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MODELLING DAILY AND HOURLY LOADS OF PHARMACEUTICALS IN URBAN WASTEWATER

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ABSTRACT

Pharmaceuticals are known contaminants of the environment. Assessing and managing the risk associated to this contamination has become an important field of study in environmental sciences. Accurately sampling and measuring pharmaceuticals concentrations in wastewater or in the environment is still costly and difficult. Thus only a few studies have looked at the temporal variability of the concentrations. In parallel, models have been proposed to predict the occurrence of pharmaceuticals. They usually assume that the loads of pharmaceuticals entering a wastewater treatment plant (WWTP) are proportional to the pharmaceuticals sales. However, most of the time, the results are difficult to interpret. The main problem with those models is the lack of data at WWTP. In this context, a stochastic model predicting daily and hourly loads is proposed to better understand the processes influencing the occurrence of pharmaceuticals in wastewater. Using accurate statistical pharmaceutical sales data, the mass consumed daily in the catchment is randomly picked from empirical probability density functions. Then, patients are randomly generated until the picked total mass is reached. For each patient, posology, metabolism and excretion rates of pharmaceuticals to the sewer system are randomly generated according to relevant literature data. In particular, time-use data are used to generate the time-use of patients to pick the times when patients consume pharmaceuticals and also when they excrete them in toilets. Applied to 9 molecules in a French catchment, results show that the model accurately and reliably predicts both the daily and hourly loads of pharmaceuticals at the inlet of the WWTP.

KEYWORDS

Stochastic modelling; Individual behaviour; Pharmaceuticals sales; Excretion rates

1. INTRODUCTION

The presence of pharmaceuticals in the environment has been established since the seventies (Garrison *et al.*, 1976; Hignite and Azarnoff, 1977). Since then, they have been detected in all types of water body and everywhere on the planet, and the state of risk assessment of pharmaceuticals in the environment has been abundantly reviewed (Halling-Sørensen *et al.*, 1998; Kümmerer, 2000; Heberer, 2002; Enick and Moore, 2007; Kümmerer, 2009; Santos *et al.*, 2010; Li, 2014; Kümmerer, 2016; Ebele *et al.*, 2017; Yi *et al.*, 2017). However, measuring concentrations of residuals of pharmaceuticals in waters is still a complex task that requires, as for other emerging pollutants, a lot of time, money and expertise. As a consequence, both temporal and spatial variability of concentrations is not well studied. Only a few studies performed state of the art repetitive measurements to study seasonal variations (Coutu *et al.*, 2013a; Ort *et al.*, 2014; Santos *et al.*, 2009; Sari *et al.*, 2014) or infra-day variations (Coutu *et al.*, 2013b; Joss *et al.*, 2005; Li and Zhang, 2011; Managaki *et al.*, 2008; Plósz *et al.*, 2010). They show that concentrations and loads of pharmaceuticals in wastewater are very variable at daily and infra-day scales and may show a seasonal dynamics.

Most of the models dealing with concentrations and loads of pharmaceuticals in wastewater are based on very similar concepts (Heberer and Feldmann 2005; Liebig *et al.*, 2006; Carballa *et al.*, 2008; Mullot, 2009; Besse, 2010; Perazzolo *et al.*, 2010; ter Laak *et al.*, 2010; Vystavna *et al.*, 2010; Zhang and Geißen, 2010; Le Corre *et*

al., 2012; Oosterhuis *et al.*, 2013; Ortiz de García *et al.*, 2013; Celle-Jeanton *et al.*, 2014; Herrmann *et al.*, 2015; Singer *et al.*, 2016). They usually assume that the mass of pharmaceuticals that reaches the WWTP or the environment is proportional to the mass of pharmaceuticals sold on the same catchment. However, comparison of predicted and measured pharmaceuticals loads or concentrations is difficult to interpret (Pouzol, 2018). Indeed, from one molecule to another and from one study to another, the ratios of predicted over measured pharmaceuticals loads or concentrations indicate either underestimation or overestimation over a great range of values. These results are mainly due to three factors: i) the lack of local detailed sales data (poor spatial and temporal resolution and lack of details), ii) insufficient and/or improper local monitoring campaigns to account for the great variability of loads and concentrations, and iii) fuzzy model parameters (for example, from one study to another the excretion rates of pharmaceuticals can significantly differ). The difficulty lies in the fact that the occurrence of pharmaceuticals is highly variable, and such variations cannot be acknowledged by means of a simple proportional model. Processes change from one person to another. Sales and loads in wastewater are also highly variable in space and time as well as consumption of purchased pharmaceuticals by inhabitants. Despite these difficulties, the authors acknowledge the importance of modelling and point out the limitations of their work.

However, different or more refined models are possible. Schowanek and Webb (2002), Götz *et al.* (2013) and Oldenkamp *et al.* (2016) for example proposed models that investigate the spatial variability of pharmaceutical occurrence alongside rivers or across Europe. Various scales of temporal variations have also been modelled: long term variability linked to demographic evolution (Tränckner and Koegst, 2010), seasonal (Marx *et al.*, 2015), daily (Gernaey *et al.*, 2011; Snip *et al.*, 2014) and hourly (Coutu *et al.*, 2016) variability.

The main objective of the research presented in this paper is to explore the possibility to simulate the daily and hourly loads of pharmaceuticals, and their variability, measured in a combined sewer system during dry weather days by developing a conceptual model accounting for the assumed most important processes from pharmaceuticals sales to excretion and transport. The model is based on i) previous modelling works published in the literature and ii) large data sets collected in a French catchment including detailed information on local sales of pharmaceuticals, inhabitants' census and time-use data, and results of *in situ* monitoring campaigns. The intent is to propose a plausible and explanatory model structure based only on prior information and data without *ad hoc* calibration and to evaluate its performance in comparison with more simple proportional models. At this stage, the model is considered as a way to structure knowledge and data, a kind of proof of concept, and not a final operational tool.

2. MATERIALS AND METHOD

2.1 Experimental site and data

The data from the experimental catchment of Bellecombe, France were used for model development and assessment. The Bellecombe catchment is located in France near the French-Swiss border. It has been studied since 2012 by the SIPIBEL, IRMISE Arve aval and SIPIBEL-RILACT research projects (Lecomte, 2016; Bertrand-Krajewski, 2018 – see also www.sipibel.org). In 2012, 30 000 inhabitants lived in the catchment (INSEE, 2012). As there are no significant tourism infrastructures and a negligible proportion of secondary houses, the population is stable through the year. It can be divided in three groups: 48 % are working adults (14 500), 28.4 % are non-working adults (retired, unemployed and others) and 23.6 % are children or students (INSEE, 2012). However, there are only 7 000 jobs identified in the catchment. This means that there is a huge variation in the number of people present through the day in the catchment, mainly due to the proximity of Switzerland which attracts many transboundary French workers.

According to local data (RDA74, 2010), out of the 30 000 inhabitants of the Bellecombe catchment, only 16 000 are connected to the sewer network. The sewer network is spread over 130 km², and includes 230 km of small circular pipes (< 0.5 m diameter). It is unmeshed but there are 29 pumping stations with pressurized pipes to overcome elevation differences (Figure 1). For the model, the catchment and its sewer system have been described in a simplified way. The individual households in the various municipalities across the catchment are

grouped as 18 “main source area” elements, keeping their geographical extension and distribution. Thus, only the main pipes (49.6 km) and 8 main pumping stations of the sewer network are described in the model.

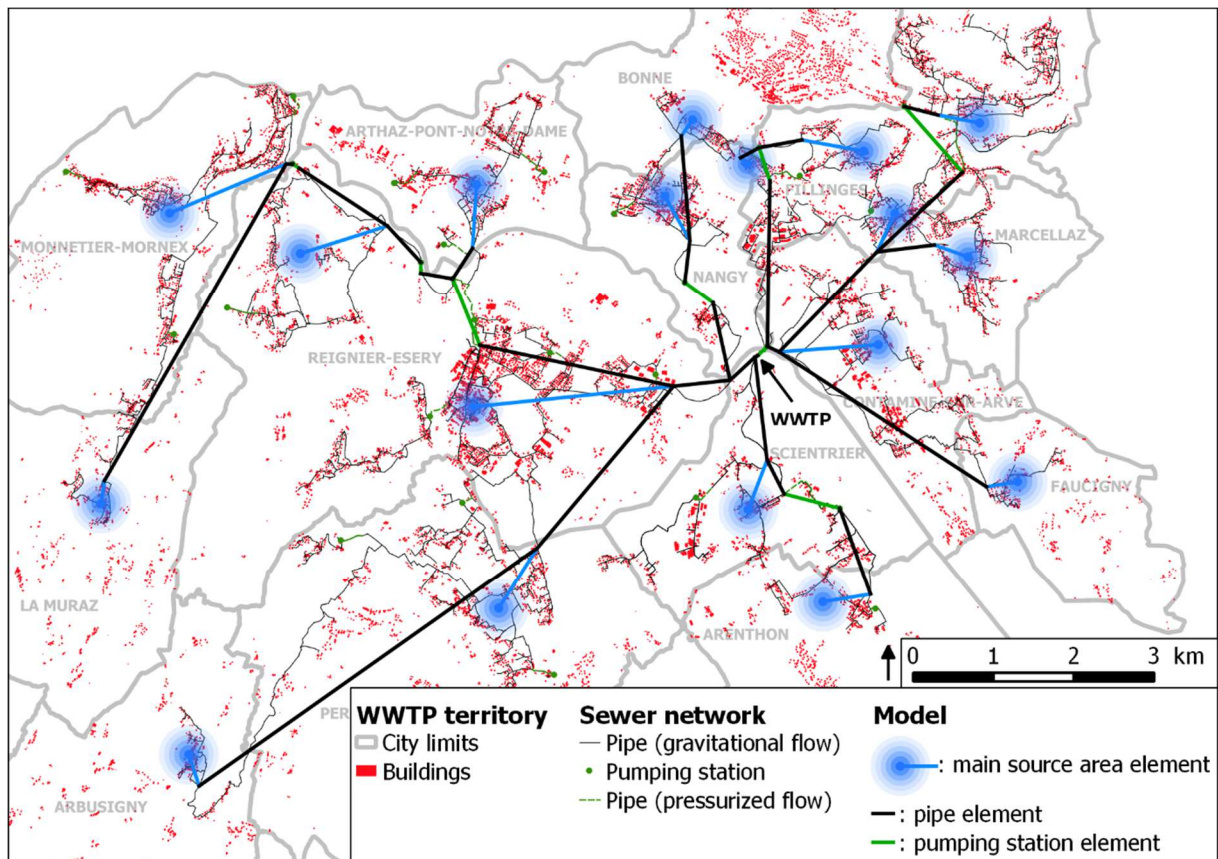


Figure 1: Bellecombe catchment with a representation of its hydraulic model. Main source area elements are a generic structure that distributes wastewater sources alongside a pipe to mimic the dispersion of households in the 14 municipalities of the catchment.

Pharmaceuticals sales data have been bought to IMS-Health, a census company in the pharmaceutical industry. Their data are grouped by package type (for example 12 tablets of 500 mg of paracetamol), thus being brand free. Grouped monthly sales for 2.5 years starting on January 2012 were obtained for the six pharmacies located in the Bellecombe catchment and also for all the pharmacies in Haute-Savoie (French administrative area with 790 000 inhabitants in 2013, with 223 pharmacies according to French Chamber of Pharmacists (2017) including the six of Bellecombe). The Haute-Savoie data allows to estimate the representativeness of the Bellecombe catchment.

Pharmaceuticals loads in wastewater have been monitored at the inlet of the WWTP as part of the SIPIBEL project. 15 molecules were selected for their potential risks towards the environment and human health and the possibility to be analysed with a multi-residue analytical method (Lecomte, 2016). Only 9 molecules (see Table 1) were almost always quantified and are thus being used to test the model. Measurements were conducted on Tuesdays only, outside of holidays and were of two types: 1) 24 h average flow proportional sample (19 campaigns) and 2) 24 consecutives 1 h average samples (4 campaigns). The characteristics of the measurement campaigns are described in Pouzol (2018) and Lecomte (2016). They were based on French technical guidelines for micropollutants sampling and analyses (Aquaref, Cemagref, 2011). The quality of both the measurement chain and the results was systematically assessed by means of a set of quality performance indicators (sampling representativeness and coverage, blank samples, conditions of washing of all vessels and equipment, detection of outliers, maximum flow in the WWTP to ensure dry weather conditions, etc. – see Lecomte, 2016). Only measurements satisfying all quality criteria were selected and used in this study.

2.2 Model

The objective of the model is to predict daily and hourly pharmaceuticals loads and concentrations (dissolved fraction) in wastewater at the inlet of the WWTP. The model is run with a one minute time step and results are summed to give either daily or hourly values. Most of the processes that influence excreted pharmaceuticals loads (posology, metabolism...) cannot be easily deterministically predicted. As a result, the model needs to be stochastic to run a thousand of simulations (Monte Carlo method) from which the average dynamics of pharmaceutical loads in the catchment is derived and compared with measurements.

The model structure is composed of two main parts: Part 1 for the hydraulic model, and Part 2 for the consumption, metabolism, excretion and transfer of pharmaceuticals in the sewer network.

Part 1 represents wastewater discharges at the inhabitant level and the hydraulic routing of wastewater and its dissolved contaminants along the sewer network. This part of the model and its performance have already been published (Pouzol *et al.*, 2015) and are thus not detailed in this paper. The simulation of wastewater discharges by inhabitants is derived from two pre-existing models. Drinking water demands of a household can be predicted using time-use census data and domestic water uses data (Blokker, 2010). Wastewater discharges can be linked to drinking water demands (Eliás-Maxil *et al.* (2014)). The hydraulic routing of wastewater is modelled by combining a Muskingum model (Mac Carthy, 1940) for pipes and a simple storage and water balance model for pumping stations. The model successfully simulates wastewater flow at the inlet of the WWTP at a one minute time step (Nash-Sutcliffe Efficiency coefficient = 0.9).

Part 2 represents pharmaceuticals discharges at the inhabitant level. This part is the focus of this paper and is described hereafter.

The discharge of pharmaceuticals by an inhabitant depends on whether or not this inhabitant is consuming the pharmaceutical. If yes, three key processes have to be accounted for:

- the specific posology the inhabitant is applying,
- the metabolism of the inhabitant,
- the times at which the inhabitant is excreting into the sewer system.

Regarding posology, metabolism and excretion pattern, data published in the literature were analysed and used to propose sub-models for each of the above key processes. They are described in the following paragraphs. However, it is important to note that there is no available statistics on whether or not a person is consuming a pharmaceutical. The only available data are pharmaceuticals sales data.

Local pharmaceuticals sales data have been first processed to establish empirical probability density functions (pdf) of daily sales for each speciality. Then, for each run of the simulation, the total mass of each pharmaceutical consumed in one day by the population is randomly picked from the corresponding pdf. Each patient consumes a different daily mass of pharmaceuticals as posology may differ from patient to patient. Thus, it is not possible to directly determine the number of patients among the population corresponding to the daily mass of pharmaceuticals consumed on a given day. This is why the number of patients for each run is determined by means of individual posology patterns that are randomly generated according to medical literature and data until the daily total mass of pharmaceutical picked up previously is reached. In other words, for each run, i) a daily mass of pharmaceuticals is randomly generated, ii) individual posology patterns are randomly generated until the daily mass is reached, and iii) the number of patients is determined from the individual posology patterns, and iv) the patients are randomly distributed across the catchment with randomly generated individual time uses.

The pdfs of pharmaceuticals sales result from a combination of the two datasets: i) sales from the 6 pharmacies of the Bellecombe catchment and ii) sales from the Haute-Savoie area. Thanks to its much larger size, the Haute-Savoie data set provides a better estimation of the level of consumption, but the monthly dynamics is smoothed. Conversely, the Bellecombe data set shows significant monthly variations but the levels of consumption are hardly estimated since it is very difficult, if not impossible, to estimate the number of inhabitants really linked to the six pharmacies of the catchment. Indeed, the inhabitants of the Bellecombe

catchment do not necessarily buy their pharmaceuticals locally: they may buy them in other pharmacies located in supermarkets or commercial centres outside the Bellecombe catchment, e.g. near their working place. However, they will partly excrete their pharmaceuticals locally when they are at home. Reciprocally, inhabitants buying their pharmaceuticals in the 6 Bellecombe pharmacies may excrete them outside, like e.g. the numerous inhabitants working daily in Switzerland. In brief, there is no exact geographical correspondence between the areas of pharmaceuticals sales and pharmaceuticals consumptions and excretion. Available local data were not accurate enough to estimate the possible bias.

Consequently, the monthly sales of the 6 Bellecombe pharmacies are used to account for the local variability but after correction by means of a proportionality coefficient aiming to account for the levels of consumption of the whole Haute-Savoie area (the correction is an indirect way to account for the fact that, at very local geographical scale, the inhabitants of a given catchment do not necessarily buy their pharmaceuticals in the local pharmacies, as mentioned in the above paragraph). This proportionality coefficient F_{corr} is the same for all pharmaceuticals and is calculated as the weighted average of the ratios between the level of consumption in the Bellecombe catchment and in the Haute-Savoie area:

$$F_{corr} = \frac{\sum_{i=1}^N \frac{M_{Bi}}{M_{Hi}} \times M_{Hi}}{\sum_{i=1}^N M_{Hi}} = \sum_{i=1}^N \frac{M_{Bi}}{M_{Hi}} = 0.6079$$

with:

M_{Bi} , M_{Hi} : respectively, the total mass sold per capita per day for speciality i for Bellecombe and Haute-Savoie.

N : the number of specialities sold in both Bellecombe and Haute-Savoie.

The correction factor was evaluated with the coefficient of determination R^2 of the linear function $M_B = F_{corr} \times M_H$. R^2 was found to be equal to 0.998.

Table 1 indicates the mean values of the 9 pharmaceuticals sales and the corresponding estimated number of patients assuming that each patient applies the average daily posology. Mean values are given for simplicity, but in the model each run generates new values of daily mass and daily posology patterns.

Table 1: Estimated mass sold and number of patients for the Bellecombe catchment. For each molecule, the table indicates the average mass sold per day. The average daily posology assumed to be the defined daily dose (DDD) then allows estimating the number of patients corresponding to this average daily mass. The mass and number of patients corresponds to the 30 000 inhabitants of Bellecombe, and only half of them are connected to the sewer network.

Molecule	Average mass sold		Estimated number of patients (patients/day)
	(mg/day)	(mg/day /capita)	
Atenolol	26 563	0.88	354
Carbamazepine	34 082	1.14	34
Diclofenac	39 330	1.31	393
Ibuprofen	510 363	17.00	425
Ketoprofen	30 468	1.02	305
Paracetamol	4 345 642	145	1 449
Propranolol	12 166	0.41	76
Salicylic acid	458 302	15.27	153
Sulfamethoxazole	11 390	0.38	6

2.2.1 Posology

The dose, number and duration between pharmaceutical intakes are all randomly picked from plausible intervals (uniform pdf) found in the pharmacy literature. These intervals are specific for each pharmaceutical speciality. In order to simulate the intake times by a given patient, the time-use of each patient that is generated from time-use pdf to predict water uses is weighed according to the recommended posology of each speciality. Intake times are then randomly picked from this weighted time-use time series. The posology descriptions are either related to meals, for example “one pill during breakfast, lunch and supper”, or more diffuse, for example “when awake and not out of the house”. All posology descriptions are provided in Appendix A.

2.2.2 Metabolism

The human metabolism for pharmaceuticals is represented in the model by a three compartments system that can be interpreted as follow (Figure 2).

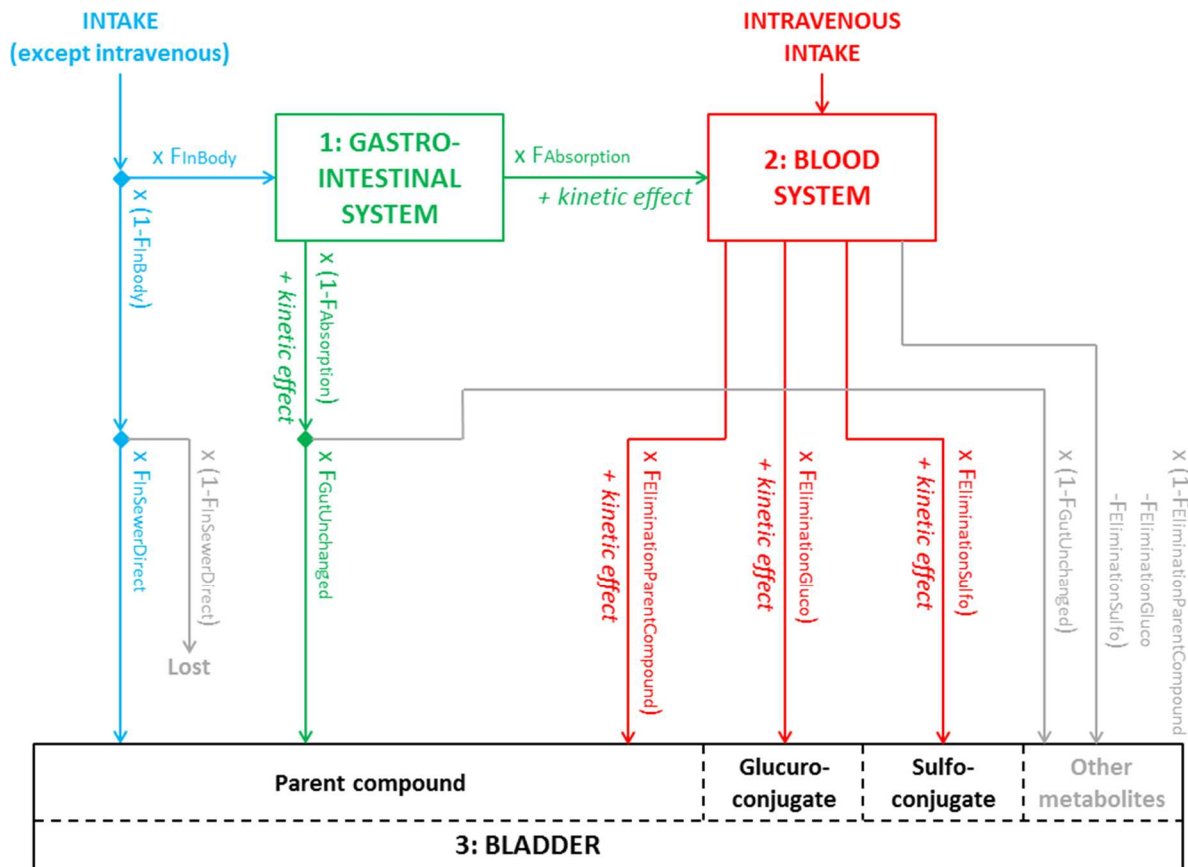


Figure 2: Metabolism diagram. Blue parts are related to the intake process. Green parts are related to the gastro-intestinal system. Red parts are related to the blood system. Grey parts are related to flux not accounted for by the model. Lastly, the black parts are related to the bladder. Whatever is in the bladder is considered ready for excretion. In reality, pharmaceuticals can be stored in other organs before excretion (like faeces). However, excretion via urine in bladder is predominant in most cases. To keep the model simple, the blue flux not entering the body is stored in the bladder even if it is not the case in reality. Glucuro-conjugates are accounted for but sulfo-conjugates are not taken into account.

When consuming an orally taken pharmaceutical, the dose enters immediately and entirely the gastro-intestinal system. From there, a fraction of it ($F_{Absorption}$) passes into the blood system over time. The kinetics is based on an exponential decay with a parameter $k_{absorption}$. The fraction that is not absorbed is partially metabolized ($F_{GutUnchanged}$) and then stored for excretion over time with the same kinetics as absorption.

In the blood system, the pharmaceutical is metabolized by the liver and, at the same time, filtered out to the bladder by the liver. As a result, the pharmaceutical is stored progressively for excretion in the bladder in both an unchanged form and as metabolites. The kinetics is based on an exponential decay with a parameter $k_{elimination}$. In our case, only one type of metabolite is included: glucuro-conjugates. The respective ratios of elimination for the parent compound and the glucuro-conjugates are noted $F_{EliminationParentCompound}$ and $F_{EliminationGluco}$.

All products reaching the bladder are considered ready for excretion.

Apart from oral products, the two most common types of products are intravenous and dermal products. For intravenous, the metabolism is the same as for oral products except that they enter directly into the blood system. Dermal products are more complex. A fraction of the consumed dose never enters the body (wiped or washed away). The fraction entering the body (F_{InBody}) can affect multiple tissues, however a simple interpretation of the three compartments model can be: superficial tissue, blood system and bladder. The fraction not entering the body is wasted and a part of it may reach the sewer system ($F_{InSewerDirect}$).

The metabolism equations are given in Table 2. The values of their parameters are given in Appendix B.

Table 2: Equations representing the metabolism. t : time (s); Δt : time step of the model (60 s); $GI(t)$: mass of pharmaceutical in the gastro-intestinal system at time t (mg); $k_{absorption}$, $k_{elimination}$: respectively the parameters for absorption and elimination kinetics (Δt^{-1}); $Intake(t)$: mass of consumed non-intravenous pharmaceutical at time t (mg); F_i : fraction i (InBody, Absorption, EliminationParentCompound, GutUnchanged, InSewerDirect, EliminationGlucos); $B(t)$: mass of pharmaceutical in the blood system at time t (mg); $IVIntake(t)$: mass of consumed intravenous pharmaceutical at time t (mg); $Bl_{PC}(t)$: mass of unchanged pharmaceutical in the bladder at time t (mg); $Bl_{GL}(t)$: mass of glucuro-conjugates in the bladder at time t (mg)

$$\begin{aligned}
 GI(t + \Delta t) &= GI(t) \times (1 - k_{absorption}) && \text{(exponential decay)} \\
 &+ Intake(t + \Delta t) \times F_{InBody} && \text{(oral intake)} \\
 \\
 B(t + \Delta t) &= B(t) \times (1 - k_{elimination}) && \text{(exponential decay)} \\
 &+ GI(t) \times k_{absorption} \times F_{Absorption} && \text{(absorbed fraction)} \\
 &+ IVIntake(t + \Delta t) && \text{(intravenous intake)} \\
 \\
 Bl_{PC}(t + \Delta t) &= Bl_{PC}(t) && \\
 &+ B(t) \times k_{elimination} \times F_{EliminationParentCompound} && \text{(eliminated fraction)} \\
 &+ GI(t) \times k_{absorption} \times (1 - F_{Absorption}) \times F_{GutUnchanged} && \text{(un-absorbed fraction)} \\
 &+ Intake(t + \Delta t) \times (1 - F_{InBody}) \times F_{InSewerDirect} && \text{(un-penetrated fraction)} \\
 \\
 Bl_{GL}(t + \Delta t) &= Bl_{GL}(t) && \\
 &+ B(t) \times k_{elimination} \times F_{EliminationGlucos} && \text{(eliminated fraction)}
 \end{aligned}$$

2.2.3 Excretion to the sewer network

The load of pharmaceuticals that accumulate in the bladder is discharged into the sewer network each time a patient goes to the toilet. These times are already simulated to predict wastewater discharges in the hydraulic part of the model, according to time-use statistics. However, if the patient is a working adult who works outside the catchment, toilet uses during “out of home” periods are not taken into account. This means that the daily variation of population in the catchment is taken into account for the prediction of loads. Due to lack of data, it is not possible to account for the fact that people taking pharmaceuticals are not following their usual time-use. However, it is suspected that this could be the case, especially for strong treatments with antibiotics.

2.2.4 Model outputs

For each simulation and for each pharmaceutical, 1000 runs are computed. All the following quantities are generated randomly and independently one from each other for each run: i) the daily mass of the pharmaceutical of interest, ii) individual daily posology patterns and the corresponding number of patients, iii) location of patients across the catchment conditioned by census statistics, iv) time use for each patient, v) metabolism parameters and iv) excretion into the sewer system. Then the excreted pharmaceutical load is transported along the sewer system by the hydraulic part of the model. After all runs are computed, mean values of outputs (daily or hourly values) at the outlet of the network are calculated for each simulation, along with quartiles, minimum and maximum values.

3. RESULTS AND DISCUSSION

3.1 Daily Loads

Results of daily loads simulations are shown in Table 3 and Figure 3. They are compared to *in situ* measurements at the WWTP inlet and also against a simpler proportional model based on Heberer and Feldmann (2005) which is described in Appendix D.

Table 3: Comparison of the measured and modelled daily loads.

Molecule	Average daily load (standard deviation) (mg/day)			Ratios of modelled over measured daily loads		Ratios of the coefficients of variation		Relative error (%)	
	Measurements	Stochastic model	Proportional model	Stochastic model	Proportional model	Stochastic model	Proportional model	Stochastic model	Proportional model
Atenolol	9 578 (2 319)	11 400 (520)	13 600	1.19	1.42	0.18	-	19	42
Carbamazepine	2 422 (639)	2 000 (220)	2 300	0.81	0.95	0.41	-	19	6
Diclofenac	3 030 (780)	5 000 (310)	2 300	1.64	0.76	0.23	-	64	24
Ibuprofen	33 043 (8 387)	57 000 (2 350)	68 000	1.73	2.06	0.16	-	73	106
Ketoprofen	5 376 (1 488)	11 800 (880)	14 400	2.19	2.68	0.26	-	119	167
Paracetamol	564 429 (192 844)	1 104 600 (27 680)	2 027 000	1.96	3.59	0.07	-	96	259
Propranolol	1 683 (487)	1 200 (110)	1 400	0.73	0.83	0.31	-	27	19
Salicylic acid	102 396 (56 090)	50 700 (2 290)	61 100	0.50	0.6	0.08	-	50	40
Sulfamethoxazole	1 709 (917)	2 000 (930)	3 400	1.17	1.99	0.83	-	17	99

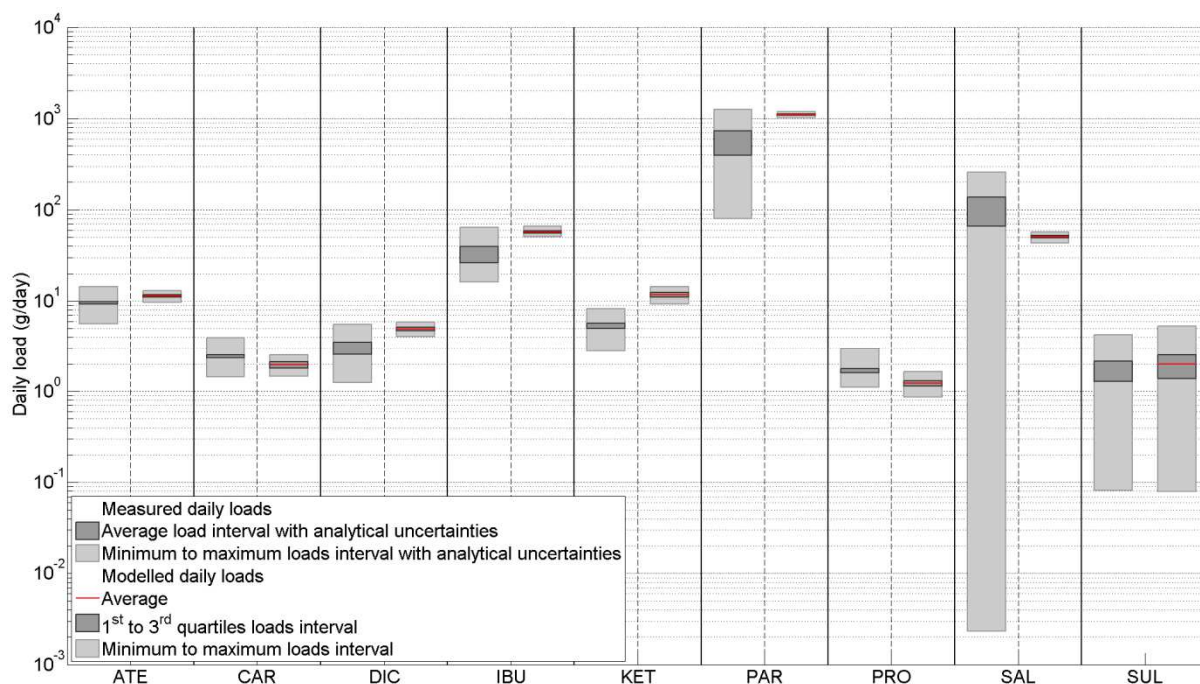


Figure 3: Modelled and measured daily loads for nine pharmaceuticals. For each pharmaceutical, there are two columns: the left box plot corresponds to the minimum, maximum and average measured daily loads with analytical uncertainties, the right one to the minimum, maximum, 1st to 3rd quartiles interval and average modelled daily loads.

Considering all uncertainties (related to sampling, analytical analyses, variability of pharmaceuticals sales and intakes, simplifications of the model, etc.), a ratio of modelled over measured daily loads between 0.5 and 2.0 is considered as a satisfactory model performance in this exploratory phase. This is the case for 8 of the 9 modelled molecules (Table 3, column 5). The less good performance for ketoprofen (ratio of 2.19) may be partly attributed to the fact that its metabolic parameters are not accurately known (range excreted as glucuro-conjugates from 66 to 95 %, Appendix B). In addition, ketoprofen and diclofenac are the only two molecules that are not sold only as oral forms: 17 % of ketoprofen and 53 % of diclofenac are used in dermal forms. As a consequence, their fractions directly discharged into the sewer (washing of hands and body, washing of clothes in contact with the molecules) are not well known and are poorly approximated by the model (from 25 to 75 %, Appendix B), which tends to over-estimates their daily loads.

Measurements shows that daily loads are highly variable with coefficients of variation mostly between 24 and 34 % (Table 3, column 7). The ratios of the coefficients of variation of modelled over measured daily loads indicate that the model is underestimating the dispersion of the daily loads, which is also evidenced in Figure 3. The fact that monthly sales data statistics (the best available information) are used to estimate daily loads pdfs can possibly explain a part of the variability underestimation.

The difference between modelled and measured loads can be attributed to many factors. A better estimation of pharmaceutical daily consumption and of its variability, a better description of human metabolism with well-defined parameters and accounting for potential physico-chemical processes transforming the molecules during their transfer along the sewer network (de-conjugation of metabolites, degradation, etc. – Bertrand-Krajewski *et al.*, 2018; Gao *et al.*, 2017; McCall *et al.*, 2016) would certainly help to produce more accurate results. In addition, in this exploratory phase, the model has not been calibrated: only prior values of pdfs and parameters were used to evaluate the capabilities of the model.

Compared to a simpler proportional model (i.e. excreted loads are proportional to sales), the proposed stochastic model performs better: more molecules (8 compared to 6) have ratios of modelled over measured daily loads within the 0.5 to 2.0 interval (Table 3 columns 5 and 6). The relative errors for the stochastic model are smaller than for the proportional model for 5 of the 9 modelled molecules (Table 3 columns 8 and 9). Also,

the average, minimum and maximum relative errors of all the molecules for the stochastic model are smaller compared to the proportional model. This indicates that the proposed stochastic model gives better results than the proportional one with the additional benefit of estimating loads variability. Apart from the stochastic nature of the proposed model, the main difference impacting the modelled daily loads is the consideration of the population dynamics during the course of the day (people leaving or entering the catchment to go to work).

3.2 Hourly loads

Only 4 experimental campaigns with hourly loads measurements are available. They show a highly variable dynamics of loads at the hourly scale, which makes difficult to estimate a reliable and representative average dynamic of hourly loads for the Bellecombe catchment.

As a result, using a normal version of the Nash-Sutcliffe Efficiency coefficient (NSE)(used to compare two time series) is not appropriate. A modification is proposed, the NSE_{fuzzy} . It integrates the stochastic nature of the developed model. For each molecule, the average of the NSE_{fuzzy} indicator calculated for each campaign is used. A score between 0.5 and 1 indicates a good fit of the model (possible values from $-\infty$ to 1). It is calculated as follows:

$$NSE_{fuzzy} = 1 - \frac{\sum_{t=1}^T (\tilde{L}_{measured}(t) - \tilde{L}_{fuzzy}(t))^2}{\sum_{t=1}^T (\tilde{L}_{measured}(t) - \bar{\tilde{L}}_{measured})^2}$$

$$\begin{aligned} \text{if } Q_1(\tilde{L}_{modelled}(t)) \geq \tilde{L}_{measured}(t) \text{ then } \tilde{L}_{fuzzy}(t) &= Q_1(\tilde{L}_{modelled}(t)) \\ \text{if } Q_3(\tilde{L}_{modelled}(t)) \leq \tilde{L}_{measured}(t) \text{ then } \tilde{L}_{fuzzy}(t) &= Q_3(\tilde{L}_{modelled}(t)) \\ \text{else } \tilde{L}_{fuzzy}(t) &= \tilde{L}_{measured}(t) \end{aligned}$$

With:

t : time

T : number of time steps in the simulation

$\tilde{L}_{measured}(t)$: normalized measured pharmaceutical hourly load at time t

$\tilde{L}_{fuzzy}(t)$: normalized modelled hourly load at time t for the NSE_{fuzzy} calculation

$\bar{\tilde{L}}_{measured}$: average normalized measured hourly load at time t

$Q_1(X)$, $Q_3(X)$: first and third quartiles of a vector of values X

$\tilde{L}_{modelled}(t)$: distribution of the normalized modelled hourly loads at time t

The results for all molecules are summarized in Table 4. For illustrative purposes, the hourly loads time series for ibuprofen and carbamazepine are given respectively in Figure 4 and Figure 5 in the main text; the seven other graphics are given in Appendix C.

Table 4: Average NSE_{fuzzy} and coefficients of variation of the modelled hourly loads time series.

Molecule	Average of the NSE_{fuzzy} for the 4 campaigns	Average coefficient of variation of the modelled hourly loads (standard deviation) (%)
Atenolol	0.18	29 (19)
Carbamazepine	0.19	51 (28)
Diclofenac	0.50	35 (16)
Ibuprofen	0.71	20 (9)
Ketoprofen	0.72	26 (12)
Paracetamol	0.53	31 (13)
Propranolol	0.65	19 (15)
Salicylic acid	0.45	39 (24)
Sulfamethoxazole	0.60	48 (23)

For seven of the nine modelled molecules, NSE_{fuzzy} values are close to or higher than 0.5 (Table 4, column 2), which indicates that the dynamics of hourly loads for these molecules is rather well simulated by the model (see Figure 4 for ibuprofen and also Appendix C for other molecules). This means that the main key processes governing the variability of hourly loads at the WWTP inlet are represented in the model. However, as the results are not perfect and still show some bias, it is likely that some other processes (e.g. in-sewer processes, inclusion of all metabolites and their possible chemical balances with parent molecules) or pdfs and parameters values should be respectively included or modified. For example, in Figure 4, the model underestimates the ibuprofen hourly loads during the night period between 1 and 5 a.m.

Atenolol and carbamazepine have lower NSE_{fuzzy} , respectively 0.18 and 0.19. The poor results for carbamazepine are mainly due to the fact that it is consumed by only a few patients every day: the mean daily load corresponds to only 11 DDD – Defined Daily Dose (i.e. mean posology), which means that the specific behaviour of each individual patient (among a population of 16 000 connected inhabitants) strongly impacts the hourly dynamics. Indeed, random looking isolated hourly peaks appear in the measurements of hourly loads (Figure 5), and with only four campaigns it is not possible to estimate the average dynamics of hourly loads. For comparison, the daily loads for ibuprofen (Figure 4) and paracetamol (Appendix C, Figure C-4)) correspond respectively to 213 and 725 DDD: when so many patients are excreting every day, it is easier to expect a more repeatable and smoothed daily profiles for hourly loads, which tends to look like daily profiles for basic pollutants like TSS (total suspended solids) or BOD5 (Biochemical oxygen demand). One random looking isolated hourly peak also appears in one of the atenolol measured hourly loads, which dramatically decreases the average NSE_{fuzzy} score (Appendix C., Figure C-1).

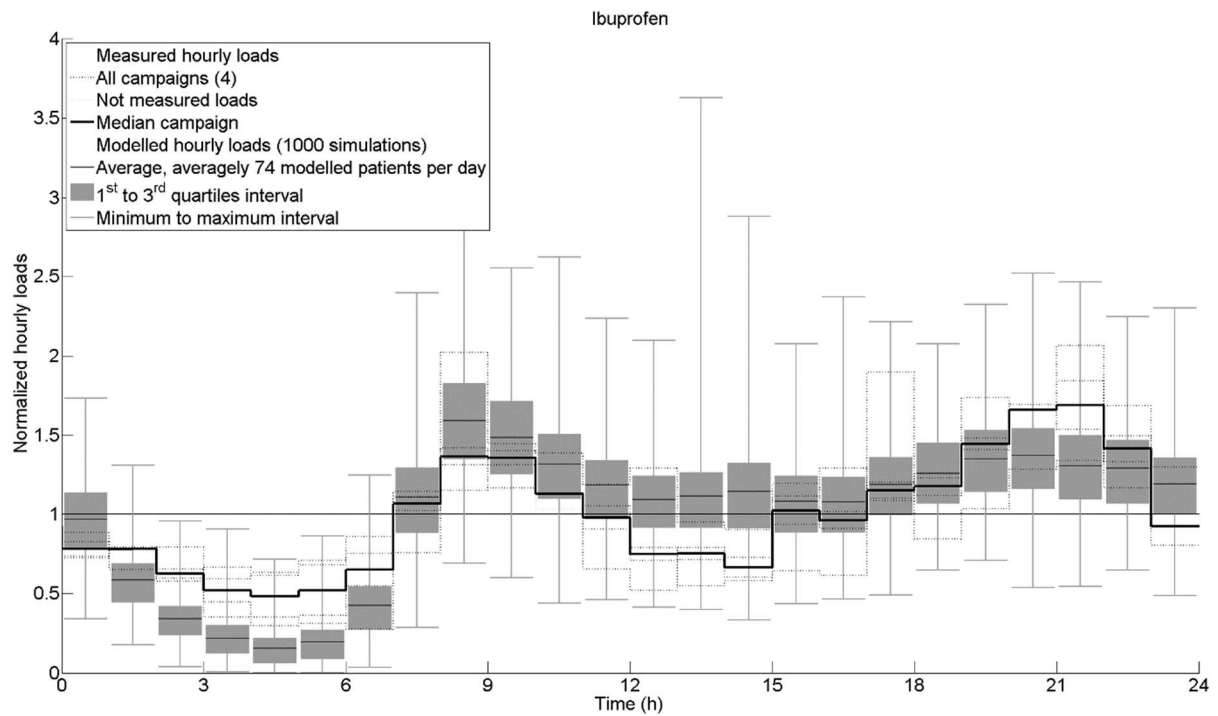


Figure 4: Comparison of the dynamics of the measured and modelled hourly loads of ibuprofen. All 4 measured campaigns are represented in dotted lines, and their median is represented by a thick black line. Modelled hourly loads are represented with boxplots (minimum, first quartile, third quartile and maximum values). The average modelled value is represented by a thin black line.

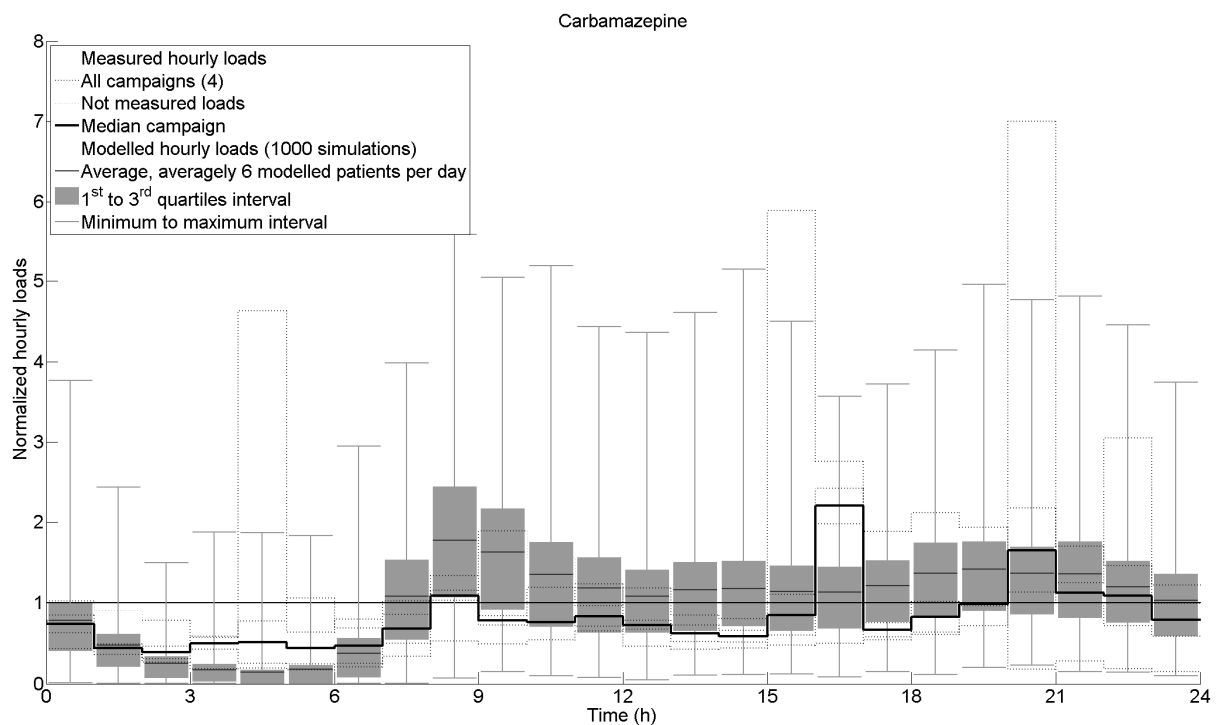


Figure 5: Comparison of the dynamics of the measured and modelled hourly loads of carbamazepine. All 4 measured campaigns are represented in dotted lines, and their median is represented by a thick black line. Modelled hourly loads are represented with boxplots (minimum, first quartile, third quartile and maximum values). The average modelled value is represented by a thin black line.

The average of the coefficients of variation of the modelled hourly loads calculated for each hour (Table 4, column 3) show that the dispersion of hourly loads is significant (19 to 51 %). This reinforces the fact that four hourly dynamic campaigns are not enough to analyse hourly dynamics of pharmaceuticals loads in a representative way.

As of today, it is not possible to compare the proposed model to other ones. The only model found in the literature that aimed to predict hourly loads of pharmaceuticals (Coutu *et al.*, 2016) does not provide any criteria to assess the model performance. However, it seems to give results with rather similar accuracy and performance compared with our proposed model.

4. CONCLUSIONS AND FUTURE WORK

A stochastic model is proposed to simulate daily and hourly loads of dissolved pharmaceuticals in wastewater at the outlet of a combined sewer system, based on available local data (statistics on inhabitants and population categories, on time-use of inhabitants, on pharmaceutical sales at local and regional scales) and literature review (key metabolism processes related to pharmaceuticals in the human body, kinetics of transformations and transfers, etc.). The model results have been compared to local daily and hourly measurements campaigns. Results show that the model is able to reliably reproduce the daily loads in the range 0.5 to 2 times the measured values, but under-estimates their observed variability. Compared to a more usual proportional model, it improves the average performance by one third while giving additional information. However, it requires much more data and expertise. The simulation of the dynamics of hourly loads also gives accurate results and satisfactory daily patterns, indicating that key processes are included in the model, even though it is challenged in cases where the pharmaceuticals are consumed by only a few patients in a catchment. It is also important to note that the model has been run directly with prior available values and statistical data, without *ad-hoc* calibration to fit parameters.

From this exploratory modelling phase, one may conclude that the model is able to represent the observations and their main patterns. Nevertheless, it is still not perfect and remains heavy to use by practitioners. This indicates two complementary main directions for future work.

The first direction is research oriented. The model should be tested with more pharmaceuticals to evaluate its capacities and on more sites to validate its genericity. This requires access to more data concerning both pharmaceutical loads, especially their variability at both daily and hourly scales, and pharmaceuticals consumption (links with sales, dynamics, variability, sold but unused pharmaceuticals, impact on time-use patterns...). In addition, some aspects and processes have not yet been included in the model, due to lack of data for comparison and testing. For example, some metabolites may play a significant role in the global mass balance, and in-sewer processes may change the balance between parent molecules and their metabolites, as observed with significant effect on concentrations under both aerobic and anaerobic conditions (e.g. Gao *et al.*, 2017; McCall *et al.*, 2017, Bertrand-Krajewski *et al.*, 2018). In the Bellecombe catchment, there are in total more than 30 pumping stations, some of them with long residence times in the pumping tank during low night flows. Storage in pumping stations for hours may change the equilibrium between parent molecules and their metabolites. Such in-sewer processes may play a significant role. This is why it was decided to not calibrate the model in this phase: tuning parameters may lead to improving results but simultaneously to masking the fact that some processes are ignored and thus giving an undue confidence in the model. Evaluating the added value of including such in-sewer processes in the model would be necessary. Then calibration of the model with a Bayesian approach to keep the stochastic nature of the model and of its results and parameter sensitivity analysis will be done.

The second direction is practice oriented. The model, in its present state, requires a lot of data that are heavy and expensive to collect. Some simplifications could be evaluated, e.g. using fixed posology patterns and time-use patterns, but local data on pharmaceutical sales will remain necessary to obtain locally pertinent results. At daily scale, the model may help to design and size micropollutants removal facilities in wastewater treatment plants thanks to a better knowledge of the incoming daily loads and of their variability. At hourly scale, the

model may help to estimate discharges of pharmaceuticals into the aquatic environment by combined sewer overflow events under rainy conditions.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDICES

APPENDIX A: Posology descriptions

Table A-1: Posology description for pharmaceutical specialities. Grey italic text indicates that the speciality is consumed at low levels (less than 0.1 % of the mass sold for the molecule). In such cases, it is not necessary to model the speciality. PI: pain increase option, increase chances at the end of day. DB, DL and DS: during breakfast, lunch or supper followed by its chances in percentage. Example: DB45 indicates that 45 % of the intakes occur during breakfast.

Speciality number	Name	Total dose (g)	Sub-dose (g)	Intake route	Speciality representation (%)	Posology description			
						Number of intakes (min –max)	Number per intake (min –max)	Duration between intakes (min –max) (h)	Time pattern
1	Atenolol, Oral 30 X 50mg	1.5	0.05	Oral	30.1	1 - 1	1 - 2	1 - 1	DB45 - DL10 - DS45
2	Atenolol, Oral 30 X 100mg	3	0.1	Oral	20.1	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
3	Atenolol, Oral 28 X 50mg	1.4	0.05	Oral	0.4	1 - 1	1 - 2	1 - 1	DB45 - DL10 - DS45
4	Atenolol, Oral 90 X 50mg	4.5	0.05	Oral	28.1	1 - 1	1 - 2	1 - 1	DB45 - DL10 - DS45
5	Atenolol, Oral 28 X 100mg	2.8	0.1	Oral	1.5	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
6	Atenolol, Oral 90 X 100mg	9	0.1	Oral	19.9	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
9	Carbamazepine, Oral 30 X 400mg	12	0.4	Oral	78.7	2 - 3	1 - 1	4 - 6	DB45 - DL10 - DS45
10	Carbamazepine, Oral 30 X 200mg	6	0.2	Oral	15.4	2 - 3	1 - 2	4 - 6	DB45 - DL10 - DS45
11	<i>Carbamazepine, Oral 1 X 20mg</i>	<i>0.02</i>	<i>0.02</i>	<i>Oral</i>	<i>0</i>				
12	Carbamazepine, Oral 50 X 200mg	10	0.2	Oral	5.9	2 - 3	1 - 2	4 - 6	DB45 - DL10 - DS45
20	Diclofenac, External use 5 X 140mg	0.7	0.14	Dermal	6.8	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
21	Diclofenac, External use 1 X 500mg	0.5	0.04	Dermal	3	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
22	Diclofenac, External use 1 X 600mg	0.6	0.04	Dermal	7.6	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
23	Diclofenac, External use 1 X 776mg	0.776	0.04	Dermal	4.9	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
24	Diclofenac, Other (intern use) 10 X 100mg	1	0.1	Rectal	0.2	1 - 2	1 - 1	4 - 6	Awake not out not meal +PI
25	Diclofenac, External use 1 X 1000mg	1	0.04	Dermal	19.2	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
26	Diclofenac, Oral 30 X 50mg	1.5	0.05	Oral	8.7	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
27	Diclofenac, Oral 30 X 75mg	2.25	0.075	Oral	26.4	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI

28	Diclofenac, Oral 15 X 100mg	1.5	0.1	Oral	3.8	1 - 2	1 - 1	4 - 6	Awake not out meal high +PI
29	Diclofenac, Oral 30 X 50mg	1.5	0.05	Oral	0.9	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
30	Diclofenac, Oral 20 X 75mg	1.5	0.075	Oral	7	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
31	Diclofenac, External use 1 X 750mg	0.75	0.75	Dermal	0.1	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
32	Diclofenac, External use 1 X 1293mg	1.293	0.04	Dermal	6.9	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
33	Diclofenac, Oral 30 X 12.5mg	0.375	0.0125	Oral	0.1	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
34	Diclofenac, External use 3 X 140mg	0.42	0.14	Dermal	0.1	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
35	Diclofenac, External use 5 X 1000mg	5	0.04	Dermal	4.1	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
36	<i>Diclofenac, Other 1 X 140mg</i>	<i>0.14</i>	<i>0.14</i>	<i>-</i>	<i>0</i>				
37	<i>Diclofenac, Oral 30 X 25mg</i>	<i>0.75</i>	<i>0.025</i>	<i>Oral</i>	<i>0</i>				
38	Diclofenac, Oral 21 X 50mg	1.05	0.05	Oral	0.2	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
39	<i>Diclofenac, Other (intern use) 2 X 75mg</i>	<i>0.15</i>	<i>0.075</i>	<i>-</i>	<i>0</i>				
40	<i>Diclofenac, Other (intern use) 10 X 250mg</i>	<i>2.5</i>	<i>0.25</i>	<i>-</i>	<i>0</i>				
41	<i>Diclofenac, Other 20 X 100mg</i>	<i>2</i>	<i>0.1</i>	<i>-</i>	<i>0</i>				
42	<i>Diclofenac, Other 100 X 100mg</i>	<i>10</i>	<i>0.1</i>	<i>-</i>	<i>0</i>				
43	<i>Diclofenac, External use 10 X 140mg</i>	<i>1.4</i>	<i>0.14</i>	<i>Dermal</i>	<i>0</i>				
70	Ibuprofen, External use 1 X 2500mg	2.5	0.2	Dermal	0.3	1 - 4	1 - 2	5 - 6	Awake not out not meal +PI
71	Ibuprofen, Oral 20 X 200mg	4	0.2	Oral	8.9	1 - 4	1 - 2	5 - 6	Awake not out meal high +PI
72	Ibuprofen, Oral 30 X 100mg	3	0.1	Oral	0.4	1 - 4	1 - 3	5 - 6	Awake not out meal high +PI
73	Ibuprofen, Oral 12 X 200mg	2.4	0.2	Oral	0.7	1 - 4	1 - 2	5 - 6	Awake not out meal high +PI
74	Ibuprofen, Oral 16 X 200mg	3.2	0.2	Oral	0.4	1 - 4	1 - 2	5 - 6	Awake not out meal high +PI
75	Ibuprofen, Oral 30 X 200mg	6	0.2	Oral	13.7	1 - 4	1 - 2	5 - 6	Awake not out meal high +PI
76	Ibuprofen, Oral 10 X 400mg	4	0.4	Oral	0.9	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI
77	Ibuprofen, Oral 12 X 400mg	4.8	0.4	Oral	30.8	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI
78	Ibuprofen, Oral 14 X 400mg	5.6	0.4	Oral	3.8	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI
79	Ibuprofen, Oral 15 X 400mg	6	0.4	Oral	1.2	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI
80	Ibuprofen, Oral 1 X 562mg	0.562	0.562	Oral	0.9	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI
81	<i>Ibuprofen, Oral 1 X 3000mg</i>	<i>3</i>	<i>3</i>	<i>Oral</i>	<i>0</i>				
82	Ibuprofen, Oral 1 X 4000mg	4	4	Oral	0.1	1 - 1	1 - 1	1 - 1	Awake not out meal high +PI
83	Ibuprofen, Oral 20 X 400mg	8	0.4	Oral	21.4	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI
84	Ibuprofen, Oral 30 X 400mg	12	0.4	Oral	14.5	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI

85	Ibuprofen, External use 1 X 5000mg	5	0.2	Dermal	0.6	1 - 4	1 - 2	5 - 6	Awake not out not meal +PI
86	Ibuprofen, Oral 40 X 100mg	4	0.1	Oral	0.4	1 - 4	1 - 3	5 - 6	Awake not out meal high +PI
87	Ibuprofen, Oral 30 X 300mg	9	0.3	Oral	0.8	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI
88	<i>Ibuprofen, External use 1 X 100mg</i>	<i>0.1</i>	<i>0.1</i>	<i>Dermal</i>	<i>0</i>				
89	Ibuprofen, External use 1 X 3000mg	3	0.2	Dermal	0.3	1 - 4	1 - 2	5 - 6	Awake not out not meal +PI
90	<i>Ibuprofen, Oral 10 X 200mg</i>	<i>2</i>	<i>0.2</i>	<i>Oral</i>	<i>0</i>				
91	Ketoprofen, Oral 20 X 25mg	0.5	0.025	Oral	0.6	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
92	Ketoprofen, Other (intern use) 12 X 100mg	1.2	0.1	Rectal	0.5	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
93	Ketoprofen, External use 1 X 3000mg	3	0.04	Dermal	15.5	1 - 3	1 - 2	4 - 6	Awake not out not meal +PI
94	Ketoprofen, Oral 20 X 100mg	2	0.1	Oral	62.8	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
95	Ketoprofen, Oral 30 X 100mg	3	0.1	Oral	16.9	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
96	Ketoprofen, Oral 10 X 150mg	1.5	0.15	Oral	0.5	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
97	Ketoprofen, Other (intern use) 6 X 100mg	0.6	0.1	Rectal	0.2	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
98	Ketoprofen, External use 1 X 1500mg	1.5	0.04	Dermal	1.6	1 - 3	1 - 2	4 - 6	Awake not out not meal +PI
99	Ketoprofen, Oral 1 X 150mg	0.15	0.15	Oral	0.1	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
100	Ketoprofen, Oral 20 X 150mg	3	0.15	Oral	0.1	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
101	Ketoprofen, Oral 14 X 200mg	2.8	0.2	Oral	1	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
102	Ketoprofen, Oral 24 X 50mg	1.2	0.05	Oral	0.1	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
103	<i>Ketoprofen, Oral 20 X 50mg</i>	<i>1</i>	<i>0.05</i>	<i>Oral</i>	<i>0</i>				
105	<i>Paracetamol, Oral 20 X 240mg</i>	<i>4.8</i>	<i>0.24</i>	<i>Oral</i>	<i>0</i>				
106	Paracetamol, Oral 24 X 250mg	6	0.25	Oral	0.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
107	<i>Paracetamol, Oral 30 X 267mg</i>	<i>8.01</i>	<i>0.267</i>	<i>Oral</i>	<i>0</i>				
108	<i>Paracetamol, Oral 8 X 280mg</i>	<i>2.24</i>	<i>0.28</i>	<i>Oral</i>	<i>0</i>				
109	Paracetamol, Oral 16 X 400mg	6.4	0.4	Oral	1.4	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
110	Paracetamol, Oral 18 X 400mg	7.2	0.4	Oral	1.2	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
111	Paracetamol, Oral 8 X 500mg	4	0.5	Oral	0.9	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
112	Paracetamol, Oral 10 X 500mg	5	0.5	Oral	0.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
113	Paracetamol, Oral 16 X 500mg	8	0.5	Oral	21.9	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
114	<i>Paracetamol, Other (intern use) 10 X 100mg</i>	<i>1</i>	<i>0.1</i>	<i>-</i>	<i>0</i>				
115	Paracetamol, Other (intern use) 10 X 150mg	1.5	0.15	Rectal	0.1	1 - 6	1 - 1	4 - 5	Awake not out not meal +PI
116	Paracetamol, Other (intern use) 10 X 200mg	2	0.2	Rectal	0.1	1 - 6	1 - 1	4 - 5	Awake not out not meal +PI

117	Paracetamol, Other (intern use) 10 X 300mg	3	0.3	Rectal	0.1	1 - 6	1 - 1	4 - 5	Awake not out not meal +PI
118	Paracetamol, Other (intern use) 8 X 1000mg	8	1	Rectal	0.1	1 - 6	1 - 1	4 - 5	Awake not out not meal +PI
119	<i>Paracetamol, Oral 1 X 60mg</i>	<i>0.06</i>	<i>0.06</i>	<i>Oral</i>	<i>0</i>				
120	Paracetamol, Oral 12 X 200mg	2.4	0.2	Oral	0.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
121	Paracetamol, Oral 12 X 300mg	3.6	0.3	Oral	0.5	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
122	Paracetamol, Oral 12 X 500mg	6	0.5	Oral	1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
123	Paracetamol, Oral 8 X 1000mg	8	1	Oral	63.3	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
124	Paracetamol, Oral 1 X 2400mg	2.4	2.4	Oral	1	1 - 6	1 - 1	1 - 1	Awake not out meal high +PI
125	Paracetamol, Oral 16 X 300mg	4.8	0.3	Oral	2.2	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
126	Paracetamol, Oral 20 X 325mg	6.5	0.325	Oral	5.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
127	Paracetamol, Oral 12 X 600mg	7.2	0.6	Oral	0.8	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
128	<i>Paracetamol, Other (intern use) 10 X 80mg</i>	<i>0.8</i>	<i>0.08</i>	<i>-</i>	<i>0</i>				
129	<i>Paracetamol, Other (intern use) 8 X 60mg</i>	<i>0.48</i>	<i>0.06</i>	<i>-</i>	<i>0</i>				
130	<i>Paracetamol, Other (intern use) 10 X 250mg</i>	<i>2.5</i>	<i>0.25</i>	<i>-</i>	<i>0</i>				
131	<i>Paracetamol, Other (intern use) 8 X 300mg</i>	<i>2.4</i>	<i>0.3</i>	<i>-</i>	<i>0</i>				
132	<i>Paracetamol, Other (intern use) 8 X 450mg</i>	<i>3.6</i>	<i>0.45</i>	<i>-</i>	<i>0</i>				
133	<i>Paracetamol, Oral 20 X 267mg</i>	<i>5.34</i>	<i>0.267</i>	<i>Oral</i>	<i>0</i>				
134	<i>Paracetamol, Oral 12 X 400mg</i>	<i>4.8</i>	<i>0.4</i>	<i>Oral</i>	<i>0</i>				
135	<i>Paracetamol, Oral 1 X 405mg</i>	<i>0.405</i>	<i>0.405</i>	<i>Oral</i>	<i>0</i>				
136	<i>Paracetamol, Other (intern use) 10 X 600mg</i>	<i>6</i>	<i>0.6</i>	<i>-</i>	<i>0</i>				
137	<i>Paracetamol, Oral 12 X 150mg</i>	<i>1.8</i>	<i>0.15</i>	<i>Oral</i>	<i>0</i>				
138	<i>Paracetamol, Oral 10 X 250mg</i>	<i>2.5</i>	<i>0.25</i>	<i>Oral</i>	<i>0</i>				
139	<i>Paracetamol, Oral 12 X 250mg</i>	<i>3</i>	<i>0.25</i>	<i>Oral</i>	<i>0</i>				
140	<i>Paracetamol, Other (intern use) 10 X 500mg</i>	<i>5</i>	<i>0.5</i>	<i>-</i>	<i>0</i>				
141	<i>Paracetamol, Oral 1 X 2700mg</i>	<i>2.7</i>	<i>2.7</i>	<i>Oral</i>	<i>0</i>				
142	<i>Paracetamol, Oral 12 X 100mg</i>	<i>1.2</i>	<i>0.1</i>	<i>Oral</i>	<i>0</i>				
143	<i>Paracetamol, Oral 12 X 80mg</i>	<i>0.96</i>	<i>0.08</i>	<i>Oral</i>	<i>0</i>				
144	Paracetamol, Oral 15 X 500mg	7.5	0.5	Oral	0.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
145	<i>Paracetamol, Oral 1 X 6000mg</i>	<i>6</i>	<i>6</i>	<i>Oral</i>	<i>0</i>				
146	<i>Paracetamol, Oral 1 X 3000mg</i>	<i>3</i>	<i>3</i>	<i>Oral</i>	<i>0</i>				
147	Propranolol, Oral 50 X 40mg	2	0.04	Oral	37.2	1 - 2	1 - 2	4 - 6	DB45 - DL10 - DS45

148	Propranolol, Oral 30 X 80mg	2.4	0.08	Oral	4.9	1 - 2	1 - 2	4 - 6	DB45 - DL10 - DS45
149	Propranolol, Oral 30 X 160mg	4.8	0.16	Oral	40	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
150	Propranolol, Oral 90 X 160mg	14.4	0.16	Oral	17.6	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
151	<i>Propranolol, Other (intern use) 5 X 5mg</i>	<i>0.025</i>	<i>0.005</i>	<i>-</i>	<i>0</i>				
152	Propranolol, Oral 90 X 80mg	7.2	0.08	Oral	0.3	1 - 2	1 - 2	4 - 6	DB45 - DL10 - DS45
153	Salicylic acid, Oral 30 X 267mg	8.01	0.267	Oral	0.4	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
154	Salicylic acid, Oral 24 X 300mg	7.2	0.3	Oral	1.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
155	Salicylic acid, Oral 20 X 324mg	6.48	0.324	Oral	0.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
156	Salicylic acid, Oral 40 X 324mg	12.96	0.324	Oral	1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
157	Salicylic acid, Oral 20 X 330mg	6.6	0.33	Oral	2.5	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
158	Salicylic acid, Oral 60 X 330mg	19.8	0.33	Oral	1.8	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
159	Salicylic acid, Oral 20 X 500mg	10	0.5	Oral	8.6	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
160	Salicylic acid, Oral 30 X 500mg	15	0.5	Oral	3.6	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
161	Salicylic acid, Oral 20 X 10mg	0.2	0.01	Oral	0.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
162	Salicylic acid, Oral 30 X 75mg	2.25	0.075	Oral	17.5	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
163	Salicylic acid, Oral 30 X 160mg	4.8	0.16	Oral	7.2	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
164	Salicylic acid, Oral 20 X 250mg	5	0.25	Oral	0.8	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
165	Salicylic acid, Oral 30 X 300mg	9	0.3	Oral	0.4	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
166	Salicylic acid, Oral 60 X 320mg	19.2	0.32	Oral	0.2	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
167	Salicylic acid, Oral 36 X 500mg	18	0.5	Oral	5	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
168	Salicylic acid, Oral 50 X 500mg	25	0.5	Oral	9.8	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
169	Salicylic acid, Oral 15 X 1000mg	15	1	Oral	1	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
170	Salicylic acid, Oral 20 X 1000mg	20	1	Oral	24.1	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
171	Salicylic acid, Oral 30 X 1000mg	30	1	Oral	13.3	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
172	Salicylic acid, Oral 30 X 81mg	2.43	0.081	Oral	0.5	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
173	Salicylic acid, Oral 90 X 81mg	7.29	0.081	Oral	0.4	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
174	Salicylic acid, Oral 6 X 900mg	5.4	0.9	Oral	0.1	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
175	<i>Salicylic acid, Oral 20 X 267mg</i>	<i>5.34</i>	<i>0.267</i>	<i>Oral</i>	<i>0</i>				
176	Salicylic acid, Oral 20 X 450mg	9	0.45	Oral	0.2	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
177	Salicylic acid, Oral 30 X 475mg	14.25	0.475	Oral	0.3	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
178	<i>Salicylic acid, Oral 20 X 320mg</i>	<i>6.4</i>	<i>0.32</i>	<i>Oral</i>	<i>0</i>				

179	Salicylic acid, Oral 28 X 325mg	9.1	0.325	Oral	0				
180	Salicylic acid, Oral 12 X 400mg	4.8	0.4	Oral	0				
181	Salicylic acid, Oral 12 X 500mg	6	0.5	Oral	0				
182	Salicylic acid, Other (intern use) 6 X 1000mg	6	1	-	0				
183	Salicylic acid, Oral 60 X 25mg	1.5	0.025	Oral	0				
184	Salicylic acid, Other (intern use) 6 X 500mg	3	0.5	-	0				
185	Sulfamethoxazole, Oral 1 X 400mg	4	4	Oral	15.1	1 - 1	1 - 1	12 - 12	Awake not out meal high
186	Sulfamethoxazole, Oral 10 X 400mg	4	0.4	Oral	17.5	2 - 4	1 - 2	12 - 12	Awake not out meal high
187	Sulfamethoxazole, Oral 10 X 800mg	8	0.8	Oral	53	1 - 3	1 - 1	12 - 12	Awake not out meal high
188	Sulfamethoxazole, Oral 20 X 400mg	8	0.4	Oral	14.5	2 - 4	1 - 2	12 - 12	Awake not out meal high

APPENDIX B: Metabolic parameters

Table B-1: Metabolic parameters of the model. Data are gathered from pharmaceutical database websites (consulted in 2014-2015): www.compendium.ch, www.doctissimo.fr, www.drugbank.ca, www.drugs.com, www.eurekasante.vidal.fr, www.medicines.org, <https://pubchem.ncbi.nlm.nih.gov/>, www.theriaque.fr, www.vulgaris-medical.com. It was completed by data from the VIDAL dictionary, a French medical dictionary that regroups information on all the commercial pharmaceutical specialities. Each number is presented as a minimum-maximum interval. Molecules that are never detected are not shown. A global excretion rate is calculated according to the metabolic scheme proposed in the main text.

Molecule	Form	$k_{absorption}$ (h ⁻¹)	$k_{elimination}$ (h ⁻¹)	F_{InBody} (%)	$F_{InSewerDirect}$ (%)	$F_{Absorption}$ (%)	$F_{GutUnchanged}$ (%)	$F_{Elimination}$ <i>PrentCompound</i> (%)	$F_{Elimination}$ <i>Glucos</i> (%)	$F_{Elimination}$ <i>Sulfo</i> (%)	F_{Global} (%) <i>Excretion</i>
Atenolol	oral	0.1 - 0.14	0.51 - 1.19	100 - 100	0 - 0	49 - 51	100 - 100	85 - 100	0 - 0	0 - 0	91 - 100
Carbamazepine	oral	0.04 - 0.08	0.16 - 0.31	100 - 100	0 - 0	85 - 95	100 - 100	1 - 5	0 - 0	0 - 0	6 - 20
Diclofenac	oral	2.2 - 8.3	0.35 - 0.72	100 - 100	0 - 0	95 - 100	100 - 100	0 - 2	5 - 10	0 - 0	5 - 17
	dermal	0.001 - 0.002		6 - 20	25 - 75						
Ibuprofen	oral	0.25 - 0.36	0.89 - 15.8	100 - 100	0 - 0	75 - 85	100 - 100	1 - 10	0 - 0	0 - 0	16 - 34
	dermal	0.001 - 0.002		6 - 20	25 - 75						
Ketoprofen	oral	0.25 - 0.86	0.89 - 4.1	100 - 100	0 - 0	85 - 95	100 - 100	7 - 9	66 - 95	0 - 0	67 - 100
	dermal	0.001 - 0.002		6 - 20	25 - 75	85 - 95	100 - 100				24 - 93
Paracetamol	oral	0.25 - 1.02	0.89 - 3.8	100 - 100	0 - 0	95 - 100	100 - 100	1 - 5	45 - 58	30 - 35	77 - 100
Propranolol	oral	0.36 - 3.9	0.06 - 0.09	100 - 100	0 - 0	95 - 100	100 - 100	1 - 5	10 - 21	0 - 0	10 - 31
Salicylic acid	oral	0.25 - 0.36	0.89 - 15.8	100 - 100	0 - 0	80 - 100	100 - 100	8 - 12	4 - 8	0 - 0	10 - 40
Sulfamethoxazole	oral	0.25 - 1.02	0.89 - 15.8	100 - 100	0 - 0	70 - 90	100 - 100	5 - 21	8 - 14	8 - 14	29 - 74

APPENDIX C: Measured and modelled hourly loads

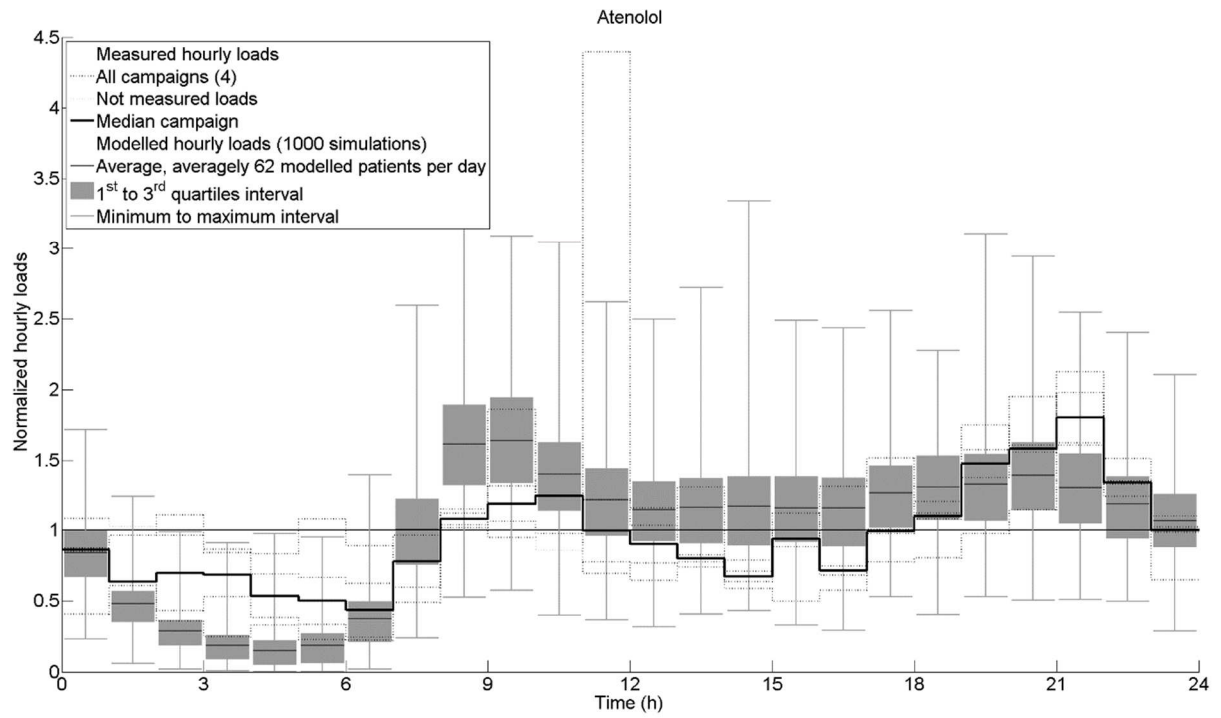


Figure C-1: Comparison of the dynamics of the measured and modelled hourly loads of atenolol.

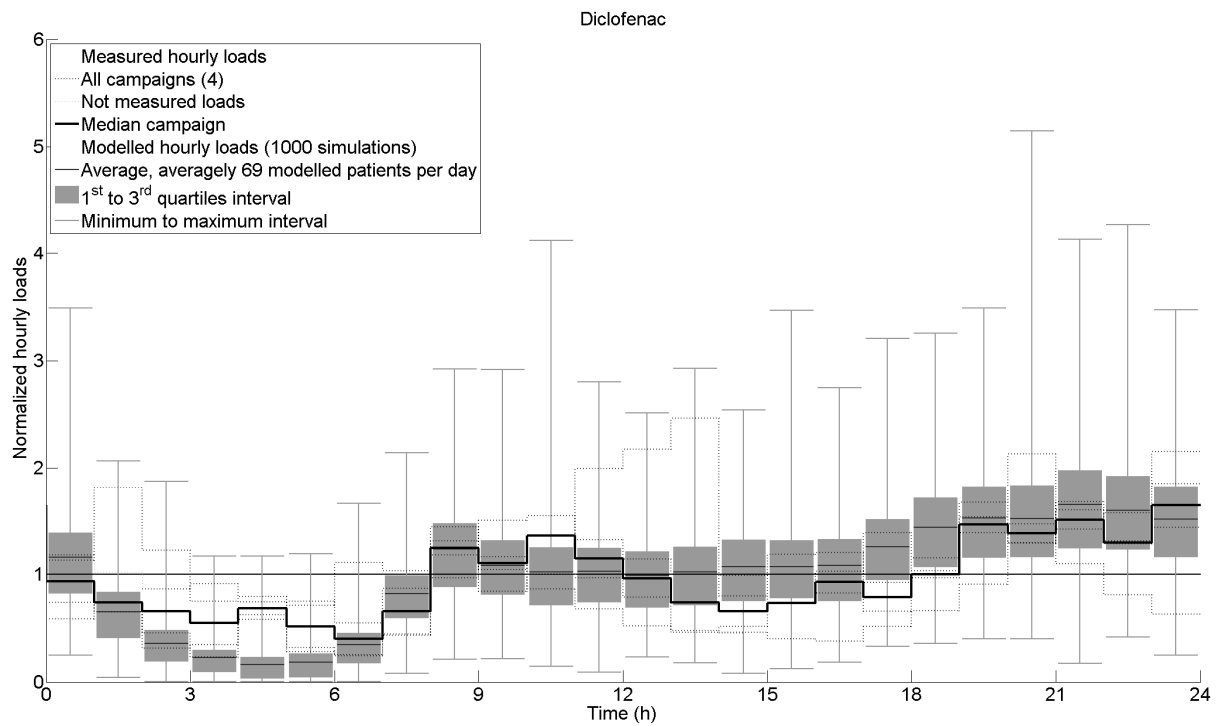


Figure C-2: Comparison of the dynamics of the measured and modelled hourly loads of diclofenac.

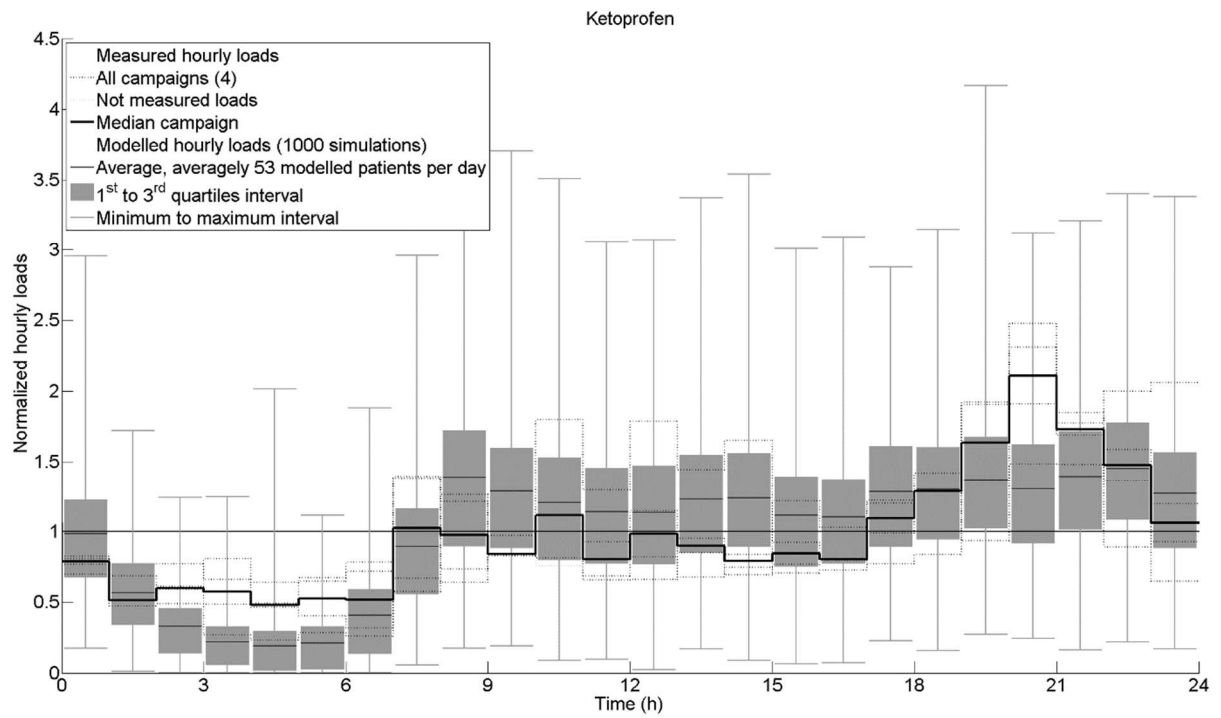


Figure C-3: Comparison of the dynamics of the measured and modelled hourly loads of ketoprofen.

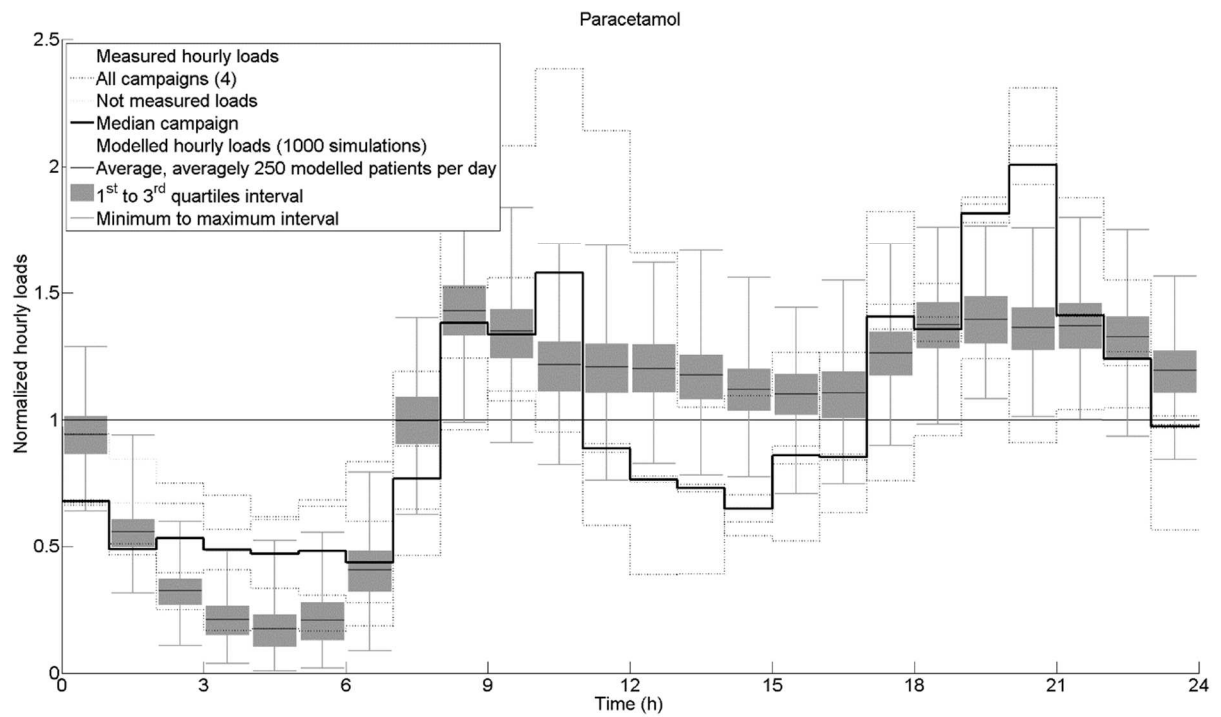


Figure C-4: Comparison of the dynamics of the measured and modelled hourly loads of paracetamol.

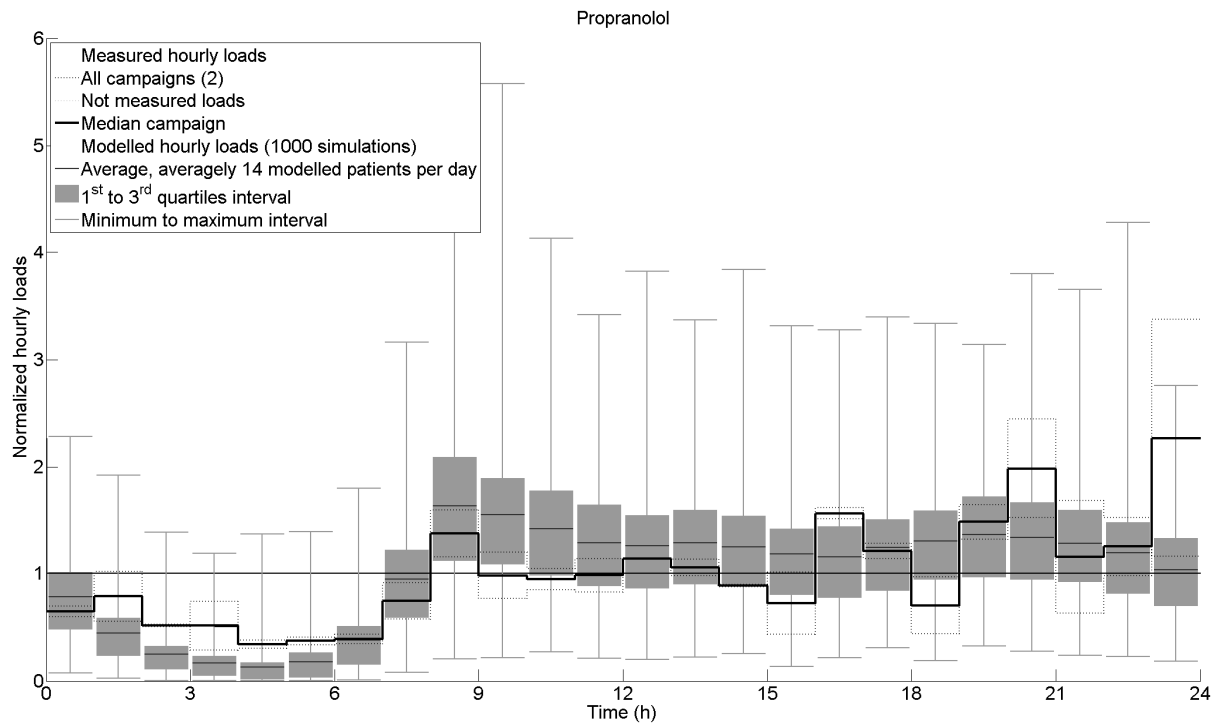


Figure C-5: Comparison of the dynamics of the measured and modelled hourly loads of propranolol.

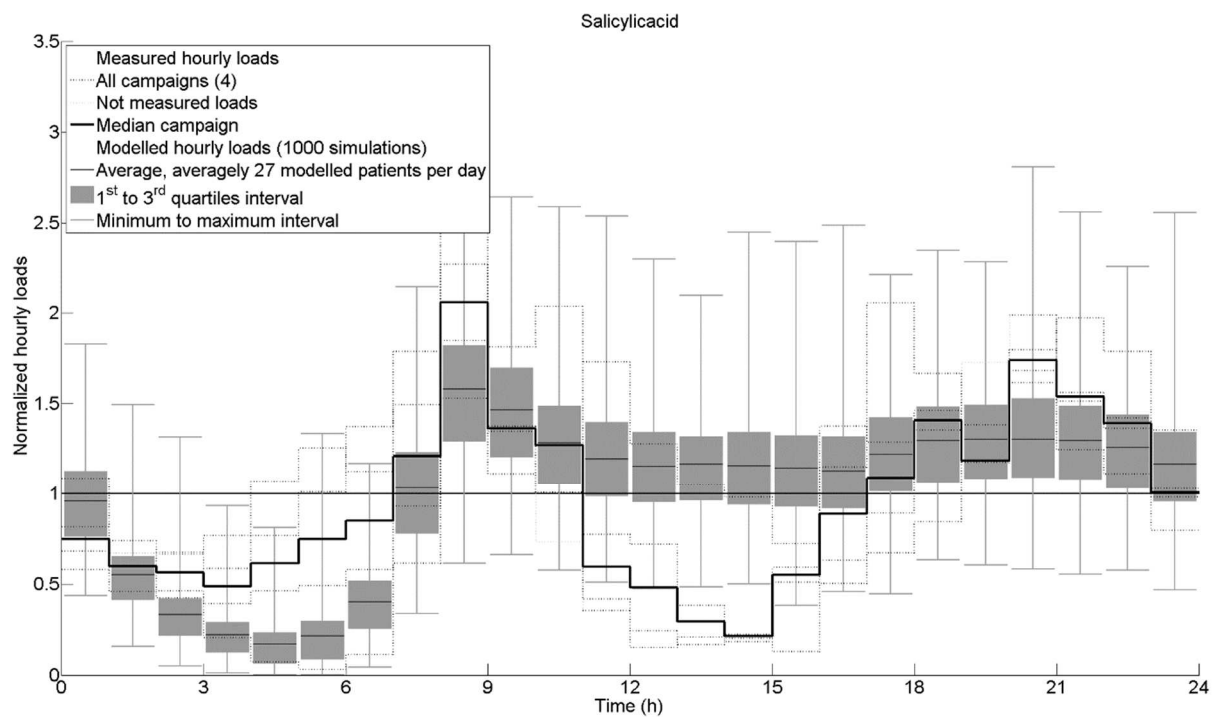


Figure C-6: Comparison of the dynamics of the measured and modelled hourly loads of salicylic acid.

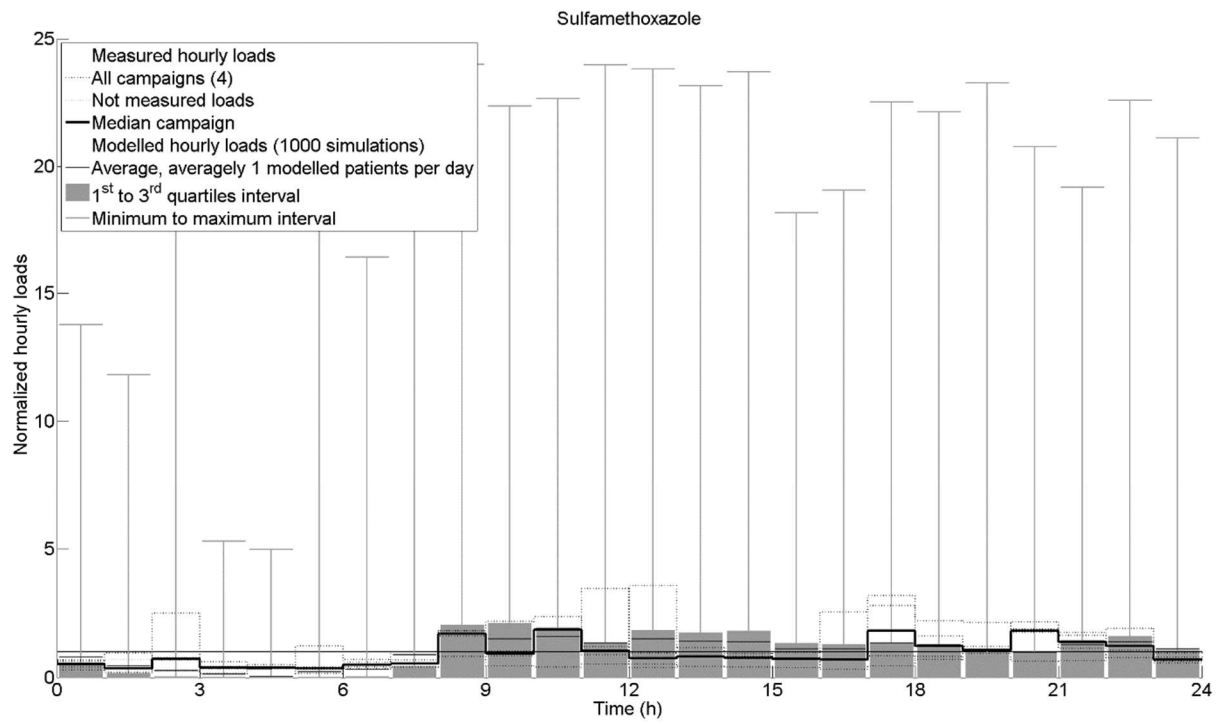


Figure C-7: Comparison of the dynamics of the measured and modelled hourly loads of sulfamethoxazole.

APPENDIX D: Implementation of a proportional model

In order to compare the performance of the proposed stochastic model, a proportional model is implemented. It is close to the model developed by Heberer and Feldmann (2005):

$$\varphi_{mod} = \alpha \times M$$

with:

φ_{mod} : modelled daily pharmaceutical load (mg/day)

α : coefficient of proportionality

M: daily mass sold or distributed (mg/day)

The coefficient of proportionality α integrates how much the pharmaceutical enters the body, is discharged directly into the sewers, is absorbed by the blood system, is transferred and metabolized as glucuro and sulfo-conjugates (using the notations introduced in the metabolism modelling section, see Figure 2 and Appendix B):

$$\alpha = (1 - F_{inBody}) \times F_{inSewerDirect} + F_{inBody} \times [(1 - F_{Absorption}) \times F_{gutUnchanged} + F_{Absorption} \times F_{eliminationParentCompound}]$$

Results are given in Table D-1.

Table D-1: Results of the proportional model.

Molecule	Average daily sales for the urban catchment (mg/day) (\approx 16 000 inhabitants)	Coefficient of proportionality α (%)	Modelled daily load (mg/day)
Atenolol	14 159	96	13 600
Carbamazepine	18 167	12.5	2 300
Diclofenac	20 965	11	2 300
Ibuprofen	272 057	25	68 000
Ketoprofen	16 241	88.5	14 400
Paracetamol	2 316 517	87.5	2 027 000
Propranolol	6 485	21	1 400
Salicylic acid	244 305	25	61 100
Sulfamethoxazole	6 071	56	3 400