CT beds*), and *CT beds* overestimated them in the other two (PAF 2.5 and 4.6, respectively, against 1.2 in *domestic*).

In the case of gadolinium, the mass flows predicted by the *MRI beds* and *MRI treatments* scenarios, AC, agreed better with the measured STP effluent mass flows (MPAF 0.79, RSD 152%, R^2 0.93 in *MRI beds* and 1.0, 99%, 0.96 in *MRI treatments;* Figure 3b) than those of the *domestic* scenario (0.56, 323%, 0.71). The advantage of the *hospital* scenarios was clearly demonstrated in the case of gadolinium, probably because predictions of gadolinium showed the largest difference among scenarios (due to the large HF), and because uncertainty in the elimination rate was very small owing to gadolinium's high persistence during conventional sewage treatment processes.[38] Five measured STP catchments exhibited relative changes of greater than 2 in *MRI beds* (AC). The *domestic* scenario underestimated the measured values in four of these catchments (PAF 0.13–0.37 in *domestic* against 0.55–2.4 in *MRI beds*). In the remaining STP, Langnau (indicated in Figures 3, S14 and S15), the catchment's PAF was better in *domestic* (0.88) than in *MRI beds* (4.0), and the ICM values were also predicted

367 better by the *domestic* scenario. In this catchment, CT and MRI facilities were only installed
368 two months before the sampling campaign, and therefore usage of contrast media was
369 probably still low, which may explain the overestimation by the *hospital* scenarios.
370 In three catchments where the treatment numbers were all actual numbers, the respective PAF
371 values for *MRI treatments*, AC (0.59, 0.75 and 0.81), were similar to those for *MRI beds*, AC
372 (0.79, 0.55 and 0.61). In five catchments where all the treatment numbers were estimated,
373 *MRI treatments* (AC) predicted well compared to the catchments with actual treatment
374 numbers, but showed greater variation (PAF 0.99–2.8, median 1.6).
375 More catchments exhibited over- or underestimation in HC than in AC, for both ICM and
376 gadolinium (Figures S14 and S15), which shows that the assumed HF_{hc} was too large.
377 In rivers, the contrast media were predicted well by both bed-specific scenarios and
378 treatment-specific scenarios in AC (e.g., MPAF 1.8, RSD 32%, R^2 1.00 in *CT beds*; and 0.67,
379 38%, 1.00 in *MRI beds*; Figures S14 and S15).
380
381 3.2.2 **Other pharmaceuticals**
382 The predictions for the other pharmaceuticals in AC did not differ much among scenarios, and
383 mostly agreed with measured loads (within a factor of 2), both in the STPs and rivers (Figures
384 S16–S19, Tables S12–S15). Interestingly, however, for cyclophosphamide, sulfamethoxazole,
385 carbamazepine and diclofenac, the *all beds* scenario generally predicted better than *domestic*
386 and *general beds* in the STP catchments where psychiatric and/or rehabilitation hospitals
387 accounted for more than half of the total hospital beds (e.g., in STP Rheinau, for
388 cyclophosphamide, PAF 0.93 in *all beds*, compared with < 0.46 in the other scenarios). This
389 suggests that the special types of hospital discharged these pharmaceuticals, unlike the
390 contrast media, at rates similar to general hospitals. Overall, these results suggest that
391 incorporating hospitals as point sources is important in catchments with high B_{1000}, even for

compounds with small HF; and that great care should be taken when estimating pharmaceutical discharges from small catchments with high B_{1000}.

4. DISCUSSION

4.1 **Parameters and scenarios**

Our results showed that, in a large proportion (> 95%) of both STP effluents and rivers in Switzerland, the predictions of the *hospital* scenarios did not differ much from those of the *domestic* scenario (e.g., relative change < 1.5). In a few percent of catchments and rivers, however, the difference from the *domestic* became larger, and the *hospital* scenarios showed greater predictive accuracy. For example, in the *all beds* scenario, with HF = 0.3, the largest relative change was 7.2, and the relative change exceeded 2 in 24 of the STP catchments, serving 2.1% of the national population (158,000). The magnitude of the difference from *domestic* values depended on B_{1000} and HF (see also S5 and Figure S20 for theoretical explanation). HF is the most critical model parameter in determining the allocation of pharmaceuticals between hospitals and households; the other parameters, such as excretion and elimination, have no effect on this allocation. The large impact of HF variation on the model predictions was demonstrated by the two cases, AC and HC. With a large HF of 0.8, the change relative to the *domestic* scenario could reach 22. Nevertheless, the agreement between the modeled and measured loads was generally better when HF was set at half of HF_{dis} or less. This shows that a significant fraction of pharmaceuticals dispensed within hospitals were discharged outside the hospitals, and that HF is therefore meaningful only if it is reduced from HF_{dis} by the appropriate portion of outpatients (see Section 2.1). It should also be noted that, even for general pharmaceuticals with small HF, the relative change can be large in catchments with high hospital bed density, where the *hospital* scenarios predict better than the *domestic* scenario (see 3.2.2). The hospital bed density can vary widely (e.g., up to 21

417 times the national average in Switzerland; see S2), often owing to the presence of special
418 hospital types (e.g., psychiatric or rehabilitation hospitals). In this study, these special types of
419 hospital were, like general hospitals, found to be the sources of many general
420 pharmaceuticals, favoring the *all beds* scenario. On the other hand, in the case of
421 pharmaceuticals used for specific treatments (i.e., in this study, ICM and gadolinium), the *all*
422 *beds* scenario should not be applicable, and the relevant hospitals must be distinguished in
423 bed-specific or treatment-specific scenarios. For such pharmaceuticals, bed-specific scenarios
424 are typically more reliable than treatment-specific scenarios, because (as in the present study)
425 bed numbers and occupancy are far more easily accessed and have smaller uncertainties in
426 estimation than treatment numbers. In the cases where treatment numbers were available in
427 this study, however, the measured values agreed as well with the predictions of the
428 treatment-specific scenarios as they did with those of the bed-specific scenarios.
429 The data used for the *hospital* scenarios can change over time, although typically not rapidly
430 (e.g., 2% annual change in Switzerland; see S3). Thus, these data would need to be updated
431 regularly (e.g., every few years). In the case of pharmaceuticals used for specific treatments
432 (e.g., ICM, gadolinium), information such as the establishment or abolishment of
433 corresponding facilities must be updated; otherwise, the discharge from hospitals may be
434 significantly over- or underestimated.
435

436 4.2 **Applicability**

437 Through the comparison of different scenarios, our study revealed the relationship between
438 spatial resolution, model complexity and predictive accuracy. At low spatial resolution (e.g.,
439 large river-catchments), the difference between scenarios was very small for all the
440 pharmaceuticals tested, as shown in the results of rivers with large upstream population. In
441 contrast, at high spatial resolution (e.g., STP catchment or small river-catchments), the

442 difference was larger, and the *hospital* scenarios showed good predictive accuracy (e.g.,
443 within a factor of 2). In this case, the *domestic* scenario could produce discrepancies of up to
444 1 order of magnitude.
445 Therefore, at low spatial resolution, the *domestic* scenario is a simple and efficient model for
446 predicting the distribution of a diverse range of pharmaceuticals. Incorporating geo-referenced
447 STP and pharmaceutical consumption data, the *domestic* scenario is suitable for identifying
448 potential river catchments of concern in a large geographical area (e.g., at the national or
449 regional level). Our results suggest that other, population-based models for predicting the
450 discharge of domestic-use compounds (e.g., carbamazepine and diclofenac)[31-33] can also
451 accurately predict hospital-use pharmaceuticals on the scale of large catchments of rivers.
452 In contrast, the *hospital* scenarios can be used most effectively at high spatial resolution.
453 These scenarios additionally incorporate geo-referenced hospital data; information on hospital
454 type, bed number and bed occupancy; and HF. Therefore, the *hospital* scenarios are most
455 suitable for the detailed evaluation of smaller regions of interest (e.g., at the county or
456 prefectural level), or catchments of particular rivers, where the related data-collection efforts
457 are justified. Large relative changes (vs. the *domestic* scenario) were found mostly in
458 suburban STPs and small rivers with high catchment B_{1000}. Nevertheless, large cities also
459 tended to have a relatively high B_{1000}, and thus significant relative change (up to 3). Therefore,
460 the *hospital* scenarios are also useful for urban STPs and their adjacent receiving waters.
461 Through field measurement, we validated our scenarios in STP catchments of various sizes
462 (1300–52,000 population). In both the *hospital* scenarios and *domestic* scenario, the predictive
463 uncertainty was less than the uncertainty in the approach of Al Aukidy et al.[8] (e.g., 2–3 orders
464 of magnitude), who used measurement-derived concentrations from the literature instead of
465 hospital consumption data. This demonstrates a significant advantage of our
466 consumption-based approach. To further improve the model's predictive accuracy, the input

467 data that were here assumed to be geographically and temporally constant (for model
468 simplicity and wide applicability) may be refined; for example, as suggested in Coppens et
469 al.,[33] by incorporating variability in consumption depending on geographic, climatic, seasonal
470 and/or socio-cultural conditions; varying the elimination of pharmaceuticals according to
471 varying sewage treatment methods; and incorporating environmental attenuation in rivers.
472 Interestingly, a similar approach, in this case using pharmaceutical consumption and animal
473 production, was proposed for predicting the discharge of veterinary antibiotics.[44]
474

475 4.3 **Implications for pharmaceutical discharge reduction and risk assessment**

476 In this study, the predicted contribution of hospitals to the total discharge at a single STP was
477 up to 92% for gadolinium (*MRI beds* scenario, AC), 82% for ICM (*CT beds*, AC), and 55%
478 for cyclophosphamide (*all beds*, AC). For catchments with such a large hospital contribution,
479 on-site treatment of hospital effluents[40,45] would be efficient in reducing pharmaceutical
480 discharge from STPs, reducing losses into the environment through sewer leakage[46] and
481 combined sewer overflows,[47] and preventing hospital wastewater-derived pathogens and
482 antibiotic multiresistant bacteria[4] from entering the environment.
483 Pharmaceutical concentrations in rivers can vary a great deal, as the predictions here reveal;
484 and in some rivers may be higher than has previously been determined. For example, in the
485 *CT beds* scenario here, a range of 0.2 ng/L to 40 μg/L (AC) and 58 μg/L (HC) was predicted
486 as the sum of the seven modeled ICM concentrations; whereas in German rivers, the
487 measured sum of several ICM was only a few μg/L.[16,43] Therefore, the *hospital* scenarios may
488 be useful for revealing such hotspots, as well as for evaluating real and potential
489 environmental impacts, and for devising countermeasures.
490

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SUPPORTING INFORMATION AVAILABLE

Details of hospital data acquisition and uncertainty, information on the STPs and rivers for field measurements, methods of sampling and analysis, QA/QC, and all results of predictions, measurements and model validation. This information is available free of charge via the Internet at http://pubs.acs.org.

FIGURES AND TABLES

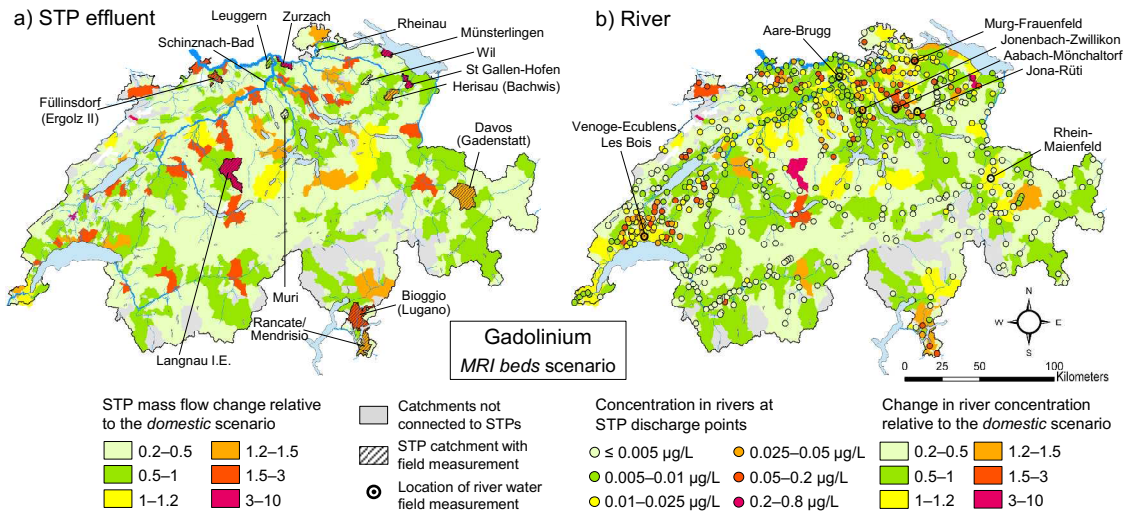
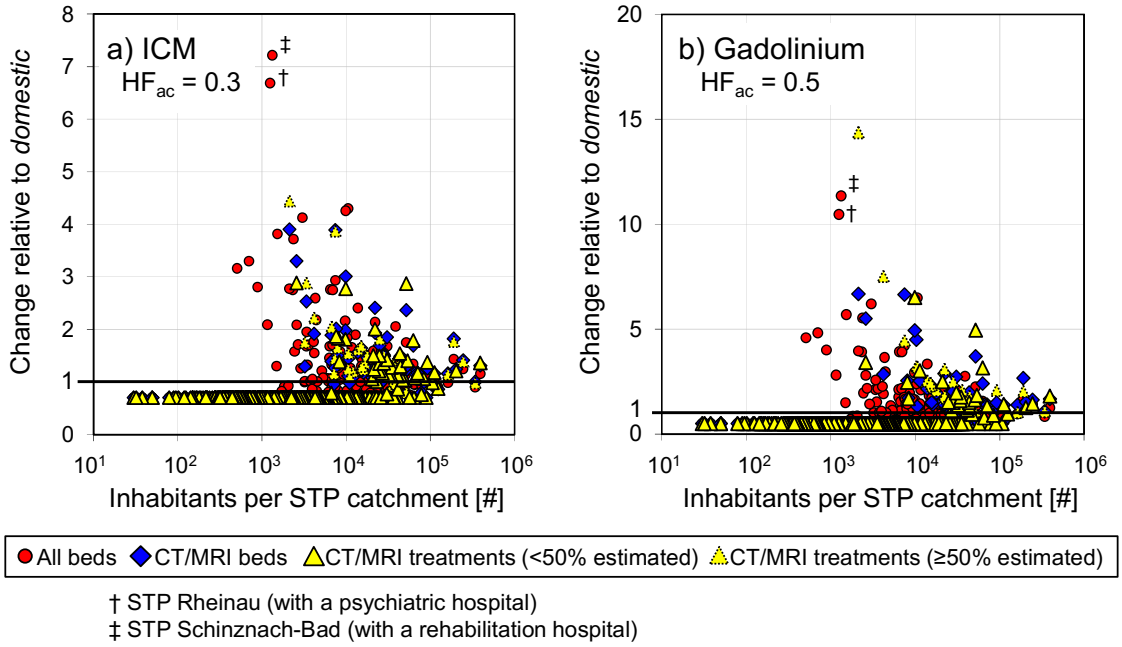


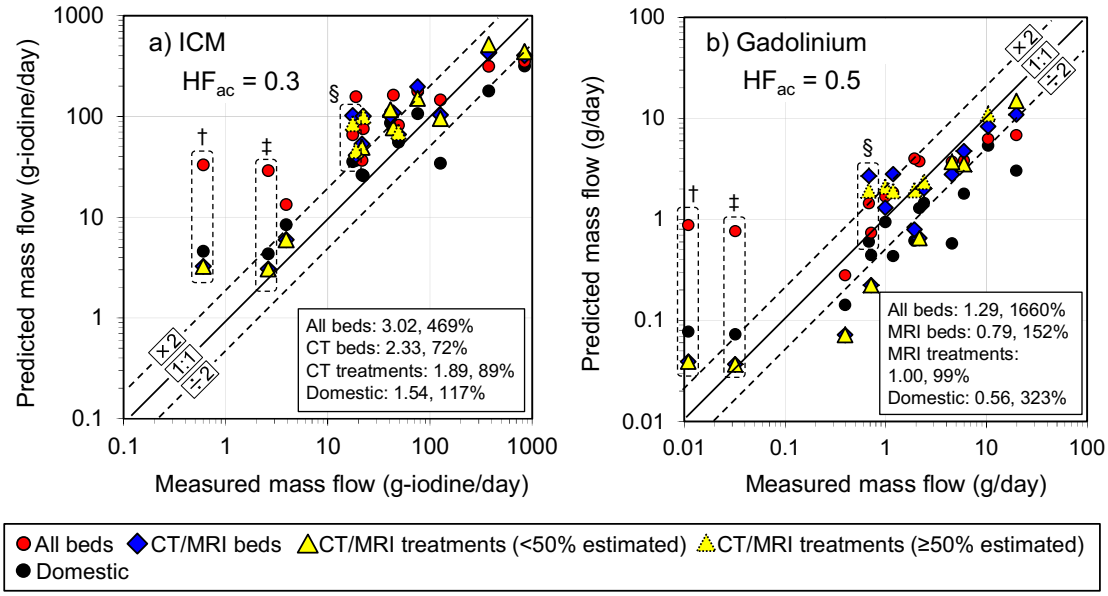
Figure 1. Predicted geographical distribution of gadolinium for (a) mass flow in STP effluents and (b) concentration in rivers. Gadolinium mass flow and concentrations are predicted by the *MRI beds* scenario (AC). The mass flow in STP effluents is shown as the change relative to the *domestic* scenario, using different colors for designated STP-catchment areas. For the rivers, the concentration change relative to the *domestic* scenario is shown using different colors for designated STP-catchment areas, and the predicted concentrations at the STP discharge points are indicated by different colored dots. The field measurement locations are also indicated, for both STP catchments and river waters.



535

536 **Figure 2.** The mass flow of (a) ICM and (b) gadolinium in STP effluents, relative to
537 catchment size, as predicted by the different *hospital* scenarios (average case). The mass flow
538 is shown as the change relative to the *domestic* scenario. Data of *CT treatments* and *MRI*
539 *treatments* are shown separately according to the ratio of the estimated treatment number (<
540 50% and ≥ 50%) to the total treatment number in each catchment (see Table S6 for the data).

541



† STP Rheinau (with a psychiatric hospital)
‡ STP Schinznach-Bad (with a rehabilitation hospital)
§ STP Langnau (CT and MRI were installed recently)

542

543 **Figure 3.** Comparison between the measured mass flow and the modeled flow of (a) ICM and
544 (b) gadolinium in STP effluents in different scenarios (average case). Data of *CT treatments*
545 and *MRI treatments* are shown separately according to the ratio of the estimated treatment
546 number (< 50% and ≥ 50%) to the total treatment number in each catchment (Table S4). The
547 MPAF and its RSD in each scenario are also shown in the figures.

548

549 Table 1. Scenarios.

scenarios	HF	distribution of pharmaceuticals
hospital scenarios		
all beds	HF_{ac} / HF_{hc}	the consumption allocated to hospitals is distributed over all hospital beds
general beds	HF_{ac} / HF_{hc}	the consumption allocated to hospitals is distributed over the beds in the general hospitals (hospitals excluding psychiatric hospitals and rehabilitation hospitals)
bed-specific scenarios: *CT beds* *MRI beds* *oncology beds*	HF_{ac} / HF_{hc}	the consumption of contrast media/cytostatics allocated to hospitals is only distributed over the beds of hospitals with their relevant departments, respectively (CT, MRI and oncology department)
treatment-specific scenarios: *CT treatments* *MRI treatments* *chemotherapy*	HF_{ac} / HF_{hc}	the consumption of contrast media/cytostatics allocated to hospitals is distributed over the number of respective treatments (CT, MRI and chemotherapy)
domestic scenario		
domestic	0	all the consumption is distributed over the population

550

551

552

553

Table 2. Parameters used for modeling ICM, gadolinium, cyclophosphamide and sulfamethoxazole.

compound	ICM (as iodine)[a]	gadolinium	cyclophosphamide	sulfamethoxazole
pharmaceutical group	contrast media	contrast media	cytostatic	antibiotic
total consumption in Switzerland (kg/year)[b]	16,064[c]	157[d]	28	2427
hospital-dispensed fraction (HF_{dis})[e]	0.58	1	0.68	0.17
effective hospital fraction, average case (HF_{ac})[f]	0.3	0.5	0.05	0.03
effective hospital fraction, high case (HF_{hc})[g]	0.5	0.8	0.34	0.17
excretion rate (combined for urine and feces)	0.97	1	0.2	0.45
elimination in STP	0.40	0	0	0.65
Scenarios				
all beds	X	X	X	X
general beds				X
CT beds	X			
CT treatments	X			
MRI beds		X		
MRI treatments		X		
oncology beds			X	
chemotherapy			X	
domestic	X	X	X	X
literature for excretion/elimination	[1] / *h*	[38] / [38]	[48] / [48]	[29] / [29, 49]

[a] Total iodine content of 7 ICM (diatrizoate, iobitridol, iohexol, iomeprol, iopamidol, iopromide and ioxitalamic acid).

[b] According to 2009 consumption data from IMS Health (Danbury, CT, USA).

[c] Iodine content of 7 ICM was calculated using confidential 2009 consumption data (information courtesy of Bayer HealthCare Pharmaceuticals (Berlin, Germany), Bracco (Milano, Italy), and Guerbet (Villepinte, France)).

[d] Gadolinium consumption in Switzerland was not known, and thus was extrapolated from the consumption in the hospital in Baden (3.1 kg, total 6728 MRI treatments) to all of Switzerland (340,376 MRI treatments).

[e] Ratio of pharmaceuticals dispensed inside hospitals to total consumption, calculated by sales data from IMS Health (Danbury, CT, USA).

[f] Outpatient-adjusted ratio of pharmaceuticals dispensed inside hospitals to total consumption (average case).

[g] Outpatient-adjusted ratio of pharmaceuticals dispensed inside hospitals to total consumption (high case).

[h] References[16,20,40-43,50]. Excretion and elimination of iobitridol was assumed to be similar to the other ICM, as no relevant literature was available.

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