Innovations & changements de pratiques
Lutte contre les micropolluants des eaux urbaines

RILACT SIPIBEL
Site Pilote de Bellecombe

Risques et leviers d'action relatifs aux rejets de médicaments, détergents et biocides dans les effluents hospitaliers et urbains

METROLOGIE ET MODELISATION DES FLUX HORAIRES ET JOURNALIERS DE MEDICAMENTS EN ENTREE DE STATION D'EPURATION A L'AVAL D'UN BASSIN VERSANT URBAIN ET D'UN HOPITAL

Tâche 2.1 "Rejet et dégradation de médicaments " – Livrable L5

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Le Livrable L5 du projet RILACT, intitulé « Métrologie et modélisation des flux horaires et journaliers de médicaments en entrée de station d'épuration à l'aval d'un bassin versant urbain et d'un hôpital », est constitué de la thèse de Tanguy Pouzol, rédigée en anglais sous le titre « Monitoring and modelling of pharmaceuticals in wastewater: Daily and hourly loads in both hospital and urban wastewater ».

Pour les lecteurs exclusivement francophones, un résumé long en français est disponible (pp. 288 à 307).

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Monitoring and modelling of pharmaceuticals in wastewater: Daily and hourly loads in both hospital and urban wastewater

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"The essence of science lies in repeatedly admitting you were wrong and accepting a new, more inclusive model, and so, unlike other belief systems, the practice of science ensures that our stories become steadily more accurate over time.

In this way, science isn't listing *what you know*: it's about *how you can come to know*. It's not a product but a process, a never-ending conversation rebounding back and forth between observation and theory, the most effective way of deciding which explanations are right and which are wrong. This is what makes science such a useful system for understanding the workings of the world – a powerful knowledge-generating machine. And this is why it is the scientific method itself that is the greatest invention of all."

Dartnell Lewis (2015).

« La nature des sciences est d'admettre continuellement d'avoir tort et d'accepter un nouveau modèle plus complet, et ainsi, à la différence d'autres systèmes de croyances, la pratique de la science assure que nos histoires deviennent toujours plus précises avec le temps.

De cette manière, la science n'est pas une liste *de ce que l'on sait* : c'est *la manière pour arriver à savoir*. Ce n'est pas un produit mais une méthode, une conversation sans fin entre observation et théorie, la manière la plus efficace de décider quelles explications sont justes ou fausses. C'est ce qui fait de la science un procédé si utile pour comprendre le fonctionnement du monde – une puissante machine générant de la connaissance. Et c'est pour cela que la méthode scientifique est, elle-même, la plus grande de toutes les inventions. »

Dartnell Lewis (2015).

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ABBREVIATIONS LIST

ATE: Atenolol
AZT: Aztreonam
CAR: Carbamazepine
CHAL: Centre Hospitalier Alpes-Léman (hospital of the study)
CIP: Ciprofloxacin
CV: coefficient of variation
DIC: Diclofenac
ECO: Econazole
EMEA: European Medicines Agency
EN: English
ETH: Ethinylestradiol
EU: European Union
FR: French
GRAIE: Groupe de Recherche Rhône-Alpes sur les Infrastructures et l'Eau (partner of the project)
IBU: Ibuprofen
ID: identity card
IRMISE Arve aval: Impact des rejets de micropolluants Issus de stations d'épuration sur l'aval du bassin versant de l'Arve (impact of discharges of micropollutants from WWTP into the Arve river)
IV: intravenous
KET: Ketoprofen
LoD: Limit of detection
LoQ: Limit of quantification
MAPE: Mean Absolute Percentage Error
MEC: Measured Environmental Concentration
MER: Meropenem
NPND: Non-parasitic non-domestic wastewater generator model
NSE: Nash-Sutcliffe model efficiency coefficient
PAR: Paracetamol
PEC: Predicted Environmental Concentration
PNEC: Predictive No Effect Concentration
PRO: Propranolol
Re: Relative error
SAL: Salicylic acid
SIPIBEL: Site pilote de Bellecombe (Bellecombe pilot site)
SIPIBEL-RILACT: risques et leviers d'action pour les micropolluants (risks and levers of actions relative to micropollutants)
STEU: station de traitement des eaux usées (French for WWTP)
SUL: Sulfamethoxazole
USA: United States of America
VAN: Vancomycin
WWTP: wastewater treatment plant

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. It is commonly admitted that the main path for pharmaceuticals to reach the environment consist of human consumption and excretion in wastewater, transfer along sewers, treatment in wastewater treatment plants (WWTP) and finally discharge in surface water. However, other sources and pathways are still discussed. One particular point of interest is the relevance of the hospital contributions.

Accurately sampling and measuring pharmaceuticals in wastewater or in environment concentrations is still costly (time and money) and difficult. Thus only a few studies have looked at the temporal variability of the phenomenon, even though assessing the variability of the phenomenon is paramount.

In parallel, models have been proposed to predict the occurrence of pharmaceuticals. They usually assume that the loads of pharmaceuticals entering a WWTP are proportional to the pharmaceuticals sales. However, most of the time, the results are difficult to interpret. The main problem of those models is the lack of data. They predict daily average concentrations using yearly sales of pharmaceuticals on larger areas (for example a country).

In this context, two sites are studied in this thesis: 1) a semi-urban catchment with 16 000 inhabitants; and 2) a general hospital with 450 beds. The work focuses on 15 molecules previously selected for their combined high sales volumes and potential eco-toxicity. Three objectives have been set and fulfilled:

- **Monitoring, for both sites, the pharmaceuticals loads entering the WWTP, compare them and assess their variability at different time scales (season, day and hour).** Several campaigns have been carried out on both sites. Some molecules were never or almost never quantified. The measured pharmaceuticals appear to be mainly present in the dissolved fraction. The daily loads are quite variable from one molecule to another (from 0.06 to 564 g/day) and from one measurement to another (coefficient of variation rarely less than 25%). No seasonal or weekly patterns have been identified. Hourly loads have shown that pharmaceuticals have their own distinctive dynamics. However, when a pharmaceutical is consumed by a limited number of patients in a catchment, the measured hourly loads are severely impacted by the random behaviour of the patients and the average dynamics is difficult to identify.
- **Acquiring and analysing detailed pharmaceuticals sales data for both sites.** For the urban catchment, monthly sales over a period of 2.5 years have been collected for the 6 pharmacies of the catchment and for the whole region (793 000 inhabitants). For the hospital, daily, weekly and monthly distributions have been collected. Analyses show that smaller scales are the most variable while the bigger ones are smoothed. However, it is not easy to know what smaller scales represent since it is hard to determine the corresponding number of patients. In addition, they can be affected by issues not related to consumptions (stock management for example). The quantities of pharmaceuticals sold or distributed are very variable. The theoretical average number of patients per day ranges from 0.4 to 1 600. Associating measured daily loads to the sales or distributions, no linear correlation was found. But measured daily loads appear more variable than the sales or distributions.
- **Modelling, for both sites, the pharmaceuticals loads entering the WWTP at the hourly time scale and incorporating the stochastic nature of the phenomenon.** A minute time step stochastic model has been proposed and applied to both sites. It produces reliable results for an urban catchment for both daily and hourly loads. The use of the model for hospitals is delicate because of their inherent specificity and their low consumptions of pharmaceuticals. In addition, the model is also able to predict the domestic wastewater flow of an urban catchment with great accuracy for both daily volumes and dynamics.

RÉSUMÉ

Les résidus de médicaments sont des contaminants connus de l'environnement. L'évaluation des risques que posent cette contamination est aujourd'hui un sujet de recherche important au sein des sciences environnementales. La consommation domestique puis l'excrétion de médicaments par l'être humain est considérée comme la principale source de médicaments à usage humain dans l'environnement. Cependant, le rôle de sources alternatives est toujours discuté, notamment la place des rejets hospitaliers.

L'échantillonnage et la mesure des médicaments à de faibles concentrations est toujours coûteuse (temps et argent) et difficile. C'est pourquoi, seulement quelques études se sont intéressées à la variabilité du phénomène, bien que cela soit indispensable.

En parallèle, des modèles ont été proposés afin de prédire la présence de médicaments. Ils supposent les flux de médicaments entrant en station d'épuration (STEU) proportionnels aux ventes de médicaments en pharmacies. La plupart du temps, les résultats de ces modèles sont difficiles à interpréter. Le principal problème est la difficulté d'accès à des données détaillées. Les flux moyens journaliers sont prédits à partir de ventes annuelles sur des territoires plus étendus que le bassin versant modélisé.

Dans ce contexte, deux sites ont été étudiés durant cette thèse : 1) un semi-urbain de 16 000 habitants ; et 2) un hôpital généraliste de 450 lits. Quinze molécules ont été présélectionnées pour leurs importants volumes de ventes et leurs potentiels écotoxique. Trois objectifs ont été définis et remplis :

- **Mesurer, pour les deux sites, les flux de médicaments entrant en STEU, les comparer et évaluer leurs variabilités à différentes échelles de temps.** De nombreuses campagnes de mesures ont été effectuées. Quelques molécules n'ont jamais, ou presque, été quantifiées. Les résidus de médicaments sont principalement retrouvés dans la phase dissoute. Les flux journaliers sont très variables selon la molécule (de 0,06 à 564 g/jour) et d'une campagne à une autres (coefficient de variations rarement en-dessous de 25 % pour chacune des molécules). Aucune dynamique saisonnière ou hebdomadaire n'a été détectée. Les flux horaires ont révélé que les résidus de médicaments présentent leurs propres dynamiques. Cependant, quand un médicament est consommé par seulement quelques patients sur un site, les flux horaires mesurés sont fortement impactés par le hasard des comportements individuels rendant ainsi la dynamique moyenne des flux horaires difficile à identifier.
- **Acquérir et analyser des données de ventes de médicaments détaillées pour les deux sites.** Pour le site urbain, les ventes mensuelles sur une période de 2,5 années ont été collectées pour les six pharmacies du basin ainsi que pour la Haute-Savoie (793 000 habitants). Pour l'hôpital, les distributions journalières, hebdomadaires et mensuelles ont été collectées. L'analyse de ces données montre que la variabilité des ventes ou des distributions de médicaments dépend à la fois de l'échelle géographique des données mais aussi de leur échelle temporelle. Plus la surface ou le temps couvert par chaque données est grand moins la variabilité est importante. Cependant, les petites échelles sont sujettes à des indéterminations car il est difficile de savoir combien de personnes s'y fournissent en médicaments. De plus, elles sont sensibles à d'autres logiques que la simple consommation (par exemple la gestion de stock). Les quantités vendues sont très variables. Le nombre moyen théorique de patients par jour varie de 0,4 à 1 600. Aucune corrélation linéaire n'a été identifiée entre les ventes de médicaments et les mesures de flux journaliers. De plus, ces derniers sont toujours plus variables que les ventes.
- **Modéliser, pour les deux sites, les flux de résidus de médicaments entrant en STEU au pas de temps horaire en considérant la nature stochastique du phénomène.** Un modèle stochastique au pas de temps de la minute a été proposé et évalué sur les deux sites. Les flux journaliers et horaires sont reproduits fidèlement pour un bassin versant urbain. Un hôpital reste difficile à modéliser du fait de sa spécificité et du relatif faible nombre de patients traités. De plus, le modèle est capable de reproduire les débits d'eaux usées d'un bassin versant urbain avec grande précision.

PREFACE (EN)

The present thesis was written in English despite the fact that French is my first language. Writing in English seemed to be the right thing to do. Indeed, almost all the literature on the thesis subject is in English and part of the PhD committee does not read French. So, in order to give the thesis a real usefulness, it appeared obvious to write it in English rather than in French.

The thesis was part of a larger project (chapter 4). This implies that some aspects were not the result of my labor. This concerns the monitoring of the pharmaceutical concentrations (chapter 4). The great majority of the sampling was done by Vivien LECOMTE working for the GRAIE (www.graie.org, a French non-profit organization linking water focused professions: city services, private contractors and researchers). The staffs of the WWTP and of the CHAL hospital were partially involved. The analyses of the samples were performed in different laboratories, especially by Laure WIEST at the Institute of Analytical Sciences in Lyon for the pharmaceuticals analyses. As all members of the project, I regularly participated in the sampling campaigns and in their preparation. The source of any picture, illustration or data in a table is given when it is not my work.

Otherwise, everything was done by me. This includes the literature review (chapters 1, 2 and 3), the analysis of all the data and measurements (chapter 6) and the modelling (chapters 5 and 7).

This work would not have been possible without the cooperation or funding of:

- Agnès Gleizes, chief pharmacist at CHAL (hospital)
- Members and partners of the SIPIBEL observatory on hospital effluents and urban wastewater treatment plants (www.sipibel.org), French-Swiss Interreg IRMISE Arve aval project (www.irmise.org) and SIPIBEL-RILACT project
- European Union (FEDER funds)
- ONEMA, National office of water and aquatic environment
- Regional Office of Health of Haute-Savoie
- Rhône-Méditerranée and Corse water agency
- Rhône-Alpes Regional Council
- All the funding organizations for their support.

The layout of the thesis follows a classic plan for simplicity purposes (Part 1 - Literature review, Part 2 - Materials and methods and Part 3 - Results and discussions).

However, it is strongly recommended to read everything that concerns the monitoring aspects of the thesis after part 1 (chapters 4 and 6) and then to read the modelling aspects (chapters 5 and 7).

PRÉFACE (FR)

Bien que ma langue maternelle soit le français, j'ai choisi l'anglais pour rédiger cette thèse. Sachant que la grande majorité de la littérature sur le sujet traité ici est elle-même en anglais, et sachant qu'une partie du jury de thèse ne maîtrise pas le français, ce choix de langue s'impose naturellement s'il on veut que ce manuscrit ait une réelle utilité.

Cette thèse a été accomplie au sein d'un projet plus large (Chapitre 4). Cela implique que certains travaux sont nécessaires pour plusieurs personnes et ne sont donc pas nécessairement réalisés par tous. Dans le cas présent, il s'agit des mesures de concentrations de médicaments (Chapitre 4). La grande majorité des mesures a été effectué par Vivien LECOMTE pour le compte du GRAIE (www.graie.org, une association française dont « la vocation est de mobiliser et mettre en relation les acteurs de la gestion de l'eau »). Les personnels de la station d'épuration ainsi que de l'Hôpital CHAL ont également été mis à contribution de manière partielle. Les analyses des échantillons ont été réalisées par différents laboratoires, notamment par Laure WIEST de l'Institut des Sciences Analytiques à Lyon pour les analyses de médicaments. Tous comme l'ensemble des partenaires du projet, j'ai régulièrement participé aux campagnes de prélèvements ainsi qu'à leurs préparations. La source des photographies, illustrations et données est précisé lorsqu'elles ne sont pas le fruit de mon travail.

J'ai accompli le reste du travail présenté ici. Cela comprend la bibliographie (Chapitres 1, 2 et 3), toutes les analyses de données et de mesures (Chapitre 6), le modèle et l'analyses de ces résultats (Chapitres 5 et 7).

Ce travail n'aurait pu être accompli sans la coopération ou le financement de :

- Agnès Gleizes, pharmacienne en chef à l'hôpital CHAL
- Les membres et partenaires de SIPIBEL, du projet Interreg franco-suisse IRMISE Arve aval et du projet SIPIBEL-RILACT
- l'Union Européenne (fonds FEDER)
- l'ONEMA, office national de l'eau et des milieux aquatiques
- l'Agence Régionale de la Santé de Haute-Savoie
- l'Agence de l'eau Rhône-Méditerranée et Corse
- la Région Rhône-Alpes
- l'ensemble des organismes financeurs pour leur soutien.

L'organisation du document suit le plan classique d'une thèse par soucis de simplicité (1- bibliographie, 2- matériels et méthodes et 3- résultats et discussion).

Toutefois, il est fortement recommandé de lire les chapitres 4 et 6 ensemble (ils parlent des données expérimentales ainsi que de leurs analyses), suivi des chapitres 5 et 7 (ils se concentrent sur le modèle proposé et l'analyse de ces résultats).

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Thanks to Audrey, my companion for your love and support. I should say that more often.

INTRODUCTION

Pharmaceuticals in surface water were first detected in the seventies. Since then they have been detected in every water body (wastewater, rivers, lakes, coastal water, groundwater, drinking water...) and everywhere on the planet. Assessing and managing the risk associated to this contamination has become an important field of study in environmental sciences.

No risk has yet been found toward human health since the reported concentrations in drinking water are low. However, risk assessment continues to be necessary because a chronic exposure of a combination of molecules can induce long term risks. Regarding the effect toward the environment, some have already been noticed (changes in fish behavior, drop in population of vultures…). Current studies concentrate on chronic effects at low concentrations via different tools (effects due to bio accumulation and concentration studies, sub-lethal indicators…).

The different sources and pathways of pharmaceuticals to the environment have been exposed but there is still some discussion on the relative importance of them. Nevertheless, it is commonly admitted that the main path for pharmaceuticals to reach the environment consist of human consumption and excretion in wastewater, transfer along sewers, treatment in wastewater treatment plants (WWTP) and finally discharge in surface water. Whether the WWTPs concentrations of pharmaceuticals are highly hospital related or not is a frequently asked question. Also, the role of veterinary pharmaceuticals is surveyed since the molecules excreted are mainly directly discharged into the environment via runoff or infiltration.

Accurately sampling and measuring pharmaceuticals in wastewater or in environment is still costly (time and money) and difficult. Thus, only few studies have looked at the temporal variability of the phenomenon. Annual, seasonal, day to day and hourly variations have been observed a few times. Assessing the variability of the phenomenon is paramount. Especially, infra-day variations are necessary to properly manage pharmaceuticals loads and proposing new solutions (new treatments, source control…). Also, in the case of combined sewer, infra-day variations are important to evaluate direct discharges to surface water through combined sewer overflow structures.

Partly to compensate the lack of measurements and also to better understand the release of pharmaceuticals, models have been developed since the late nineties. Almost all models focus on the main pathway of pharmaceuticals or on a part of it (*i.e.* human consumption, excretion to sewers, treatment and discharge by WWTPs, environmental dispersion). Focusing on the first steps (consumption to WWTPs inflow), all the models assumes that the loads of pharmaceuticals entering the WWTPs are proportional to the pharmaceuticals sales. The coefficient of proportionality usually corresponds to the rate of pharmaceuticals excreted as unchanged molecule by the human body. However, most of the time, the results are difficult to interpret. This is mainly due to four types of problems that are encountered:

- Imprecision of the sales data: it is difficult to obtain pharmaceuticals sales data. Most of the time, only yearly consumptions over an entire country are available, and they sometimes do not cover the sales that are not reimbursed. This hides the spatial and temporal variability of the sales.
- Difference between sales and consumptions: sales and consumptions do not match in either volumes or dynamics. Some pharmaceuticals can be unused, or are consumed over long periods of time. This implies that the day to day variations in sales and consumptions are not necessarily of the same magnitude. Looking at infra-day variations, it is clear that sales data (even extremely precise ones) cannot be easily linked to consumptions patterns.
- Simple and not well defined parameters: the parameters used in the models do not reflect the variability of the phenomenon they represent, such as the global excretion rate of parent pharmaceuticals by the human body. It varies greatly from one individual to another. Also the different administration routes of a pharmaceutical are not taken into account.

- Not captive population: the inhabitants of the modelled catchment are not necessarily the only ones excreting pharmaceuticals into the sewers. Workers or visitors can come from outside. Also, the inhabitants can leave the catchment. In large catchments, it can be negligible when an equilibrium between ins and outs could exists. But on smaller catchments ins and outs can be strongly unbalanced.

The common denominator of these problems is the importance of detailed data on the modelled catchment. But those data are not always easily accessible.

Nevertheless, some studies have elaborated more precise models by:

- using precise sales data (spatially and temporally),
- describing more complex phenomenon,
- using statistical distribution for either the pharmaceuticals sales or the parameters of the model to reproduce the stochastic nature of pharmaceuticals contamination,
- incorporating demographic projections to study the long term evolution of the contamination,
- modelling the time-use pattern of persons to explore infra-day variations of pharmaceuticals loads (one study done in parallel of this thesis).

In this context, two sites are studied in this thesis: 1) a semi-urban with 16 000 inhabitants covering roughly 130 km²; and 2) a general hospital with of 450 beds (not included in the previous one). The work focuses on 15 molecules previously selected for their combined high sales volumes and potential eco-toxicity. The objectives of the thesis are:

- Monitoring, for both sites, the pharmaceuticals loads entering the WWTP, compare them and assess their variability at different time scales (season, day and hour),
- Acquiring and analyzing detailed pharmaceuticals sales data for both sites,
- Modelling, for both sites, the pharmaceuticals loads entering the WWTP at hourly time scale and incorporating the stochastic nature of the phenomenon.

The work is presented in a classic layout:

- The first part gives some elements of contexts (chapter 1) and reviews the literature on the subject (chapter 2 for the environmental risk of pharmaceuticals and chapter 3 for the modelling of pharmaceuticals),
- The second part describes the materials and methods. Chapter 4 focuses on the presentation of the sites, the monitoring of pharmaceuticals loads and the molecules themselves. Chapter 5 describes the proposed model,
- In the third part, the results are presented and discussed (chapter 6 for the data and measurements analysis and chapter 7 for the model results),
- Lastly, a general conclusion and perspectives are proposed.

In order to keep the main text as clear and simple as possible, some information and graphics are presented in appendixes.

PART 1: CONTEXT AND LITTERATURE REVIEW

This part is divided in three chapters.

Chapter 1 introduces the notion of pharmaceuticals and its limits.

Chapter 2 and 3 explores past works. Chapter 2 focuses on the occurrence and effects of pharmaceuticals in the water cycle, while chapter 3 focuses on modelling of pharmaceuticals in wastewater.

CHAPTER 1: PHARMACEUTICALS

In the field of water contamination, researchers are looking in different water bodies for certain molecules sometimes labelled as pharmaceuticals.

P*harmaceutical*

Pharmaceutical, pharmaceutical drug, pharmaceutical product, medicinal product, medicine, medication, medicament, cure, remedy, drug… there are a lot of words or expressions to refer to the same concept: the notion of pharmaceutical. Definitions found in University courses or Pharmacy Orders documentations are always derived from the laws of their respective country. The two main regulations towards pharmaceuticals are found in the United States of America (USA) and the European Union (EU). Luckily, they are not really different one from another. As a reference, the EU regulations are chosen here, but the USA regulations are given in appendix 1.

As of today, the notion of pharmaceuticals, named "medicinal product", is defined by EU regulations as follows (THE EUROPEAN PARLIAMENT AND THE COUNCIL, 2001 a):

> *"**Medicinal product**:*
>
> *(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*
>
> *(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."*

One can note that the same definition is given for *"Veterinary medicinal product"* with the word *"animals"* instead of *"human beings"* (THE EUROPEAN PARLIAMENT AND THE COUNCIL, 2001 b). Also the definition for *"Plant protection product"* (sub category of pesticide) is not far from the one of medicinal product (EUROPEAN COMISSION, 2016). One can easily generalize the concept of medicinal product and apply it to different alive beings (human, animal or plant).

In addition, the directive gives three additional definitions that complete the previous one:

- ***Substance**:*

  "Any matter irrespective of origin […]*"*

- ***Active Substance**:*

  "Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis."

- ***Excipient**:*

  "Any constituent of a medicinal product other than the active substance and the packaging material."

Therefore, in this thesis, a pharmaceutical or a medicinal product is the sum of different substances respecting condition (a) or (b) (of the EU directive cited above) that could be divided in three classes: active substance, excipient and package.

However, it is not a perfect definition. It overlooks two main problems: societal and historic context, and dosage.

The first problem can be illustrated with the case of caffeine. It is presented as a simple cup of coffee in many cases but is also presented as a pharmaceutical in order to treat bronchopulmonary dysplasia for premature infants, apnoea of prematurity and orthostatic hypotension. Also, it is toxic when consumed in high quantity. The same molecule is treated in two different ways with no rational explanations. It shows that to be recognized as a pharmaceutical, a product needs to comply with more than just a few rules. It also depends on its intended use and its historical and societal context. Many food products or other products have the same problem. Another example concerning walnuts in the USA is developed in appendix 1.

P*harmaceutical in water*

Whether or not a molecule is a pharmaceutical, is not a definitive property. When discharged in water (wastewater, river, lake, groundwater…), a pharmaceutical molecule becomes a pollutant. However the notion is widely used in the field of water contamination. It simply and rapidly conveys information on the supposed contextual origin of the molecule.

However, “pharmaceutical” molecules have no other common denominator than their societal context. There are approximately 3 000 different active substances authorized in Europe (ANSM, 2014). Their physical and chemical properties are widely spread, and so are their behaviours within the environment. They do not affect the environment the same way and at the same concentrations. The work done by the Stockholm County Council provides a perspective on this subject (STOCKHOLM COUNTY COUNCIL, 2014). They propose a classification of pharmaceutical molecules according to their inherent possibility to affect the environment, using data on their persistence, bioaccumulation and toxicity properties. As a result, there is no specific way to approach pharmaceuticals in the field of environmental contamination. So studying the effect of “pharmaceuticals” in water should not be significantly different than studying other “micro pollutants”.

Even in the present case of modelling the source of those molecules in wastewater, it is a fragile notion. Of course the context in which a molecule is used will affect its modelling as a source of water contamination, but as the notion is flawed, it may not be specific to those. Caffeine could be treated the same way as a pharmaceutical when modelling its presence in wastewater. On the contrary, many metals are present as active substances in medicinal products but are not viewed as pharmaceuticals when found in wastewater because the main pathway for such products is not from medical context.

The intention here is not to ban this notion in the water contamination field, but rather to clarify what information it conveys and what limits it is bound to. It does not diminish the attention that should be paid to those molecules commonly labelled as pharmaceuticals during their whole life cycle from their legal status definition to their residual presence in water bodies. The reader will find many occurrences of the notion in the rest of this thesis as he would also in scientific literature. As it is exposed here, it is a familiar but blurry notion (like many others), and it is used as a short-cut to give context on the contamination studied and where it comes from. As such, one could understand **pharmaceutical in the context of environmental contamination** as:

> *A molecule or an ion or a metal which was mainly part of products labelled as pharmaceuticals before being consumed or discarded.*

In any case, when practical, it would be simply better to refer to the actual name of the molecule studied. This thesis focuses on 15 molecules which are described in chapter 4. They are: Atenolol, Aztreonam, Carbamazepine, Ciprofloxacin, Diclofenac, Econazole, Ethinylestradiol, Ibuprofen, Ketoprofen, Meropenem, Paracetamol, Propranolol, Salicylic acid, Sulfamethoxazole and Vancomycin.

Finally, a few definitions are given below to help the reader unfamiliar with the concepts surrounding pharmaceuticals:

- **Speciality:** a specific presentation of a pharmaceutical molecule. A new pharmaceutical speciality exists whenever one of the following things differs from pre-existing specialities: form of the units (pills, drops, intravenous (IV)), dose of the units, composition of the units (pharmaceutical molecules and excipients dosage), number of units in the package, or brand of the package. The 2 800 pharmaceutical molecules authorized in France are sold as more than 11 000 specialities (ANSM, 2014).

- **Posology:** the study of the dosage of pharmaceuticals and their intakes pattern. By extension, the doses and pattern at which a pharmaceutical is consumed by a patient.

- **Human metabolism and excretion of pharmaceuticals:** the entire processes (mechanical and bio-chemical) transforming or not any pharmaceutical molecule in the human body until it is eliminated (completely transformed or excreted).

- **Pharmaceutical metabolite:** any molecule that is the product of a metabolic reaction involving a pharmaceutical molecule.

- **Pharmaceutical or pharmaceutical metabolite transformation product:** any product that is the product of a reaction operating outside the human body and involving either a pharmaceutical molecule or a pharmaceutical metabolite.

CHAPTER 2: PHARMACEUTICALS IN THE WATER CYCLE

The occurrence of a substance in the water cycle is only relevant if it poses a risk. In this case, to evaluate the risk of a substance one must determine its level of exposure and the hazards it causes. The intersection between the two gives the risk factor of the substance. As such, a highly toxic molecule that is never found poses no risk. Conversely, a near non-toxic substance that is everywhere could poses risks. It is traditionally done by comparing measured or predicted environmental concentrations (MEC or PEC) to predicted no effect concentrations (PNEC).

The risk assessment of pharmaceuticals in the environment is an important field of studies in environmental sciences. Many articles deal with the subject. As a reference point, a request for “pharmaceuticals”, in the field of “environmental science” on the website www.sciencedirect.com, returns 47 442 articles. Also, it has been abundantly and regularly reviewed (Halling-Sørensen *et al.*, 1998; Kümmerer, 2000; Heberer, 2002; Enick and Moore, 2007; Kümmerer, 2009; Santos *et al.*, 2010; Li, 2014; Ebele *et al.*, 2017; Yi *et al.*, 2017).

This chapter’s goal is to provide a quick review of this field of studies and especially the difficulties and challenges of today’s research. The next three sections are about the presence of pharmaceuticals in the environment (section 2.1), then the sources and pathways of pharmaceuticals to the environment (section 2.2) and lastly their hazard levels (section 2.3).

2.1 EXPOSURE TO PHARMACEUTICAL MOLECULES

The history of research on pharmaceuticals in the environment is told in many articles. One does it in an original way by bibliometric analysis (Daugthon, 2016). The short version is as follows. Pharmaceuticals were first measured in water during the seventies, especially by Garrison *et al.* (1976) and Hignite and Azarnoff (1977). Following the evolutions of the analytical methods of pharmaceuticals in water, especially by mass spectrometry coupled with either gas or liquid chromatography, the topic persisted until the late nineties when it became an important field of study (Halling-Sørensen *et al.*, 1998; Ternes, 1988; Daugthon and Ternes, 1999; Hirsch *et al.*, 1999). Nowadays, it is still an important and productive field of study.

Pharmaceuticals have been found in every water body:

- Domestic wastewater (Radjenović *et al.*, 2009; Ort *et al.*, 2010a)
- Hospital wastewater (Verlicchi *et al.*, 2010; Brelot and Lecomte, 2015)
- WWTP effluents (Santos *et al.*, 2009; Unceta *et al.*, 2010)
- Landfill leachates (Eggen *et al.*, 2010; Masoner *et al.*, 2014)
- Rivers (Aminot *et al.*, 2016; Paíga *et al.*, 2016)
- Lakes (Perazzolo *et al.*, 2010; Archundia *et al.*, 2017)
- Coastal waters (Bayen *et al.*, 2013; Seabra Pereira *et al.*, 2016)
- Groundwater (Qian *et al.*, 2015; Saby *et al.*, 2017)
- Drinking water (Simazaki *et al.*, 2015; Furlong *et al.*, 2017)

And they were found everywhere on the planet:

- Africa (Madikizela *et al.*, 2017)
- America (Bartelt-Hunt *et al.*, 2009; Causanilles *et al.*, 2017)
- Antarctica (González-Alonso *et al.*, 2017)
- Asia (Liu and Wong, 2013; Balakrishna *et al.*, 2017)
- Europe (Bound and Voulvoulis, 2006; Brelot *et al.*, 2013)
- Australia (Stewart *et al.*, 2014; Roberts *et al.*, 2015).

However, measuring pharmaceuticals is still a complex task that requires, as for other emerging pollutants, a lot of time, money and competences. As there are not necessarily available for all researchers, the variability, both temporal and spatial, of the phenomenon is not well studied. Moreover, as pointed out by Ort *et al.* (2010b), many studies lead to possible wrong conclusions due to improper sampling methods. Also, most of the time, the particulate fraction of pharmaceuticals, their metabolites and transformation products are not measured even if they can have similar or more toxic properties (Magdeburg *et al.*, 2014).

Only a few studies perform 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 (both daily and infra-day variations) and can present seasonal dynamics.

Concerning the fifteen molecules of interest of this study, the ranges of their reported concentrations in domestic wastewater are presented in table 1. The literature is not equal towards every molecule. Some are much more studied than others (Carbamazepine, Diclofenac, Ibuprofen, Sulfamethoxazole…). For some molecules, it is very difficult to find any literature (Aztreonam, Econazole, Meropenem…). The ranges of the reported concentrations are very wide and it is hard to conclude on their usual levels. This is because pharmaceuticals consumption is not spatially uniform and is temporally very variable.

Table 1: Concentration of pharmaceuticals in urban domestic wastewaters reported in literature. 1: Adler *et al.*, 2010; 2: Batt *et al.*, 2007; 3: Behera *et al.*, 2011; 4: Bendz *et al.*, 2005; 5: Carballa *et al.*, 2008; 6: Choi *et al.*, 2008; 7: Fatta-Kassinos *et al.*, 2010; 8: Gao *et al.*, 2012; 9: Gómez *et al.*, 2007; 10: Gracia-Lor *et al.*, 2012; 11: Gros *et al.*, 2006; 12: Janex-Habibi *et al.*, 2009; 13: Kasprzyk-Hordern *et al.*, 2009; 14: Loos *et al.*, 2013; 15: Martin *et al.*, 2010; 16: Miège *et al.*, 2006; 17: Nie *et al.*, 2012; 18: Oosterhuis *et al.*, 2013; 19: Rossmann *et al.*, 2014; 20: Santos *et al.*, 2009; 21: Singer *et al.*, 2010; 22: Stamatis *et al.*, 2010; 23: Stamatis and Konstantinou, 2013; 24: Terzić *et al.*, 2008; 25: Vieno *et al.*, 2006; 26: Yu and Chu, 2009; 27: Zhou *et al.*, 2010; 28: Zorita *et al.*, 2009; 29: Zuccato *et al.*, 2010.

Molecule	Concentration in domestic wastewaters (minimum – maximum) (ng/L)	References
Atenolol	30 – 33 100	1, 3, 4, 11, 13, 20, 24, 25
Aztreonam		None found
Carbamazepine	40 – 3 780	3, 4, 5, 6, 8, 9, 11, 13, 14, 18, 20, 21, 24, 25, 27
Ciprofloxacin	8 – 3 700	2, 7, 18, 25, 29
Diclofenac	160 – 94 200	3, 4, 5, 9, 10, 11, 13, 14, 18, 20, 22, 23, 24, 27, 28
Econazole		None found
Ethinylestradiol	1 – 3	5, 12, 17, 18
Ibuprofen	4 – 603 000	3, 4, 5, 9, 10, 11, 13, 14, 20, 21, 22, 24, 26, 28
Ketoprofen	4 – 8 560	3, 4, 10, 11, 13, 14, 21, 24, 27
Meropenem		None found
Paracetamol	130 – 569 000	3, 6, 9, 10, 11, 20, 24
Propranolol	50 – 290	4, 11, 16
Salicylic acid	580 – 63 700	10, 13, 22
Sulfamethoxazole	3 – 2 800	2, 3, 4, 5, 6, 7, 8, 10, 11, 13, 14, 15, 20, 23, 24, 29
Vancomycin	41 – 664	17, 29

Concerning the fifteen molecules of interest of this study, the ranges of their concentrations in hospital wastewater are presented in table 2. As the one for domestic wastewater, one observes unequal reporting in literature and wide ranges. Thus it is hard to draw conclusions.

Table 2: Concentration of pharmaceuticals in hospital wastewaters reported in literature. 1: Almeida *et al.*, 2013; 2: Gómez *et al.*, 2006; 3: Hartmann *et al.*, 1999; 4: Huschek *et al.*, 2004; 5: Khan and Ongerth, 2004; 6: Langford and Thomas, 2009; 7: Lin *et al.*, 2008; 8: Lin and Tsai, 2009; 9: Lindberg *et al.*, 2004; 10: Maurer *et al.*, 2007; 11: Santos *et al.*, 2013; 12: Sim *et al.*, 2011; 13: Ternes, 1998; 14: Thomas *et al.*, 2007;15: Verlicchi *et al.*, 2012.

Molecule	Concentration in hospital wastewaters (minimum – maximum) (ng/L)	References
Atenolol	595 – 5 800	2, 4, 5, 7, 9, 10, 11, 15
Aztreonam		None found
Carbamazepine	123 – 1 123	1, 4, 5, 7, 11
Ciprofloxacin	457 – 101 000	7, 9, 11
Diclofenac	46 – 2 737	1, 2, 4, 5, 7, 8, 11, 12, 13, 14, 15
Econazole		None found
Ethinylestradiol	32 – 432	7, 8
Ibuprofen	119 – 19 770	1, 2, 4, 5, 7, 8, 11, 13, 14, 15
Ketoprofen	10 – 1 100	1, 5, 7, 8, 11, 15
Meropenem		None found
Paracetamol	2 500 – 329 852	1, 2, 4, 5, 7, 8, 11, 14, 15
Propranolol	18 – 15 500	2, 3, 6, 7, 8, 11, 15
Salicylic acid	383 – 2 817	11
Sulfamethoxazole	191 – 12 800	3, 7, 8, 9, 11
Vancomycin		None found

2.2 SOURCES AND PATHWAYS OF PHARMACEUTICALS INTO THE ENVIRONMENT

The sources and pathways of pharmaceuticals into the environment have been identified for quite some time. Indeed, they are explored in most of the reference cited in the previous section. The issue has been summarized by some publications (Heberer, 2002; Ritter *et al.*, 2002; Santos *et al.*, 2010; Qian *et al.*, 2015) which proposed very similar diagrams with some variations.

A short summary of those articles and a new diagram that represent the dispersion of pharmaceuticals into the environment is proposed (figure 1).

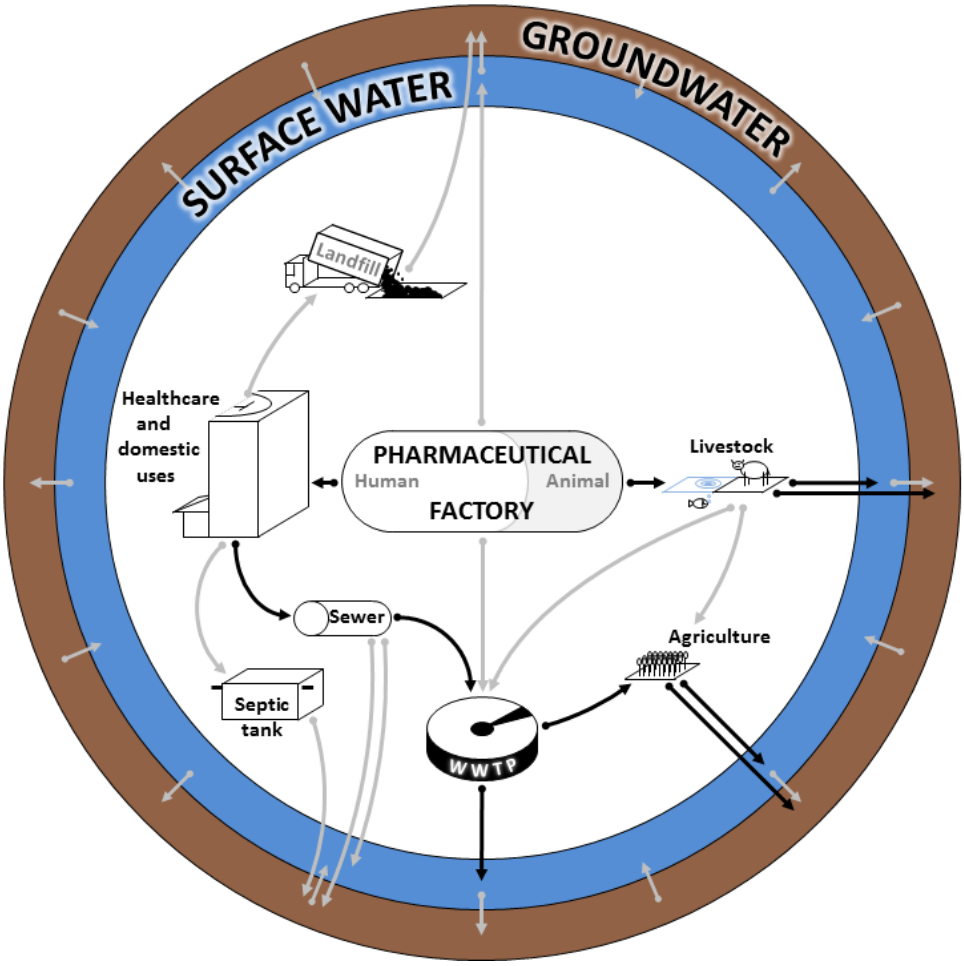


Figure 1: Dispersion of pharmaceuticals in the environment: sources and pathways. Black arrows represent the main pathways. Grey arrows represent secondary pathways. Pathways on which pharmaceuticals are removed (*i.e.* incinerators) are not represented.

Whether they are for human or veterinary purposes, pharmaceuticals products are manufactured in specialized factories. It has been reported that pharmaceuticals molecules can be found in the effluents of these factories. Sometimes, the effluents are directly discharged into surface water or they can be redirected to WWTPs.

Veterinary products are used almost completely for livestock (farming and aquaculture). They are used for diseases treatment and prevention and in some countries for growth. A small proportion of veterinary products are used for pet animals that can excrete pharmaceuticals almost everywhere (ground, surface water or sewer via drained surfaces). Animals metabolize pharmaceuticals and eventually excrete a certain fraction of the molecule unchanged via urine and faeces. The fate of urine and faeces differs depending on the type of animal.

They can be discharged into surface water (open-sea aquaculture, run-off from farms or land application), infiltrated in the ground and eventually groundwater (farms) or sometimes drained and directed to a WWTP.

Products for human uses are distributed via domestic circuits (pharmacies) or healthcare facilities (all types of hospital, nursing home…). The importance of hospitals, as places of high pharmaceuticals consumption, has been studied intensively. Most of the time, hospital wastewater is more concentrated in pharmaceuticals than domestic ones, but their loads are much lower. This is, however, not true for large hospitals connected to small WWTPs, and for pharmaceuticals that are preferably or exclusively consumed in hospitals. Consumed pharmaceuticals are metabolized by humans and a certain fraction is excreted as unchanged molecules. Then, it is either discharged to a sewer system or a septic tank. Pharmaceuticals eventually leaks from septic tanks to the ground and groundwater. Sewers transport pharmaceuticals to a WWTP. However, pharmaceuticals can reach surface water, the ground and ground water if the sewer system has leaks or in case of overflows (storm, dysfunctional pumping stations…). Unused pharmaceuticals are either discharged to sinks and endure the same fate as metabolized pharmaceuticals, collected with garbage and put in landfill or eliminated in incinerators, or collected via special programs for unused pharmaceuticals and eliminated. Unused pharmaceuticals stored in landfills can eventually leach to the ground and groundwater.

At the WWTP, the collected pharmaceuticals are unequally transformed. Traditional WWTPs were not design to remove such molecules, thus their efficiency towards pharmaceuticals is very variable. A fraction of them are discharged with WWTPs effluents into surface water. Another fraction is concentrated in sludge and can be either incinerated or used in agriculture. From there it either reaches the ground and infiltrates to groundwater or reaches surface waters via run-off.

In the environment, pharmaceuticals can pass from surface water to groundwater (infiltration or managed aquifer recharge) and the other way around (exfiltration).

Lastly, via drinking water treatment plants, pharmaceuticals could be redirected everywhere. Also, products from livestock and agriculture could be contaminated by pharmaceuticals and reach humans.

In every step, pharmaceuticals are susceptible to be transformed (sorption to solids and biofilms, degradation by solar exposition, absorption by wildlife or plants…). Such transformations are seldom studied, especially concerning in-sewer processes.

This cycle strongly depends on each country context. Pharmaceuticals consumption differs, as does sewage management. However, in western countries, the main source of pharmaceuticals is considered to be human consumption, excretion to sewers and discharge to surface water after treatment at the WWTPs. Discharge into surface water and infiltration to groundwater of veterinary products is considered another non negligible source. Still, each pathway can have a significant impact on certain locations.

2.3 RISK OF PHARMACEUTICALS CONTAMINATION

Pharmaceuticals effects on living organisms are:

- **Acute or chronic**: if an organism reacts when exposed one time to a specific concentration of a pharmaceutical, the effect is acute. However, if the organism only reacts when exposed for a prolonged time or repetitively, the effect is chronic.
- **Deterministic or stochastic** (Ritter *et al.*, 2002): "*effect for which the severity of the damage caused is proportional to the dose and for which a threshold dose exists below which they do not occur are called deterministic effects. […], effects for which the probability of occurrence, rather than severity, is proportional to the dose are referred to as stochastic effects.*"

These distinctions make the determination of the risk of pharmaceuticals very difficult. Lethal effects are not the only effects that are targeted, sub-lethal effects (malformations, immobilizations, changes in behavior) are also critical to understand the hazard of pharmaceuticals.

Effects of pharmaceuticals on humans are observed… In fact, that is what they were designed for. But, it's happening at relatively high doses, most of the time at a few hundred mg. In comparison such doses represent a large volume of wastewater since their pharmaceuticals concentrations are never greater than a few hundred µg/L, and an even larger volume of environmental or drinking water. However, chronic exposure to low concentrations of many pharmaceuticals could be harmful, even if it has not been observed yet and in addition with all other pollutants present in the water. Increases of antibiotic-resistant micro-organism populations, hormonal perturbations, cancers frequencies or frequencies of allergies are possible (Kümmerer, 2016).

Concerning wild life, the situation is a bit different. Populations of vultures in south Asia have declined after ingestion of Diclofenac (Green *et al.*, 2004; Oaks *et al.*, 2004; Shultz *et al.*, 2004). Population of fish feminized in Lake Ontario (Canada) after exposition to synthetic estrogen (Kidd *et al.*, 2007). Fish changed behavior (much more aggressive) after exposition to Oxazepam in Sweden (Brodin *et al.*, 2013).

Apart from those spectacular examples, the challenges of pharmaceuticals risk studies are still important. Studies on chronic effects are scarce (Santos *et al.*, 2010). Normalizing the uses and interpretations of eco-toxicological tests focusing on sub-lethal effects has to be done, especially for studying "cocktails" of pharmaceuticals (Vasquez *et al.*, 2014) and/or with other pollutants.

CHAPTER 3: PHARMACEUTICALS FATE MODELLING

Measuring pharmaceuticals in the environment is very costly, and so models are a precious tool to save money and time. But they are also necessary to gain valuable comprehension of the studied processes. It is a necessary part of the scientific method.

Almost all the models developed are considering human pharmaceuticals only and especially their consumption, metabolism, excretion to the sewers, treatment by the WWTP and discharge into the environment. Depending on the study, models can predict any step from pharmaceuticals in urine (Winker *et al.*, 2008a; Winker *et al.*, 2008b) to pharmaceuticals in the environment (Bendz *et al.*,2005; Bound and Voulvoulis, 2006). Modelling each step accurately is paramount to assess environment risk. In this chapter and, by extension, in this thesis, modelling is focused on the first steps (*i.e.* consumption, metabolism, excretion to sewers until entry into the WWTPs).

The first publications of pharmaceuticals fate and occurrence models are dated 1997. The European Medicines Agency (EMEA) published a draft of what would become "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA, 2006; EMEA, 2010). It proposed a methodology in a few steps. The most "refined" proposed formula to calculate predicted environmental concentration (PEC) can be seen as a concentration fraction between the mass of pharmaceutical consumed and discharged in the environment and the volume of water in which it is diluted. The formula of the mass of pharmaceuticals consumed and discharged by a specific set of population over a certain period can be generalized as follows:

$$M_{discharged} = \frac{M_{sold,T}}{T} \times \frac{P_{catchment}}{P_{sales}} \times f$$

With:
$M_{discharged}$: mass of pharmaceuticals consumed and discharged in the environment in a certain catchment (kg/day)
T: duration covered by the sales data (day)
$M_{sold,T}$: mass of pharmaceuticals sold to a certain population set (for example a country) during T days (kg)
$P_{catchment}$ and P_{sales}: respectively, the number of persons in the modelled catchment and to whom pharmaceuticals are sold
f: proportional factor including the influence of any process transforming pharmaceuticals (for example human metabolism, WWTP treatment…)

The first research oriented application of this formula was done in Europe (Kümmerer *et al.*, 1997; Henschel *et al.*, 1997; Christensen, 1998; Stuer-Lauridsen *et al.*, 2000; Huschek *et al.*, 2004), in the USA (Sedlak *et al.*, 2001) and in Australia (Kahn and Ongerth, 2004). When the predicted loads could be compared to measured ones, the model shown questionable results as it can be expected due to its crudeness and hypotheses (some of which are "worst case scenario").

In 2005, Heberer and Feldmann proposed a more refined model. Still proportional, it uses detailed pharmaceuticals sales data (short repeated time periods (weekly, monthly) on defined places (hospitals, city) and detailing the sales of pharmaceuticals by specialities and not molecule) combined with information on the administration routes and detailed data on human metabolism (different rates and metabolites production: glucuro and sulfo conjugates are assumed to rapidly and completely transform back to the parent molecule in wastewater). Tested for Carbamazepine and Diclofenac, it gave interesting results. The ratios of predicted over measured loads ranged from 0.5 to 1.6 for Carbamazepine (average of 0.9) and from 1.3 to 3.2 for Diclofenac (average of 2.0). Hypotheses for the overestimation of Diclofenac were given.

However, acquiring such detailed pharmaceutical sales data is not easy and not often done. Mainly for this reason, most of the studies trying to compare predicted and measured pharmaceuticals loads or concentrations only use the EMEA model or a variation of it (Liebig *et al.*, 2006; Carballa *et al.*, 2008; Besse *et*

al., 2010; Perazzolo *et al.*, 2010; ter Laak *et al.*, 2010; Vystavna *et al.*, 2010; Zhang and Geiβen, 2010; Oosterhuis *et al.*, 2013; Singer *et al.*, 2016). Comparison of predicted and measured pharmaceuticals loads or concentrations gave results difficult to interpret. 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. For example, Oosterhuis *et al.* (2013) reported, for wastewater influent, ratios of 3.27 and 1.95 for Carbamazepine; and 1.38 and 1.72 for Diclofenac. Carballa *et al.* (2008) reported, for wastewater influents, ratios ranging from 0.13 to 14.63 for Carbamazepine; and from 0.04 to 3.87 for Diclofenac. These results are mainly due to three factors: the lack of detailed sales data (poor spatial and temporal resolution and low details), insufficient and/or improper monitoring campaigns, and shadowy models 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 very variable, and such variations are not acknowledged by a simple proportional model. Processes change from one person to another. Sales and loads in water are highly variable in space and time. Despite these difficult results, all authors acknowledge the importance of modelling and point out the limitations of their work. Also, one can note that the modelling approach is the same whether it deals with domestic or hospital wastewaters.

It is difficult to conclude on this type of models. Indeed, they do not model the same things (concentrations or loads in different locations and different type of water) and their objectives are not the same (precise comparison with measures, prioritization of molecules for risk assessment…).

However, some efforts have been made to try to overcome these difficulties.

Some studies managed to acquire detailed pharmaceuticals sales data. Some managed to obtain spatially accurate data describing hospitals or cities (Kümmerer *et al.*, 1997; Heberer and Feldmann, 2005). Others used both spatially and temporally accurate data describing monthly, weekly or even daily sales for hospitals, cities and regions (Mullot, 2009; Coutu *et al.*, 2013; Celle-Jeanton *et al.*, 2014; Marx *et al.*, 2015; Herrmann *et al.*, 2015).

In 2013, Ortiz de García detailed a methodology to estimate the pharmaceuticals consumption from two incomplete pharmaceuticals sales data sources. However, the results remained difficult to interpret since the ratios of predicted over measured loads of 54 pharmaceuticals ranged from 0.0005 to 8 (33 ranging from 0.5 to 2), with a global overestimation of 57.4%.

Two studies (Mullot, 2009; Le Corre *et al.*, 2012) embraced the variability of the subject and included it in their model via statistical distributions for sales data and model parameters (figure 2).

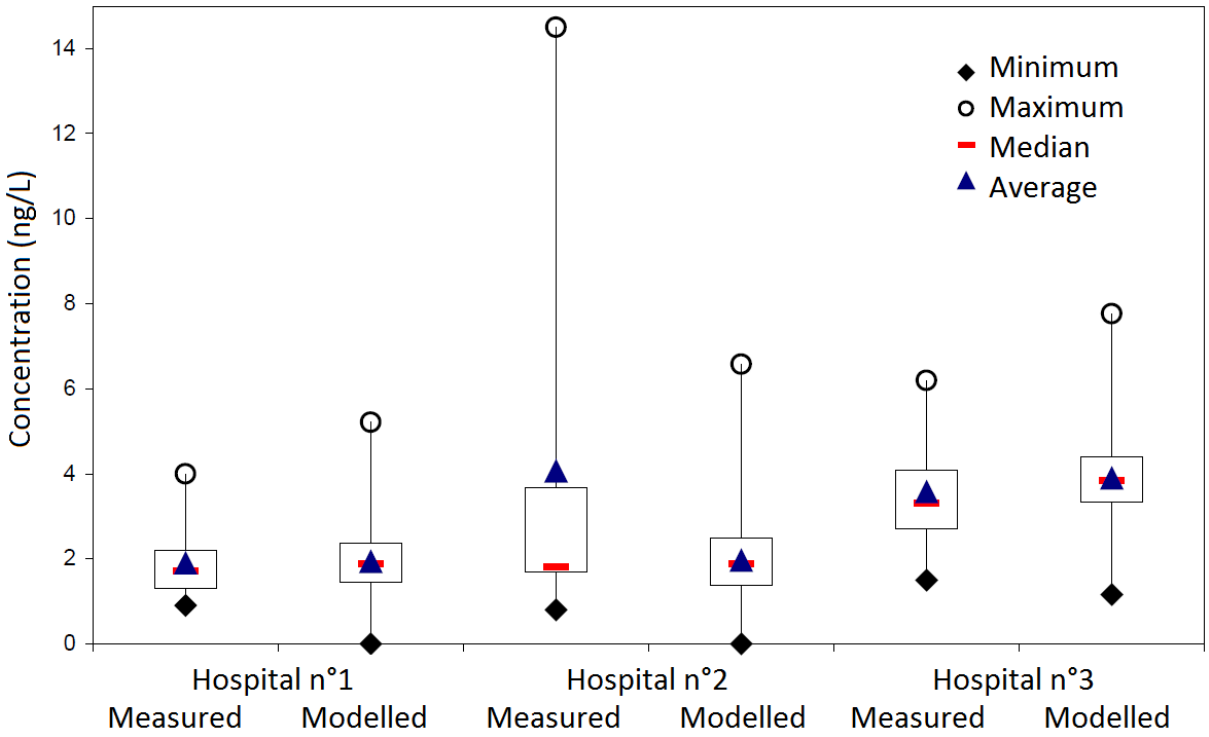


Figure 2: From Mullot (2009), results of the modelling of Atenolol in wastewaters from different hospitals in France (translated from French).

Models have been developed to assess the spatial variability of pharmaceutical occurrence. The idea is to add the different contributions of pharmaceuticals alongside rivers in a catchment (Schowanek *et al.*, 2002 ; Götz *et al.*, 2013) or even the whole European area (Oldenkamp *et al.*, 2013; Oldenkamp *et al.*, 2014; Oldenkamp *et al.*, 2016). Their results corroborated the fact that pharmaceutical occurrence is highly variable in space.

Other models explored the temporal variability of pharmaceutical occurrence. Demographic evolution in Germany (population growth and ageing) has been used to study long term trends (Tränckner and Koegst, 2010). Seasonality in antibiotics prescription was studied and modelled to predict monthly average pharmaceuticals loads (Marx *et al.*, 2015). Day to day variations have been modelled by combining phenomenological and stochastic processes using Markov chains (Gernaey *et al.*, 2011; Snip *et al.*, 2014). Finally, a stochastic model integrating posology, pharmacokinetics and toilet flushes dynamics was developed by Coutu *et al.* (2016) to represent hourly variations of the antibiotic Ciprofloxacin for a city in Switzerland. Without any objective indicator, the author conclude that, for dry weather periods, the model successfully reproduced the hourly variations of Ciprofloxacin at the Inlet of the WWTP while showing the important variability of the phenomenon (figure 3): *"all measured Ciprofloxacin concentrations lie within the range of model predictions"*. This model is, in its principle, very similar to the one that was constructed in this thesis although they were made separately in parallel. Thus their details are quite different. Also, it does not provide any objective criteria to assess the performance of the model.

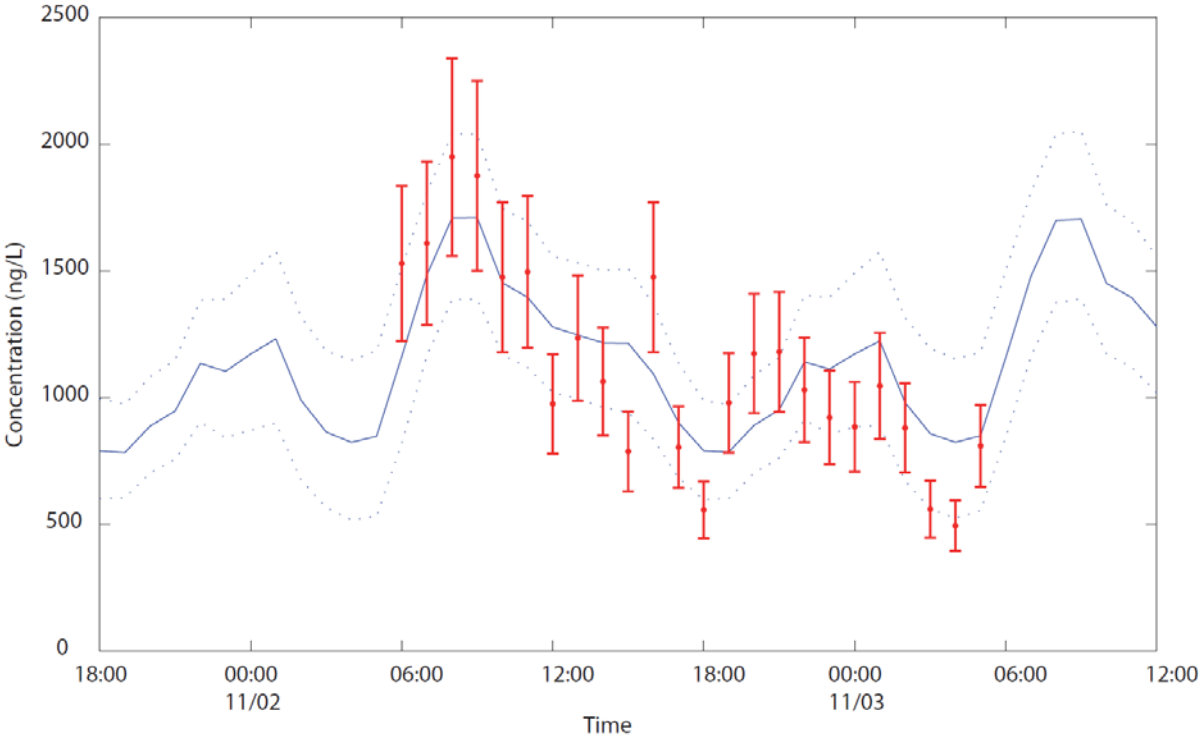


Figure 3: From Coutu *et al.* (2016), results of the proposed model. In red: measurements and their uncertainties. In blue: modelled concentrations. The dashed lines correspond to the uncertainty in the model prediction. Uncertainty corresponds to the 5th and 95th percentiles of the distribution of the simulated values.

Another strategy to avoid the shadowy definitions of some parameters is to ignore their reported values and to calibrate them. Using a small scale catchment and calibrating the parameters of the model, it is then possible to apply the model to larger areas (Boxall *et al.*, 2014). For infra-day variations, it is more difficult, but using complex calibrating process allows calibrating and modelling a city hydrodynamics and water quality including pharmaceuticals products (Kaeseberg *et al.*, 2016).

A specific use of pharmaceutical occurrence modelling consists of reversing the model to try and predict the consumption of product rather than their discharge. It is used for monitoring illicit drugs consumption and has the same difficulties as classic pharmaceutical modelling (Karolak *et al.*, 2010; Lai *et al.*, 2011).

PART 2: MATERIALS AND METHODS

This part is divided in two chapters.

Chapter 4 presents the surrounding projects of this thesis, the two experimental sites studied, the 15 monitored pharmaceutical molecules and all the monitoring aspects of the thesis.

Chapter 5 extensively describes the model proposed in the thesis.

CHAPTER 4: EXPERIMENTAL SITES AND MONITORING

The SIPIBEL observatory and two associated projects are described in section 4.1. Then, both experimental sites are precisely described in sections 4.2 and 4.3. In section 4.4, the 15 pharmaceuticals investigated in the thesis are described.

Finally, measurement techniques and sampling strategies are described in section 4.5.

4.1 SIPIBEL PROJECTS

The thesis was done in the frame of the SIPIBEL, IRMISE Arve aval and SIPIBEL-RILACT research projects. They all focus on the same area: the catchment of the Bellecombe WWTP and the nearby environment including the impact on the Arve River. Bellecombe WWTP is located in France near the French-Swiss border (figure 4). Treated water is discharged into the Arve river which, after a few kilometres, enters the Swiss territory and then joins the Rhône river which enters into France and, finally, ends into the Mediterranean sea.

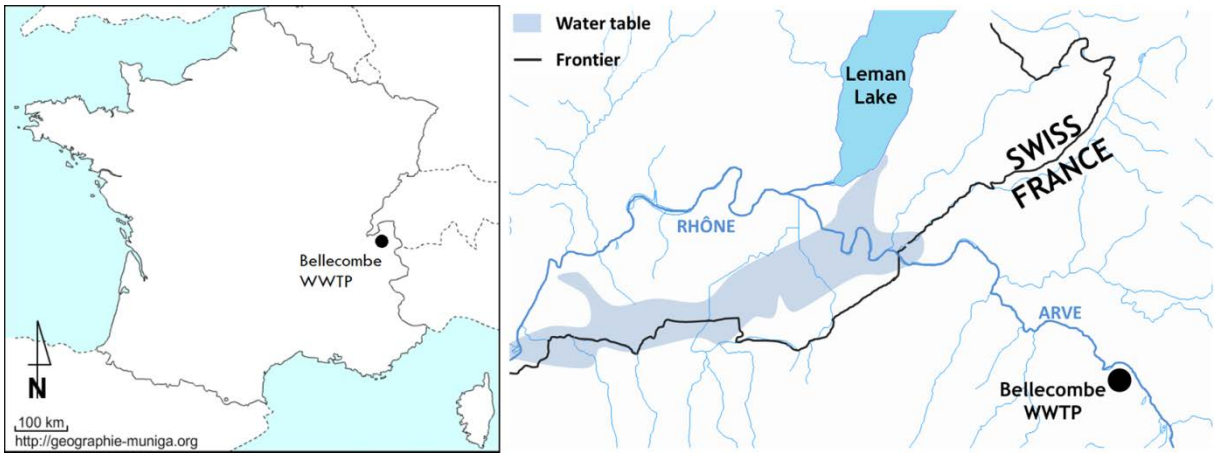


Figure 4: Bellecombe WWTP geographic location (Left from http://geographie-muniga.org, consulted 2017, right modified from GRAIE, 2016).

Programmed to open in February 2012, a new hospital (Centre Hospitalier Alpes Léman, CHAL) was supposed to be connected to the nearby Bellecombe WWTP. However, the water authorities decided that the wastewater from the hospital, because of potential risks due to pharmaceuticals, would have to be treated separately from other urban wastewater into a specific WWTP. Because of the high cost, risks and difficulties to manage a WWTP in an hospital, the CHAL hospital and local authorities asked to water authorities for starting a research program, for at least 3 years, in order to characterize the wastewater of the hospital in comparison to "urban domestic" wastewater. The study has to demonstrate if the mix of hospital wastewater and urban ones in only one WWTP can be safe for Arve river, sludge disposal and potable water production downstream. It was planned to divide the Bellecombe WWTP in two parts: one part for the hospital wastewater and another one for the urban wastewater; creating two WWTP inlets and two WWTP outlets.

In this context, a first project started in 2010: SIPIBEL (which means Pilot site of Bellecombe). It was focused on the characterization of wastewater in Bellecombe WWTP and effects on Arve water quality. It quantified daily many parameters, including pharmaceuticals loads, at both inlets and both outlets (hospital and urban), and also in the receiving water (Arve river) upstream and downstream the WWTP.

In parallel, to expand the scope of SIPIBEL and to complete it, another project started in 2012: IRMISE Arve aval, standing for impact of discharges of micro-pollutants coming from WWTP into the river Arve. The intent was to investigate the dispersion of pharmaceuticals downstream the WWTP. Concerns about water contamination in the area are sensitive especially because of the French-Swiss border and the fact that water from the Arve river is injected directly into the water table that provides potable water to nearby cities (especially Geneva). More measures were added to quantify pharmaceuticals loads in rivers (Arve and Rhône), at other WWTP outlets and in the water table (figure 5). Also three 7 consecutive days daily sampling campaigns were done at both inlets of Bellecombe WWTP to examine pharmaceuticals loads day to day variations.

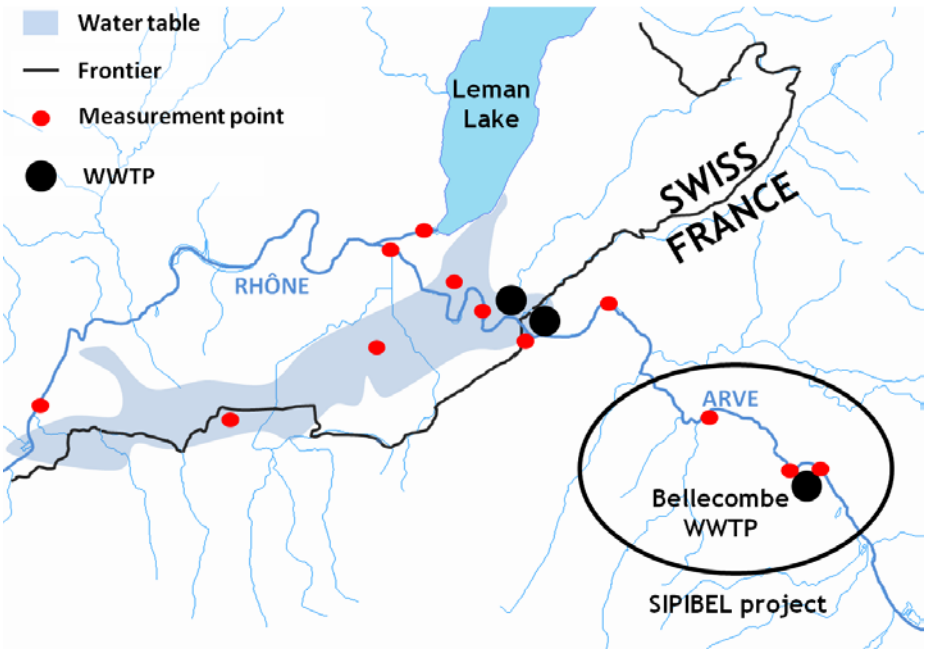


Figure 5: Locations of measurements in SIPIBEL and IRMISE projects (From GRAIE (2016))

A third project started in 2014 to further develop the research: SIPIBEL-RILACT for risks and levers of actions relative to micro-pollutants. New measurements were planned to explore hourly variations of pharmaceuticals loads at both inlets of Bellecombe WWTP, and also degradation of pharmaceuticals inside sewers (in-situ and laboratory measurements).

The three projects have many more objectives. Complete descriptions can be found at www.sipibel.org (Lecomte, 2016).

4.2 THE URBAN CATCHMENT

Population

The WWTP collects the wastewater of 14 small cities, which account for approximately 30 000 inhabitants in 2013. However, the characteristics are not homogeneous within the site (table 3). Population ranges from a little more than 500 inhabitants to more than 7300 per city.

Table 3: City by city information on population, jobs and connection to the sewer system.

City name	Estimated population in 2013	Number of active people in 2012	Proportion of active people in the population (%)	Number of jobs in the city in 2012	Number of active people per job	Estimated number of households connected to the WWTP in 2013	Proportion of connected people (≈2.23 people per household)(%)
Arbusigny	1 071	568	53	152	3.74	112	23
Arenthon	1 569	791	50	218	3.63	149	21
Arthaz-Pont-Notre-Dame	1 317	611	46	135	4.53	319	54
Bonne	3 141	1 446	46	703	2.06	114	8
Contamine-sur-Arve	1 747	843	48	1 421	0.59	453	58
Faucigny	523	256	49	78	3.28	111	47
Fillinges	3 289	1 595	48	954	1.67	1 133	77
La Muraz	1 102	571	52	81	7.05	167	34
Marcellaz	890	450	51	70	6.43	317	79
Monnetier-Mornex	2 408	1 039	43	474	2.19	1 040	96
Nangy	1 687	890	53	236	3.77	551	73
Pers-Jussy	2 792	1 354	48	440	3.08	501	40
Reignier-Ésery	7 353	3 510	48	1 694	2.07	1 692	51
Scientrier	1 126	608	54	359	1.69	396	78
TOTAL	**30 015**	**14 532**		**7 015**		**7 055**	
Minimum	523	256	43	70	0.59	111	8
Average	2 144	1 038	49	501	3	504	53
Maximum	7 353	3 510	54	1 694	7.05	1 692	96

According to local statistics (INSEE, 2012), one can divide the population in three groups: 48 % are working adults, 28.4 % are non-working adults (retired, unemployed and others) and 23.6 % are children or students. The distribution of these groups seems quite homogenous throughout the site. Indeed, the proportion of active people in the population of each city ranges from 43 to 54 % (table 3). The statistics for the composition of households are shown in table 4.

Table 4: Composition of households. The number of children distribution are identical for both households with one or two adults, this is because available data did not allow distinguishing the two cases.

Household type	(%)	Number of children (%)				
		0	1	2	3	4+
Single adult	35.1	100	-	-	-	-
2 adults without child	26.6	100	-	-	-	-
2 adults with child	29.8	-	43.2	41.5	12.4	2.9
1 adult with child	8.5	-	43.2	41.5	12.4	2.9

In 2012, approximately 14 500 active people were living in the Bellecombe site, but there was only approximately 7 000 jobs. As a result, there is a huge variation in the number of people present through the day. Here again, the situation is quite different from one city to another. The number of active people per job in the city ranges from 0.6 to 7. Only one city has a ratio under 1, it is the city of Contamine-sur-Arve in which the new CHAL hospital was constructed. One should note that the area is not far from Geneva and that a lot of French workers are crossing the border every day. Minimal seasonal variations are expected as there are no significant tourism infrastructures and a negligible proportion of secondary houses.

Pharmaceuticals sales

Gaining access to local and detailed pharmaceuticals sales data can be quite a journey. The goal here was to try and obtain the most spatially and temporally accurate data.

The first option was to ask governmental heath care system agencies. But the only available data are national or regional yearly sales of reimbursed drugs. In other words, they are inaccurate and incomplete.

The second option was to identify the pharmacies that provide the urban catchment and ask for their sales data. Six pharmacies were identified (Tillon, 2013). Five of them agreed to share their sales data on a weekly basis. But, the only possible next step was to print their complete sales record and to later search for the products containing the investigated molecules. For one year of weekly sales it would represent a total of more than 7 000 pages…

Pharmacies are resupplied by only a few companies (3 for those 6 pharmacies). So the third option was to contact the GIE-GERS an economic interest group which gathers all main pharmaceutical companies as the pharmacies suppliers. One of the GIE-GERS missions is to collect sales data. Unfortunately, they did not want to share their records with the requested level of details.

The final option was to buy the data from 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. The obtained data were:

- grouped monthly sales of the six pharmacies in the urban catchment for 2.5 year starting on January 2012,
- grouped monthly sales of the pharmacies in Haute-Savoie for 2.5 years starting on January 2012. Haute-Savoie is a French administrative area with a population of 793 342 inhabitants in 2013 and with 223 pharmacies (French Chamber of Pharmacists, 2017) including the six of Bellecombe.

Also, a few healthcare organisations have been identified in the catchment (Tillon, 2013). Some of them are not prone to discharge pharmaceuticals due to their activity. The others are mainly supplied by the local pharmacies, so their pharmaceutical consumption and their potential of discharge are accounted for.

Water usages and wastewater

A diagnostic of the sewer system was made in 2012, primarily to investigate infiltration and inflow (RDA74, 2010). The diagnostic also explored drinking water demand and wastewater contributions.

Water is used for a few different activities. Depending on the activity, wastewater can be produce and maybe collected by the sewer system. Three main activities have been identified on the catchment:

- Domestic: an important part of the population of the urban catchment is not connected to the sewer system and uses individual septic tanks. But, approximately 7 055 households are connected to the sewers in 2013. That represents roughly 16 000 inhabitants (a little more than 50 % of the total population). The situation is quite contrasted from one city to another, as the connection proportion ranges from 8 to 96 % (table 3). The city with 8 % connected households is a particular case as most of it is connected to another sewer system.
- Agriculture and livestock farming: those activities consume a large volume of water. Most of it is not discharged to the sewers and reaches directly the environment.
- Other economic activities (industry, service firms…): summing drinking water volumes used by those companies, one can estimate that they contribute to 20.5 % in the production of wastewater.

Sewer system

According to the diagnostic study (RDA74, 2010), the sewer network is spread over 130 km², and includes 230 km of circular pipes never larger than 0.5 m in diameter (figure 6). The sewer structure is not meshed, so the flow direction is always known. It is mostly a separate network (a few hundred meters are combined).

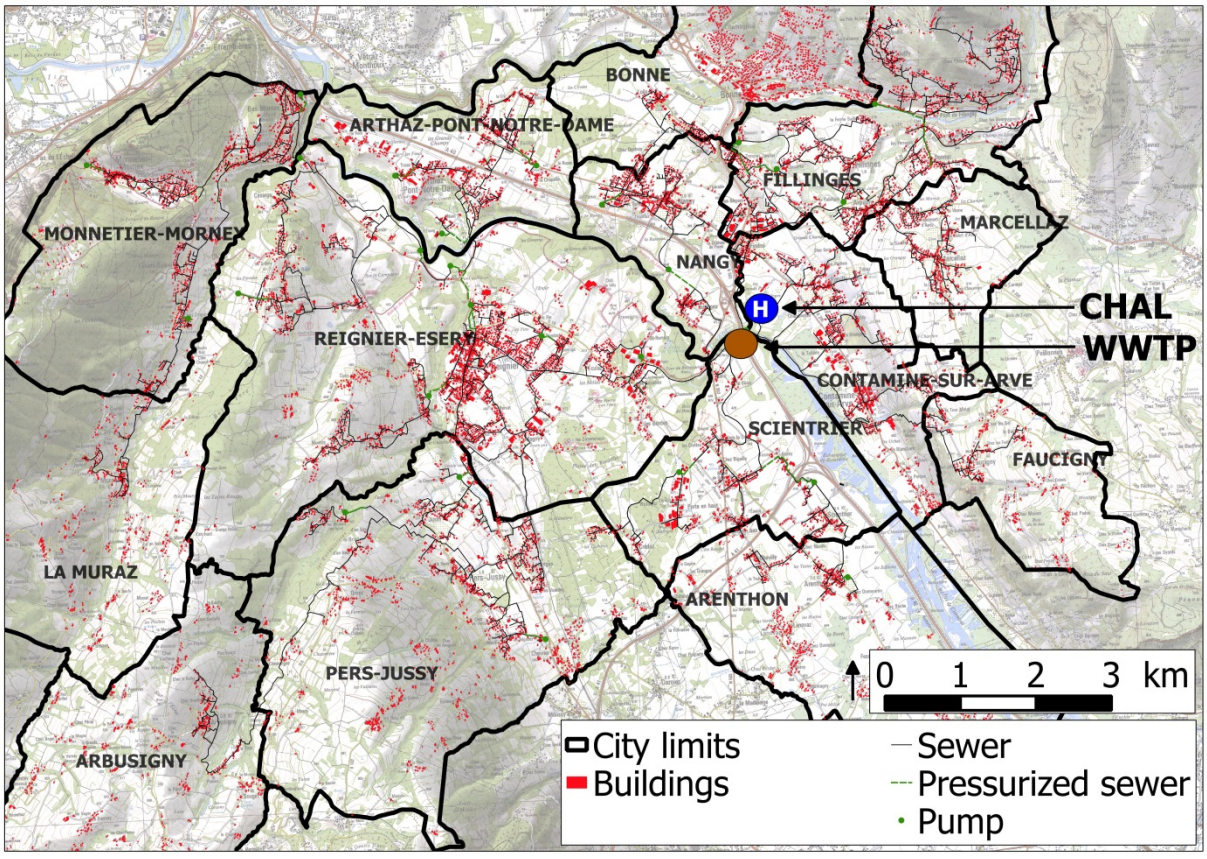


Figure 6: Bellecombe urban catchment map with sewer system (From RDA74 (2010)).

The landscape is quite hilly, indeed the altitudes of the households range from 405 to 1 303 m and the WWTP is situated at 439 m. As a consequence, there are 29 pumping stations with pressurized pipes to overcome the elevation differences. Some pumping stations are structurally important and receive large volumes of wastewater. For example, one station is located just upstream the WWTP and receives approximately 31 % of the wastewater daily volume (figure 7). It impacts greatly the shape of the daily hydrograph at the inlet of the WWTP, creating a much hatched profile.

Figure 7: Example of a pumping station. Under A: chamber inlet, under B: water level probes, under C: pumps and under D: pumps exhaust pipes

Finally, it has been reported important problems of infiltration and inflow in the sewer system (RDA74, 2010) as probably rain and groundwater infiltrations.

4.3 THE CHAL HOSPITAL

Hospital activities and frequentation

The CHAL is a general hospital with all the main specialties: maternity, gynaecology, surgery, cancerology, ophthalmology… There are approximately 450 beds available and an important ambulatory activity. The staff is composed of approximately 1 500 agents on shifts. Laundry services are not on site, so they do not affect the wastewater flow.

Duration of hospitalization

French statistics (SAE Diffusion, 2015) indicate that the average duration of hospitalization is 5.17 days and that 9.9 % of patients stay 0 day (no night). It can be represented by a floored lognormal distribution with parameters μ equal to 1.262 and σ equal to 0.974. It is then possible to calculate, for a random patient on a random day, the probable remaining hospitalization duration. It is fitted to a floored lognormal distribution with parameters μ equal to 0.546 and σ equal to 1.133 (figure 8).

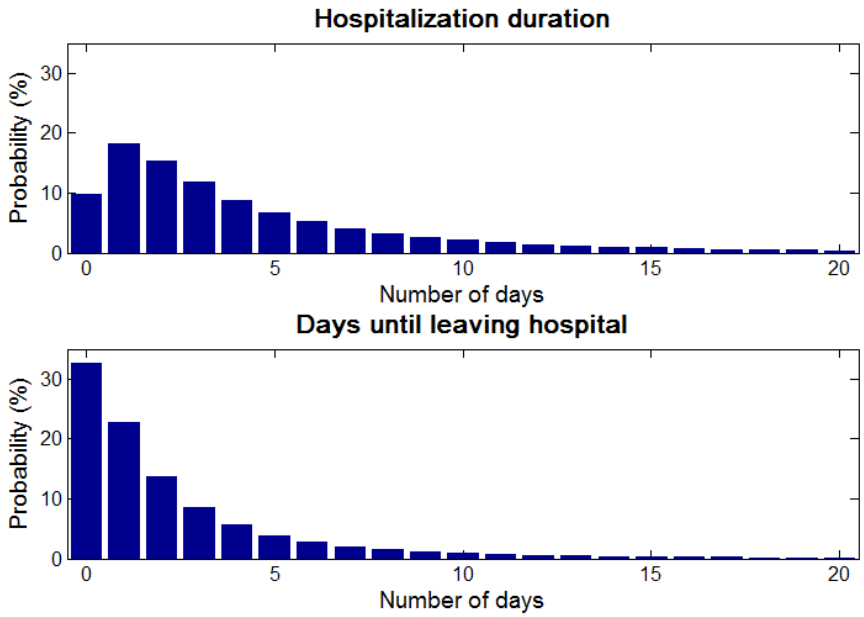


Figure 8: Probability of the total hospitalization duration and the remaining hospitalization duration for any patient on a random day.

Pharmaceuticals distribution

Each service has its own local pharmacy. But they are all provided by a unique central pharmacy that deals with stocks and sales. As the hospital is a partner of the SIPIBEL projects, there were no administrative or technical difficulties to gain access to distribution data. The best time resolution available is daily distribution and the data are brand specific. The following data were retrieved from to March 2012 to October 2014:

- 120 days of distribution: the dates corresponds to the sampling campaigns and the four previous days,
- 138 consecutive weeks of distribution,
- 32 consecutive months of distribution.

The inventory of the central pharmacy is managed by a robot (figure 9). Any in or out is processed by it. This ensures an optimal confidence level in the data provided.

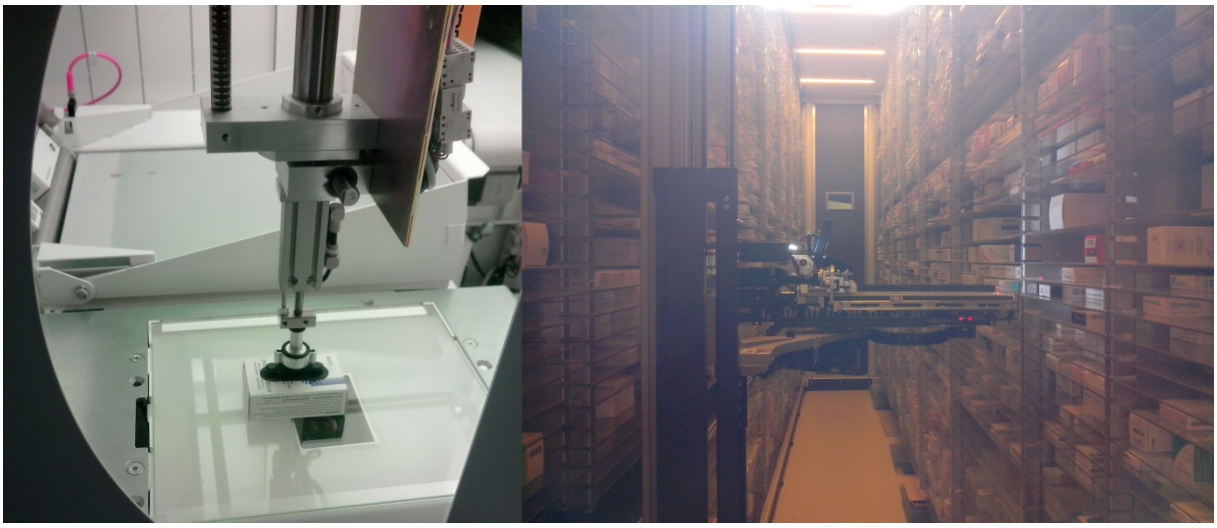


Figure 9: CHAL central pharmacy robots. On the left, the first robot scans every package entering the central pharmacy. On the right, one of the robots that store and retrieve packages on demand.

Sewer system network

As the hospital wastewater was required to be treated separately from other urban wastewater, a new sewer system was built. The hospital is located only a few hundred meters from the WWTP. So the network consists of one relatively straight pipe of approximately 500 m and a pumping station just upstream the WWTP (figure 10).

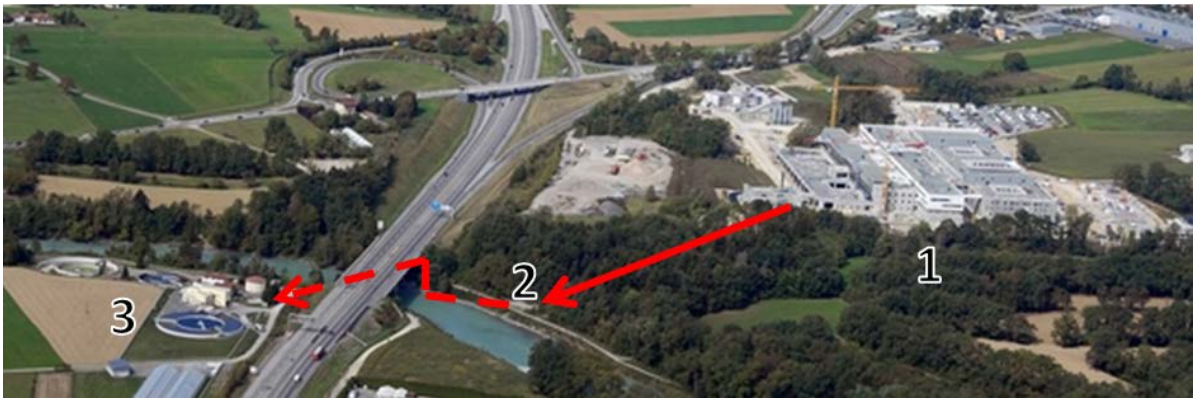


Figure 10: CHAL location (Source: modified from Bellecombe Syndicate). Above number 1 is the CHAL under construction. Number 2 is the pumping station necessary to cross the Arve river. Next to number 3 is the Bellecombe WWTP that treats separately the wastewater coming from the CHAL and the urban catchment. The plain arrow represents the gravitational pipe part of the sewer, and the dotted arrow represents the part where the wastewater is under pressure.

4.4 MOLECULES OF INTEREST

In Europe, more than 3 000 active substances of pharmaceutical drugs are sold in the form of more than 11 000 different products. With the available technology it is impossible to measure all of them at reasonable costs. Thus, prior to this thesis and at the beginning of the SIPIBEL project, pharmaceutical molecules were screened to establish a list of molecules of interest. Using the pharmaceutical consumptions of the hospital which was being replaced by the CHAL, and different studies (Besse, 2010; Boillot, 2008; Mullot, 2009), 47 molecules were selected (appendix 22) for their consumption levels and potential risks towards the environment and human health. This list of 47 molecules was compared to the analytical capabilities and prices of three laboratories (CNRS-SCA in Solaize, TZW in Karlsruhe and LPTC-LDE in Bordeaux). Due to the volume of sample necessary for such analyses, only one laboratory could be chosen. CNRS-SCA was finally selected. Its objectives were to develop multi-residues methods for the dissolved fraction, the particulate fraction and metabolites. For the dissolved fraction, limits of detection (LoD) close or inferior to 0.1 ng/L were expected. At the end, 15 molecules could be analysed simultaneously thus saving money, time and volume of samples.

In order to gain rapid knowledge about the selected molecules a short generic identity card (ID) is presented for each of them. Those IDs were established regarding the further objectives of the thesis. The information was gathered in the course of the years 2014-2015 on several pharmaceutical database websites (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) and with the VIDAL dictionary (a French medical dictionary that regroups information on all the commercial pharmaceutical specialities). The coefficients found in other water contamination studies were not used, because they are derived from the same medical sources and they are interpreted in their own context.

The IDs contain the following information:

- **Abbreviation**: in this document the first three letters of the molecule.
- **Chemical formula** and its graphical representation (https://en.wikipedia.org)
- **Therapeutic class**: indicates what function the molecule fulfils. Some molecules have many functions. Only the mains functions are cited here.
- **Main medical use(s)**: main diseases or problems treated with the molecule.
- **French legal status**: indicates the condition of sale. A molecule can be bought “over the counter” in some products and by prescription only in other products. Some molecules are only accessible via hospital structures (or likewise structures). Here, it is the most permissive option that is displayed (for one molecule some specialities can be restricted to hospital uses, while the rest of them can be bought without prescription). It could be one of three options (most to least permissive): no prescription needed, prescription only and prescription only in hospital.
- **DDD**: stands for Defined Daily Dose. According to the World Health Organisation (WHO, 2014):

  “The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.”

  It is a statistical indicator assessing the consumption of pharmaceuticals and helps to compare consumption between different countries. It does not reflect the recommended posology, which could in fact change from one country to another.

- **Main administration routes and dosages**: pharmaceuticals can be consumed in many different ways, thus having many different behaviours and kinetics properties. The main administration routes, with decreasing importance, are: oral route via tablets, soluble powder or syrup; injection especially in blood (intravenous: IV); dermal application via creams and gel; eye drops; inhalation... Here, only the mains routes of administration are cited jointly with the dosage of the molecule in the products.
- **Posology**: pharmaceuticals are meant to be consumed at specific dosage respecting a specific daily pattern. Here, the recommended dosage and consumption pattern of the molecule is described. More than one dosage/pattern pair can be described if necessary, especially for molecules with multiple administration routes.

- **Pharmacokinetics**: it is the study of the fate of pharmaceutical throughout the body. It especially assesses the transformation a molecule undergoes and the rate at which it happens. As pharmaceuticals cover a vast range of molecules with many different properties, their subsequent routes, transformations and rates inside the human body could be very different. Also from one human being to another all those parameters may change. However, the basic pattern for an orally taken product is the following one:

  After oral ingestion of a pharmaceutical product, the molecule is released inside the gastrointestinal tract. From there, a fraction of it (the absorbed fraction) passes into the blood system. This absorbed fraction is most of the time partly metabolized by the liver and then filtered out to the bladder by the kidneys. Finally it will be excreted from the body, most of the time via urine and faeces.

  Intravenous products directly enter the blood system, and then follow the same fate as orally taken products.

  This description is a rough attempt to give a generic idea of what might happen in the human body. Many more complicated processes can and do happen frequently. For example, the molecule often dispersed itself in other body parts (muscle, fat…). Also, the molecule may circulate back to the gastrointestinal tract and again to the blood system. Lastly, other body systems or organs, such as the biliary system, may play important roles.

- **Metabolites**: the products of the molecule transformation are called metabolites. They can be inactive or active in the human body and in the environment. In the huge range of metabolites, some are just the result of a conjugation reaction, and may sometime be easily de-conjugated afterward in water, making the parent compound reappearing. For those reasons it is important to investigate both the molecule and its metabolites. As exposed in the literature review (chapter 3), there are two types of conjugated metabolites that are assumed to de-conjugate easily in the environment and in wastewater: glucuronic acid conjugates and sulphate conjugates. Here the focus is set on those two metabolites as they will play a role in the modelling part of the thesis

These ID cards are meant to be as precise and complete as possible, but it is not always possible. Also, both Paracetamol and Salicylic acid have an additional first entry on their ID card because of their specificity.

4.4.1 ATENOLOL

Abbreviation: ATE

Chemical formula: $C_{14}H_{22}N_2O_3$

Therapeutic class: beta blocker

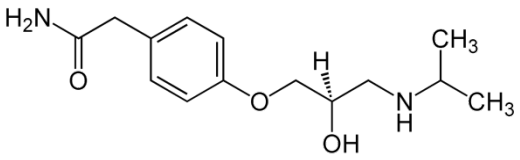


Figure 11: Atenolol molecular structure

Main medical uses: cardiovascular diseases such as hypertension, angina pectoris, and myocardial infarction

French legal status: prescription only

DDD: 75 mg

Main administration routes and dosages: mainly as oral tablets (50 or 100 mg), and IV (5 mg)

Posology: for oral tablets, 50 to 100 mg once a day for an adult (recommended in the morning); for IV, during myocardial infarction, 5 to 10 mg during the crisis, injected slowly 1 mg per minute.

Pharmacokinetics: after an oral intake, the dose is rapidly but incompletely absorbed from the gastrointestinal tract (approximately 50 %). The un-absorbed fraction is excreted unchanged. Maximum concentration in blood is reached between 2 and 4 h after intake. The absorbed fraction undergoes little metabolism by the liver and is primarily eliminated by renal excretion. Approximately 50 % of the dose is found unchanged in the faeces, and 40 to 50 % in the urine. For IV dose, over 85 % of the dose is found in the urine. The total elimination half-life ranges from 6 to 7 h.

Metabolites: no glucuronic acid or sulphate reported

4.4.2 AZTREONAM

Abbreviation: AZT

Chemical formula: $C_{13}H_{17}N_5O_8S_2$

Therapeutic class: antibiotic

Main medical use: infection

French legal status: prescription only in hospital

DDD: 225 mg

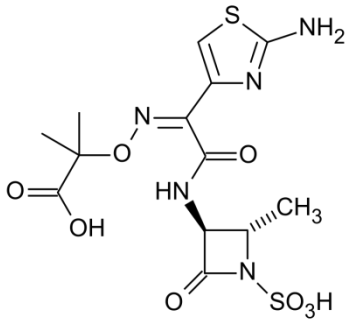


Figure 12: Aztreonam molecular structure

Main administration routes and dosages: injection (1 g), or inhalation (75 mg)

Posology: for injection, 2 to 3 g per day every 12 or 8 hours; for inhalation, 75 mg 3 times a day up to 28 days with at least 4 hours between intakes.

Pharmacokinetics: the molecule is badly absorbed from the gastrointestinal tract (less than 1 %), so it is never administered as such. Approximately 90 % of the dose is found unchanged in the urine. The blood half-life ranges from 1.5 to 2 h.

Metabolites: no glucuronic acid or sulphate reported.

4.4.3 CARBAMAZEPINE

Abbreviation: CAR

Chemical formula: $C_{15}H_{12}N_2O$

Therapeutic class: anticonvulsant

Main medical uses: epilepsy and neuropathic pain

French legal status: prescription only

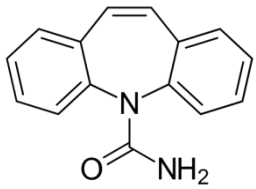


Figure 13: Carbamazepine molecular structure

DDD: 1 g

Main administration routes and dosages: oral tablet (rarely 20 mg, mainly 200 and 400 mg), can be found as extended-release tablet

Posology: 200 to 1600 mg per day in 2 to 3 intakes

Pharmacokinetics: the absorption from the gastrointestinal tract is almost complete (approximately 90 %) but slow. Maximum concentration in blood is reached between 6 and 12 h for normal tablets (up to 24 h for extended-release tablets). It is heavily metabolized by the liver. Approximately 2 % of the dose is found unchanged in the urine. The total elimination half-life ranges from 25 to 65 h (down to 12 to 17 h on repeated doses).

Metabolites: most of the molecule is excreted as metabolites (approximately 88 %). Its main metabolite is carbamazepine - 10, 11 epoxide which presents the same active properties as carbamazepine. Glucuronic acid is sometimes reported.

4.4.4 CIPROFLOXACIN

Abbreviation: CIP

Chemical formula: $C_{17}H_{18}FN_3O_3$

Therapeutic class: antibiotic

Main medical use: infection

French legal status: prescription only

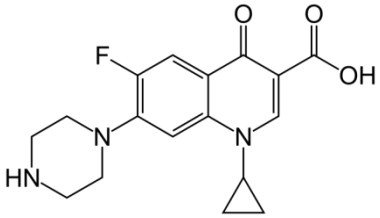


Figure 14: Ciprofloxacin molecular structure

DDD: 1 g

Main administration routes and dosages: mainly oral tablet (250, 500 and 750 mg), IV (200 mg or 400 mg) and eye drops (10 mg)

Posology: for tablets, 250 to 750 mg twice a day during 7 to 14 days; for IV, 400 mg in 60 minutes 2 to 3 times a day

Pharmacokinetics: the absorption from the gastrointestinal tract is important (70 to 80 %) and rapid. Maximum concentration in blood is reached between 1 and 2 h after intake. Approximately 45 % of the dose is found unchanged in the urine. The total elimination half-life ranges from 4 to 7 h.

Metabolites: 4 metabolites have been identified that account for approximately 15 % of an oral dose. One of them is sulfo-ciprofloxacin.

4.4.5 DICLOFENAC

Abbreviation: DIC

Chemical formula: $C_{14}H_{11}Cl_2NO_2$

Therapeutic class: nonsteroidal anti-inflammatory with antipyretic and analgesic actions

Main medical uses: pain, inflammatory disorders and dysmenorrhea

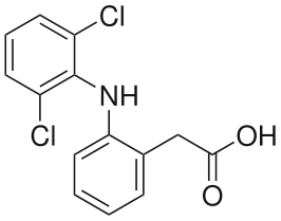


Figure 15: Diclofenac molecular structure

French legal status: no prescription needed

DDD: 100 mg

Main administration routes and dosages: mainly oral tablets (mainly from 50 to 100 mg), and dermal application (mainly from 500 to 1000 mg)

Posology: for tablets, 50 to 200 mg in 2 to 3 intakes preferably not during meal; for dermal forms, approximately 40 mg 3 times a day.

Pharmacokinetics: the absorption from the gastrointestinal tract is almost complete (approximately 100 %) and rapid. Maximum concentration in blood is reached between 0.33 and 1 h. For dermal forms, the dose entering the body is relatively low (6 to 20 %) and the process is quite slow (peak blood concentration from 10 to 20 h). Once in the blood system, the molecule is rapidly and heavily metabolized (half-life from 1 to 2 h). Approximately 1 % of the dose is found unchanged in the urine.

Metabolites: glucuronic acid and sulphate are found and account for 5 to 18 % of the dose.

4.4.6 ECONAZOLE

Abbreviation: ECO

Chemical formula: $C_{18}H_{15}Cl_3N_2O$

Therapeutic class: antifungal

Main medical use: skin infections

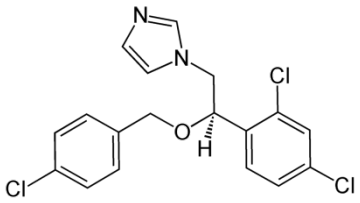


Figure 16: Econazole molecular structure

French legal status: prescription only

DDD: 88 mg

Main administration routes and dosages: dermal application (300 mg), or intravaginal (150 mg)

Posology: approximately 40 mg twice a day

Pharmacokinetics: extremely low absorption rate from dermal application. It is metabolized by the liver. It is intended to stay on the skin.

Metabolites: no glucuronic acid nor sulphate reported.

4.4.7 ETHINYLESTRADIOL (EE2)

Abbreviation: ETH

Chemical formula: $C_{20}H_{24}O_2$

Therapeutic class: hormone

Main medical use: oral contraception

French legal status: prescription only

DDD: 25 µg

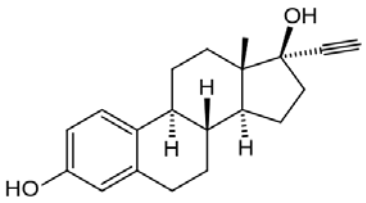


Figure 17: Ethinylestradiol molecular structure

Main administration routes and dosages: mainly oral tablet (from 0.02 to 0.05 mg)

Posology: one tablet once a day

Pharmacokinetics: the molecule is rapidly (peak blood concentration approximately 2 h) and almost completely absorbed (approximately 90 %). It is heavily metabolized with recirculation metabolism processes. The total elimination half-life ranges from 23 to 49 h.

Metabolites: no glucuronic acid or sulphate reported.

4.4.8 IBUPROFEN

Abbreviation: IBU

Chemical formula: $C_{13}H_{18}O_2$

Therapeutic class: nonsteroidal anti-inflammatory

Main medical uses: pain, fever and inflammation

French legal status: no prescription needed

DDD: 1.2 g

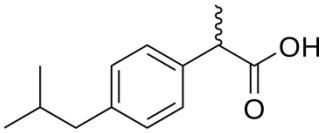


Figure 18: Ibuprofen molecular structure

Main administration routes and dosages: mainly oral tablet (mainly 100 to 400 mg, also rarely 3 g and 4 g), dermal application (3 or 5 g)

Posology: 200 or 800 mg with 6 h between intakes and a maximum daily dose of 1.2 g

Pharmacokinetics: the absorption from the gastrointestinal tract is almost complete (approximately 80 %) and rapid. Maximum concentration in blood is reached between 15 minutes and 2 h. It is heavily metabolized by the liver. Less than 10 % of the dose is found unchanged in the urine. The total elimination half-life ranges from 2 to 4 h.

Metabolites: approximately 90 % of the dose is found metabolized in the urine, mainly as glucuronic acid.

4.4.9 KETOPROFEN

Abbreviation: KET

Chemical formula: $C_{16}H_{14}O_3$

Therapeutic class: nonsteroidal anti-inflammatory

Main medical use: arthritis-related inflammatory pains

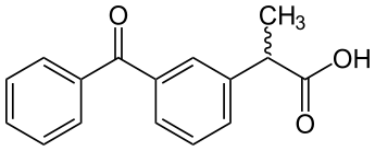


Figure 19: Ketoprofen molecular structure

French legal status: prescription only

DDD: 100 mg

Main administration routes and dosages: oral tablet (mainly 50 to 200 mg), IV (100 mg) and dermal application

Posology: for tablets, 25 to 200 mg 1 to 4 times a day, with a maximum daily dose of 200 mg; for creams, approximately 40 mg 1 to 3 times a day

Pharmacokinetics: the absorption from the gastrointestinal tract is almost complete (approximately 80 %) and rapid. Maximum concentration in blood is reached between 30 minutes and 2 h. It is heavily metabolized by the liver. Less than 10 % of the dose is found unchanged in the urine. The total elimination half-life ranges from 1.1 to 4 h.

Metabolites: approximately 80 % of the dose is metabolized, mainly as glucuronic acid.

4.4.10 MEROPENEM

Abbreviation: MER

Chemical formula: $C_{17}H_{25}N_3O_5S$

Therapeutic class: antibiotic

Main medical use: infections

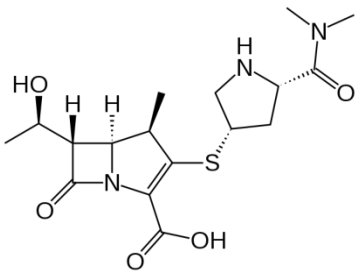


Figure 20: Meropenem molecular structure

French legal status: prescription only in hospital

DDD: 2 g

Main administration routes and dosages: IV (1 g)

Posology: 0.5 to 1 g every 8 h injected in 15 to 30 minutes

Pharmacokinetics: approximately 70 % of the dose is found unchanged in the urine. The total elimination half-life is approximately 1h.

Metabolites: one inactive metabolite

4.4.11 PARACETAMOL

Other name: the molecule is also known as acetaminophen

Abbreviation: PAR

Chemical formula: $C_8H_9NO_2$

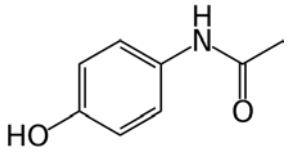


Figure 21: Paracetamol molecular structure

Therapeutic class: analgesic, antipyretic

Main medical uses: pain and fever

French legal status: no prescription needed

DDD: 3 g

Main administration routes and dosages: mainly oral tablet (mainly 500 mg and 1 g) and IV (mainly 500 mg and 1 g)

Posology: 500 mg to 1 g every 4 h minimum with a maximum daily dose of 3 g

Pharmacokinetics: the absorption from the gastrointestinal tract is almost complete (approximately 100 %) and rapid. Maximum concentration in blood is reached between 30 minutes and 2 h. It is heavily metabolized by the liver. Less than 5 % of the dose is found unchanged in the urine. The total elimination half-life ranges from 1 to 4 h.

Metabolites: the molecule is primarily excreted in urine as glucuronic acid (45 to 55 %) and sulphate (30 to 35 %)

4.4.12 PROPRANOLOL

Abbreviation: PRO

Chemical formula: $C_{16}H_{21}NO_2$

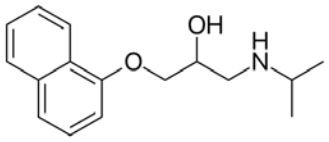


Figure 22: Propranolol molecular structure

Therapeutic class: beta-blocker

Main medical uses: cardiovascular diseases such as hypertension, angina pectoris, and myocardial infarction

French legal status: prescription only

DDD: 160 mg

Main administration routes and dosages: oral tablet (40, 80 or 160 mg), rarely IV (5 mg)

Posology: 40 to 160 mg 1 to 4 times a day with a maximum daily dose of 160 mg

Pharmacokinetics: the absorption from the gastrointestinal tract is almost complete (approximately 100 %) and fairly rapid. Maximum concentration in blood is reached between 1 and 6 h. It is heavily metabolized by the liver. Less than 5 % of the dose is found unchanged in the urine. After injection in the blood system the total elimination half-life ranges from 8 to 12 h.

Metabolites: direct glucuronidation is one of the three main metabolism pathways for the molecule (approximately 17 %).

4.4.13 (ACETYL)SALICYLIC ACID

IMPORTANT comment: salicylic acid is actually a metabolite of acetylsalicylic acid with the same therapeutic properties. Since acetylsalicylic acid is not excreted but salicylic acid is, the latter is always measured instead of the parent compound. However, acetylsalicylic acid is described here. The molecule is also known as aspirin.

Abbreviation: SAL

Chemical formula: $C_9H_8O_4$

Therapeutic class: analgesic, antipyretic, anti-inflammatory and anti-coagulant

Main medical uses: pain, fever, inflammation and secondary prevention in cardiovascular diseases

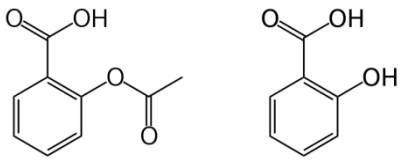


Figure 23: Acetylsalicylic acid (left) and salicylic acid (right) molecular structure

French legal status: no prescription needed

DDD: 3 g

Main administration routes and dosages: oral tablet or powder (mainly 75, 160, 300, 500 and 1 000 mg)

Posology: 500 mg to 1 g every 4 h minimum with a maximum daily dose of 3 g

Pharmacokinetics: the absorption from the gastrointestinal tract is almost complete (approximately 100 %) and rapid. Maximum concentration in blood is reached between 15 and 40 minutes. It is heavily metabolized. The molecule is not excreted unchanged.

Metabolites: the molecule is rapidly and completely metabolized. The molecule is transformed in salicylic acid, which is then partially metabolized in salicyluric acid and glucuronic acid. The total elimination half-life for salicylic acid ranges from 2 to 4 h. Excretion rates for those metabolites are highly variable especially due to pH. Salicylic acid and its glucuronic acid form seem to compensate each other to account globally for approximately 40 % of the original dose of aspirin (salicylic acid: 1.3 to 31 %, glucuronic acid form: 0.8 to 42 %).

4.4.14 SULFAMETHOXAZOLE

Abbreviation: SUL

Chemical formula: $C_{10}H_{11}N_3O_3S$

Therapeutic class: antibiotic

Main medical use: bacterial infection

French legal status: prescription only in hospital

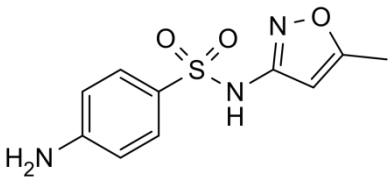


Figure 24: Sulfamethoxazole molecular structure

DDD: 2 g

Main administration routes and dosages: oral tablet (200, 400 and 800 mg) and IV (400 mg)

Posology: 800 mg every 12 h minimum (duration of IV: 60 minutes)

Pharmacokinetics: the absorption from the gastrointestinal tract is important (70 to 90 %) and rapid. Maximum concentration in blood is reached between 0.5 and 2 h. Approximately 20 % of the dose is found unchanged in the urine. After injection in the blood system the total elimination half-life is approximately 8.5 h.

Metabolites: Glucuronic acid conjugates of the molecule are found in urine and represent 15 to 20 % of the original dose.

4.4.15 VANCOMYCIN

Abbreviation: VAN

Chemical formula: $C_{66}H_{75}Cl_2N_9O_{24}$

Therapeutic class: antibiotic

Main medical use: bacterial infection

French legal status: prescription only in hospital

DDD: 2 g

Main administration routes and dosages: IV (125, 250, 500 and 1 000 mg)

Posology: 500 mg every 6 h, or 1 g every 12h (maximum daily dose 2 g)

Pharmacokinetics: the molecule undergoes little or no metabolism. After injection in the blood system the total elimination half-life ranges from 4 to 11 h. After 24 h, 75 % of the original dose is recovered unchanged in the urine.

Metabolites: no glucuronic acid nor sulphate reported.

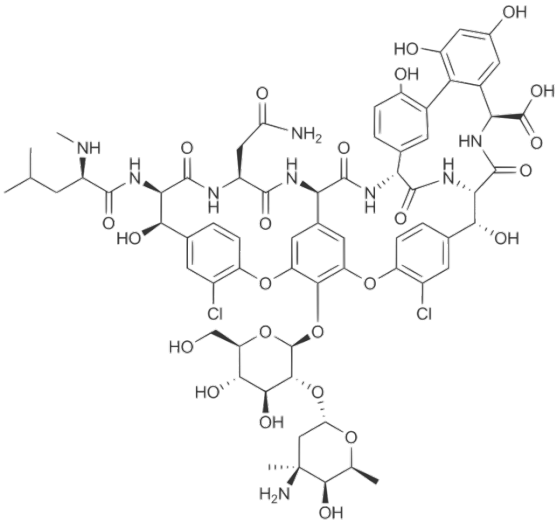


Figure 25: Vancomycin molecular structure

4.5 MEASUREMENT TECHNIQUES AND SAMPLING STRATEGIES

4.5.1 DISCHARGE MEASUREMENTS

For both inlets, urban catchment and CHAL hospital, the wastewater flow is measured at a minute time step by a Venturi channel coupled with an ultrasonic probe (table 5).

Table 5: Wastewater flowmeter and sampler information

		Venturi channel	Ultrasonic probe	Water sampler
Urban	Brand	Endress-Hauser	Endress-Hauser	Endress-Hauser
WWTP inlet	Type	QV 308	FMU 861 / FDU 80	ASP Station A
Hospital	Brand	ISMA	Endress-Hauser	Endress-Hauser
WWTP inlet	Type	Type 2	Prosonic FMU 90	ASP Station 2000

Two full years (2012 and 2013) were retrieved for analysis. Also, daily and hourly wastewater volumes are recorded whenever a measurement campaign happen.

4.5.2 PHARMACEUTICALS CONCENTRATION MEASUREMENTS

Four types of measurements campaigns have been done:

- "**24 h**": from March 2012, one 24 h average sample every month, always starting on a Tuesday at 8 am with analysis only of the dissolved fraction. 36 campaigns were made for the urban catchment and 47 for the CHAL hospital.
- "**7 x 24 h**": 7 consecutives 24 h average samples, with analysis only of the dissolved fraction. 3 campaigns were made for both sites starting on 25/06/2013, 18/09/2013 and 21/05/2014.
- "**24 x 1 h**": 24 consecutives 1 h average samples, always starting on a Tuesday at 8 am with analysis only of the dissolved fraction. For the urban catchment, 4 campaigns were made (29/09/2015, 17/11/2015, 19/01/2016 and 15/03/2016) and 3 for the CHAL hospital (27/10/2015, 17/11/2015 and 09/02/2016).
- "**24 h particulate**": one 24 h average sample, always starting on a Tuesday at 8 am with analysis only of the particulate fraction. 8 campaigns were made for both sites between 2013 and 2015.

All the campaigns dates were a compromise between regularity (one per month for "24h"), technical feasibility, rain conditions (huge infiltrations in the sewer system dilute pharmaceuticals) and calendar specificity (no vacation period, no weekend).

The objective of the measurements was to quantify the 15 molecules investigated amongst numerous other parameters (more than 130 parameters in total). As very low pharmaceutical concentrations were expected (a few ng to µg), huge efforts have been made to minimize contamination problems. As a result the whole procedure evolved until the summer of 2013. Blank samples were regularly tested to detect problems and correct data if possible.

The characteristics of the measurements are described by Lecomte (2016). They are strongly derived from French technical guidelines (Aquaref, Cemagref, 2011). They are summarized and translated in English here:

- **Sampling strategy**: a volume proportional strategy was used. The volume of each sub-sample is 100 mL (a 24 h average daily sample contains roughly 200 sub-samples). Knowing the wastewater discharge from the day before, the volume of wastewater triggering a sample is calculated to fill in one day a 20 L bottle for daily samples and a 1 L bottle for hourly samples. The models of the samplers are given in table 5.
- **Materials**: in order to minimize contamination and adsorption problems, all the parts of the sampling chain (from primary sampling to sub-sampling) and final container are preferably made of glass or polytetrafluoroethylene (PTFE or Teflon) when glass was not possible. Before each campaign, all materials is washed according to a standard protocol (appendix 2).
- **Sub-sampling method**: the primary sample is mechanically homogenized and distributed with a small peristaltic pump into different containers for the different analyses. For the pharmaceuticals analysis, a 1.5 L tinted glass bottle is used. To maximize homogeneity, the first third of all the containers are filled at the same time then the second and finally the third one.
- **Pharmaceutical analytical method**: in the 24 h after sampling, the samples are filtered, spiked with internal standards, extracted on solid phase and frozen until analysis by liquid chromatography in tandem with mass spectrometry. Limits of quantification ranges from 0.5 to 35 ng/L. This step is conducted by the Institute for analytical sciences (Lecomte, 2016 for details), one of the projects partner. Analytical uncertainties and average limits of detection (LoD) and quantification (LoQ) for the 15 molecules are presented in table 6.

Table 6: Analytical uncertainties and limits of detection and quantification for the 15 studied molecules (Source: Institute for analytical sciences). Analytical uncertainties are not provided for Aztreonam, Ethinylestradiol and Meropenem.

Molecule	LoD (ng/L)	LoQ (ng/L)	Analytical uncertainties at the measured concentration (%)
Atenolol	0.5	4.1	3
Aztreonam	8	50	-
Carbamazepine	0.2	0.6	4
Ciprofloxacin	3.5	35.3	27
Diclofenac	1	5	16
Econazole	0.6	1.2	27
Ethinylestradiol	0.4	7.3	-
Ibuprofen	0.2	0.5	20
Ketoprofen	1	9.8	7
Meropenem	8	50	-
Paracetamol	1.1	12.2	30
Propranolol	0.2	0.6	5
Salicylic acid	0.7	13.3	35
Sulfamethoxazole	1.2	5.9	25
Vancomycin	8	50	50

- **Data banking and quality rating**: all the analyses data are regrouped in one database by one single person to ensure coherence. A quality rating is attributed to each result: “Correct”, “Uncertain” or “Incorrect”. The rating was an aggregation of a set of indicators like: events during sampling, proper preparation of materials, proper sub-sampling, analyses problems, blank problems… (Lecomte, 2016).

CHAPTER 5: ABOUT THE MODEL

The goal of the model is to predict pharmaceutical loads of two consecutive week days at the inlet of a WWTP at a one minute time step resolution. The intent is to present a model as generic as possible that is not specific to the studied locations and that can be easily completed to fit situations not encountered here. It is fully developed on Matlab®2012a.

Whatever the catchment studied, the pharmaceutical loads (or any pollutant loads) at the outlet of the catchment are the result of the interactions between the sources of the pollutant and a converging structure that concentrates the pollutant at the outlet of the catchment. More than one type of source can be present. One should identify all types of source and quantify their contributions. Converging structures could be any element of a sewer network, or any natural hydrological system. One should describe pollutants transport and their possible transformations across the converging structure.

Three sources of pharmaceuticals in wastewater can be identified: human excretion, non-used pharmaceuticals direct discharges and industry discharges (chapter 2). In most cases, the predominant source is human excretion. Industry discharges depend on the industry presence and the characterization of its discharges. It is rather a special case, which is not occurring in the sites studied in this work. Direct discharges of non-used pharmaceuticals likely happen where there is human consumption. However, it is relatively difficult to assess them with accuracy. In the French context, one can expect that they are negligible in an urban catchment since the collection of unused pharmaceuticals is relatively efficient (Cyclamed, 2014). For the hospital, it is harder to assess. There is no national or local data on this subject. However, the regulation requires treating them as dangerous medical waste to be incinerated. In the CHAL hospital, it has been reported that intravenous bags have occasionally been emptied directly in sinks (Laquaz, 2015). In conclusion, it is acceptable, for both sites, to treat human excretion as the only source of pharmaceuticals in wastewater in the model.

However, most of the time, a catchment includes different types of population with different behaviours regarding pharmaceuticals consumption and discharge. So, it is necessary to identify these population sets and to quantify their contributions. In our case, three types of population are considered: inhabitants and workers for the urban catchment, and bedded patients for the CHAL hospital.

After being metabolized by the human body, pharmaceuticals can be found as untransformed compounds or metabolites. Some of those metabolites can be transformed back to the parent compound in sewers. Those metabolites need to be modelled as well, in order to model pharmaceuticals loads at the inlet of the WWTP. In this study, only two types of metabolites are investigated as they are known to be transformed back to the original pharmaceutical molecule (chapter 3): glucuronic acid conjugates and sulphate conjugates. Other metabolites could be modelled but are neglected here since there is only sparse data available.

Most of the processes that influence the sources contributions over time are not easily deterministically predicted. As a result, the model needs to be stochastic to try to represent a statistical truth about the catchment.

For both sites, the converging structure is a sewer network including pipes and pumping stations. As pollutants emitted at the same time in two different places are likely to reach the WWTP at different times, it is necessary to describe the sewer network.

Pharmaceuticals loads travel with the wastewater flow. So, it is necessary to model the wastewater contribution of the sources and the hydraulic behaviour of the different elements of the sewer network.

Thus, the model is a set of three fundamental elements that can be arranged in structures of different level of complexity to fit to the studied catchment and the available data relative to it. The three fundamental elements are: i) wastewater and pharmaceutical source, ii) pipe and iii) pumping station. They are capable to

either generate or transfer wastewater flow, pharmaceuticals loads and their glucuronic acid and sulphate conjugates.

The input data of the model are all relevant properties of the catchment (population description, sewer structure…) and records of pharmaceutical sales and distributions as precise as possible in both space and time. Dealing with the multiple scales of the available data is one of the main challenges of the model.

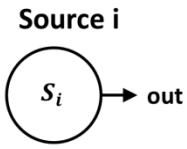
The first three parts of this chapter describe the three fundamental elements of the model: source (section 5.1), pipe (section 5.2) and pumping station (section 5.3). For each element, a brief introduction provides a graphic symbol, the input(s), the output(s), the parameter(s) and the goal of the element. Then the wastewater flow part of the model is described followed by the pharmaceutical loads part. For each fundamental element, the modelling of the pharmaceutical loads is, at least, partly linked to the modelling of the wastewater flow. Those descriptions are presented as a list of steps, without any justifications to keep the description of the model easy to follow. Finally, the hypotheses and choices of the model are discussed.

In section 5.4, the structures of both sites made with the three fundamental elements are presented. First, a generic structure of sources and pipes is presented. Named “main source area”, it simplifies the construction of the structure for both sites that are presented after. Finally, the resulting structures are discussed.

Finally, in section 5.5, the calibration and verification methods for the wastewater flow part of the model are presented, followed by the presentation of the verification methods of the pharmaceutical loads part of the model.

5.1 MODEL FUNDAMENTAL ELEMENT: SOURCE

Graphic symbol:



In: none

Out: wastewater flow and pharmaceuticals loads.

Parameters: number of households N_{house}, number of workers N_{worker} and number of hospital beds N_{H-bed} present in the source.

Goal: to generate the wastewater flow and pharmaceuticals loads of a population set from a determined source.

5.1.1 GENERATION OF WASTEWATER FLOW

The model generates the wastewater flow produced by the inhabitants of one household. It is meant to be used as many times as there are households in the source. Wastewater inflows are modelled as a series of pulses of a certain duration at a certain intensity and happening at a certain time.

The model is based on the simple hypothesis that the generation of domestic wastewater is linked to the drinkable water demand. Many studies have proposed models to predict water demands (Alcocer-Yamanaka *et al.*, 2012; Blokker, 2010; Blokker *et al.*, 2009; Buchberger and Wu, 1995; Buchberger and Wells, 1996; Buttler and Graham, 1995; García *et al.*, 2004). They are based on describing water demands as pulses. Using only census data on population and water uses (no calibration needed), the model proposed by Blokker *et al.* (2010) successfully predicts water demand flow in a small area in the Netherlands. Then Elías-Maxil *et al.* (2014) adapted it to predict wastewater in a small catchment in Amsterdam (295 inhabitants). It works under the assumption that a wastewater pulse is linked to a drinking water demand pulse. It is just delayed in time and has a different intensity, but the volume is conservative (figure 26).

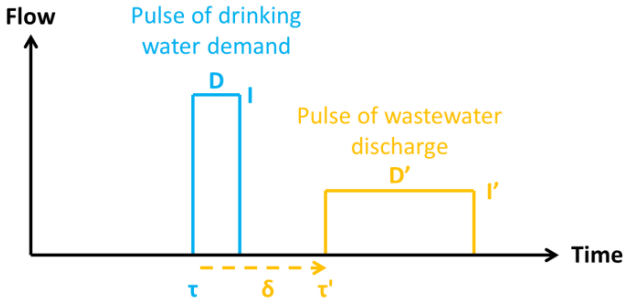


Figure 26: Link between a drinking water pulse and a wastewater pulse. D, I and τ are respectively the duration, intensity and occurring time of the drinking water pulse. D', I' and τ' are respectively the duration, intensity and occurring time of the wastewater pulse. The delay between the two pulses is noted δ.

$$D \times I = D' \times I'$$

$$\tau' = \tau + \delta$$

With:
D: duration of the pulse of drinking water demand (s)
I: intensity of the pulse of drinking water demand (m^3/s)
D': duration of the pulse of wastewater (s)
I': intensity of the pulse of wastewater (m^3/s)
τ': time of the pulse of wastewater
τ: time of the pulse of drinking water demand
δ: delay between the two pulses (s)

The model presented here is inspired by the model of Elías-Maxil *et al.* (2014) with modifications to fit a French context. The model includes six steps:

- **Inhabitants of the household**: determining the composition of the household (number of working adults, non-working adults and children or students).
- **Water appliances of the household**: determining the water appliances in the household.
- **Number of water uses**: determining the number of uses of each water appliance for each inhabitant.
- **Durations and intensities of the water uses**: determining the durations and intensities of the wastewater pulses created by each water use.
- **Time-use pattern of the inhabitants**: determining the time-use pattern of each inhabitant.
- **Times of the water uses**: determining the time of discharge of each water use by each inhabitant according to their time-use pattern.

At the end of the six steps, the model provides a list of wastewater pulses with individual times, durations and intensities that allows constructing a wastewater flow time-series. The details of the steps are given in the next six sections.

5.1.1.1 INHABITANTS OF THE HOUSEHOLD

The number and types of inhabitants in the household are randomly picked. All the required statistics are described in chapter 4. Each inhabitant can be a working adult, a non-working adult or children/student. The model follows the following steps:

- **Household type**: the type of household is randomly picked (1 adult = 35.1 %, 2 adults = 26.6 %, 2 adults with children = 29.8 %, 1 adult with children = 8.5 %)
- **Type of adults**: randomly chosen between working (62.8 %) and not working adult (37.2 %).
- **Number of children**: if there are children in the household, their number is randomly picked (1 child = 43.2 %, 2 children = 41.5 %, 3 children = 12.4 %, 4 or more children = 2.9 %).

5.1.1.2 WATER APPLIANCES OF THE HOUSEHOLD

Seven types of water appliances are identified. Their actual presence in the household is randomly picked according to their market penetration rates (table 7). There are three types of toilets depending on their flush mechanisms. The model assumes that there is only one kind of toilet per household.

5.1.1.3 NUMBER OF WATER USES

The number of times each water appliance is used by each inhabitant is randomly picked (table 7). Kitchen tap uses are picked once for the whole household, because its uses seem to be more linked to the household than to individuals (Blokker *et al.*, 2009).

One water appliance can be used for more than one type of use (for example washing hands or brushing teeth at the bathroom tap) and each different type of use is defined by different water demand pulses. The type of uses for each water appliance use is randomly picked (table 7).

5.1.1.4 DURATIONS AND INTENSITIES OF THE WATER USES

The duration and intensity of the wastewater pulse induced by each water appliance use is randomly picked (table 7).

Table 7: Parameters of the water appliances in the household. Only one type of toilet is allowed per household. The dishwasher and washing machine both create a series of 4 wastewater pulses. Some water is drunk or used for other purposes such as watering plants/animals or outside. It is considered to be not discharged in the sewer network. All the statistics are from Blokker *et al.* (2009).

Appliance	Occurence	Number of uses (/day)		Possible uses		Duration of discharge			Intensity of discharge		Delay
	(%)	Distribution type			(%)	Distribution type			Distribution type	(L/s)	(min)
Bathtub	36	Poisson	λ=0.044	Bath	100	Fixed	10 (min)		Fixed	0.2	0
Bathroom tap	100	Poisson	λ=4.1	Washing hands/shaving/…	33	Lognormal	mean: 40 (s)	variance: 1.3 x mean	Uniform	[0 - 0.084]	0
				Brushing teeth	67		mean: 15 (s)				
Dishwasher	57	Poisson	λ=0.3	4 cycles program	100	Fixed	6/3/3/3 (min)		Fixed	0.017	60/80/100/110
Kitchen tap	100	Negative binomial	r= 3 p= 0.194	Washing dishes	25	Lognormal	mean: 48 (s)	variance: 1.3 x mean	Uniform	[0 - 0.125]	0
				Washing hands	25	Lognormal	mean: 15 (s)	variance: 1.3 x mean	Uniform	[0 - 0.084]	0
				Drinking	37.5	not discharged			not discharged		0
				Others (watering plants…)	12.5	not discharged			not discharged		0
Washing machine	57	Poisson	λ=0.3	4 cycles program	100	Fixed	4/2/2/2 (min)		Fixed	0.083	60/80/100/110
Shower	100	Binomial	n=1 p=0.7	Shower	100	χ^2	8.5 (min)		Fixed	0.142	0
6 L Toilet	16.4	Poisson	λ=5	6 L flush	100	Fixed	10 (s)		Fixed	0.6	0
6 L Toilet (Water-saving)	33.3	Poisson	λ=5	6 L flush	20	Fixed	10 (s)		Fixed	0.6	0
				3 L flush	80		5 (s)				0
9 L Toilet	50	Poisson	λ=5	9 L flush	100	Fixed	15 (s)		Fixed	0.6	0

5.1.1.5 TIME-USE PATTERN OF THE INHABITANTS

The probability of using water depends on the activities of the inhabitants of the household. Thus it is necessary to construct a time-use pattern for each inhabitant.

The model assumes that one inhabitant can be in three different states: awake at home, asleep or out of home. To construct the time-use pattern of one day D, it is necessary to consider the previous and next days also (D-1 and D+1) because human behaviour patterns expand from one day to another. Thus to construct a series of N days, it is necessary to consider N+2 days.

All data necessary to construct these patterns are extracted from a French time-use survey (INSEE, 2010). It is composed of 27 903 periods of time-use. Each time-use covers a 27 hours period from 21 h to 0 h the next day. Along with personal details (age, job…), the interrogated person gives its location and its main activity for each 10 minutes interval of the 27 hour period. Some data are removed (weekends, vacations, people living in cities significantly larger than the Bellecombe ones) to fit the context of this study and to match with the sampling rules (always on Tuesday for "24 h" campaigns). At the end, only 9 956 periods are left for further analysis. The analysis reveals that one can describe five fundamental patterns of time-use. The first type corresponds to "out for one long duration" (more than 7 hours). The second type corresponds to "out in the morning". The third type corresponds to "out in the afternoon". The fourth type corresponds to "out in the morning and again in the afternoon". The fifth type corresponds to "never out". Of course, the parameters of the five time-use patterns are to be calculated for each type of people and only for week days in this case, thus giving 15 types of time-use patterns (weekend days should provide 15 more patterns if weekend days were to be simulated). Table 8 gives the distribution of the time-use patterns for each type of inhabitant. All five types of days are well represented. Only a small percentage of all the days recorded in INSEE (2010) does not fit. They represent odd behaviours that are hard to model and classify. Those unclassified days are neglected in the model.

Table 8: Distribution of the time-use patterns for each type of people (INSEE, 2010).

Type of people	Pattern 1	Pattern 2	Pattern 3	Pattern 4	Pattern 5	Not classified
Working adult	40.1 %	9.9 %	10.5 %	26.8 %	12.7 %	5.3 %
Non-working adult	17.1 %	14.8 %	17.4 %	30.4 %	20.3 %	5.1 %
Children or student	31.6 %	12.4 %	13.1 %	25.2 %	17.8 %	6.1 %

To construct N consecutive time-use patterns, the model follows the following steps:

- **Type of days**: a type of day is randomly picked for each of the N+2 days needed (table 8).
- **"Asleep" periods**: depending on the person type and the day type, wake-up times and sleep durations are randomly picked for each of the N+2 days according to INSEE (2010). Figure 27 shows an example with N=1. With this example, one can see the necessity to consider one more day at the end. Indeed the "asleep" period from day D+1 starts during day D.

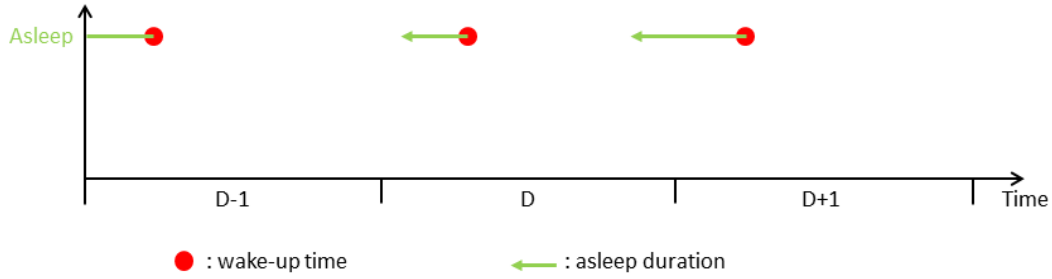


Figure 27: Example of a time use pattern construction (N=1): "asleep" periods.

- **"Out of home periods"**: depending of the person type and the day type, before leaving and "out of home" durations are randomly picked for each of the N+1 first days according to INSEE (2010). Starting at the wake-up time of the day, before leaving and "out of home" durations alternate as many times as required by the type of day (0, 1 or 2 times). Figure 28 shows an example. Day D-1 represents an "out in the morning and again in the afternoon" type of day. Day D represents an "out for one long duration" type of day.

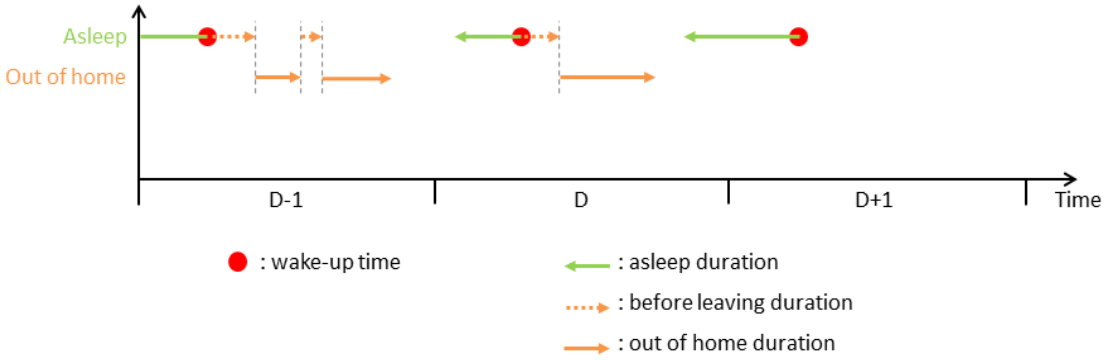


Figure 28: Example of a time use pattern construction (N=1): "out of home" periods.

- **"Awake at home" periods**: periods that are not "asleep" or "out of home" periods are assumed to be "awake at home" periods. However, those are divided in two categories: "stable" and "transition" periods. "Transition" periods are periods that are just before or after "asleep" and "out of home" periods. They can be no more than half an hour each. Depending of their position they are identified by a number from 1 to 6. The remaining periods are "stable". Figure 29 shows an example. "Transition" periods 1 and 6 are respectively the one just after and before "asleep" periods. "Transition" periods 2 and 5 are respectively the one just before the first and after the last "out of home" periods. "Transition" periods 3 and 4 are respectively between two "out of home" periods.

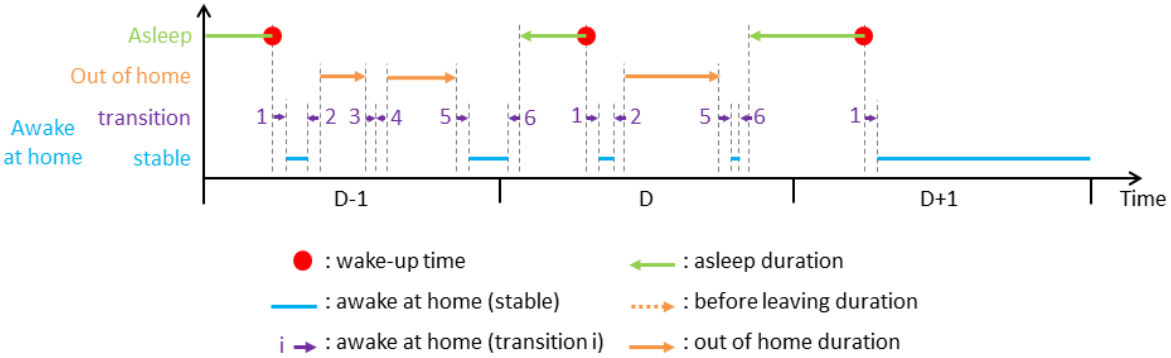


Figure 29: Example of a time use pattern construction (N=1): "awake at home" periods.

5.1.1.6 TIMES OF THE WATER USES

The time-use pattern of each inhabitant is weighted to represent the probability to use water through the day. Then the time of each water use is randomly picked with the weighted time-use pattern. The model follows the following steps:

- **Primary weighting**: "Awake at home (stable)" periods are rated 1, it represents the default value. "Asleep" periods are rated 0.1, it corresponds to the low probability to use water during the night. "Out of home" periods are rated 0 since the inhabitants are unlikely to use any water when they are outside the household (even if it can happen with programmable household appliances). However, for toilet uses "Out of home" periods are rated 0.2, as it is possible to use toilets outside the households. This is because the probability of one person to use toilets a certain number of times is defined for one whole day, whether those uses take place in the household or not. The ratings for the 6 types of "Awake at home (transitions)" periods are expected to be higher than 1 but needs to be calibrated because no data was available to estimate their contributions.

- **Secondary weighting**: weighted time-use patterns of certain water appliances are multiplied with specific activities probability profiles extracted form INSEE (2010). The probability profile of activities linked to personal care is used to weigh bathtub, bathroom tap and shower uses. The probability profile of activities surrounding meals is used to weigh kitchen tap uses.

  The primary and secondary weightings provide four weighted time-use patterns: one for bathtub, bathroom tap and shower uses, one for kitchen tap uses, one for washing machine and dishwasher uses and one for toilet uses.

- **Times picking**: a time of water demand is randomly picked for each water appliances use and each inhabitant with the corresponding weighted time-use pattern. For toilet uses, the weighted time-use pattern of the same inhabitant is modified to lower the probability to use the toilet twice in a short time (figure 30). Toilet uses happening during "out of home" periods are set aside. They are assumed to happen outside the catchment, thus producing no wastewater discharge in the catchment.

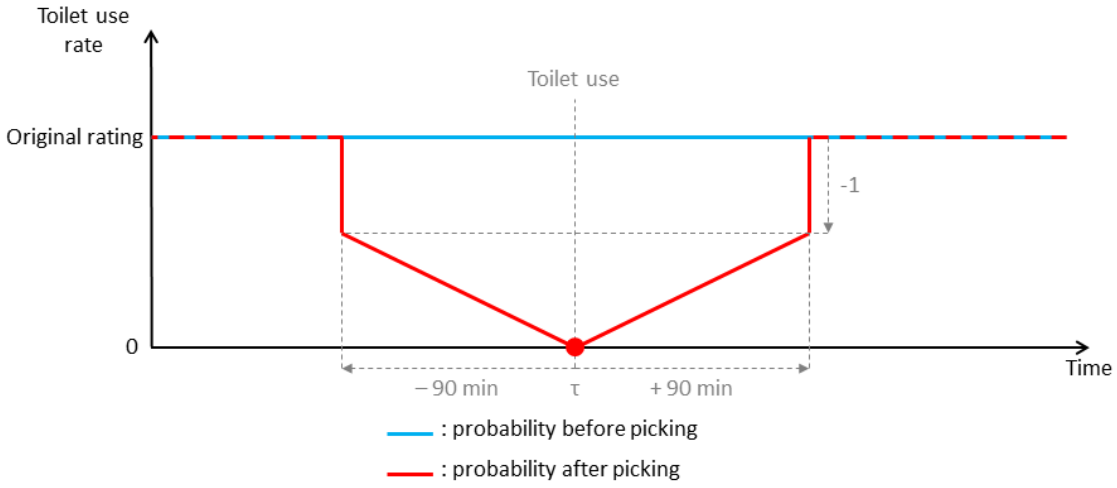


Figure 30: Toilet use weighted time-use pattern modification. The probability after picking cannot be negative, so any negative value produced by this process is set to 0.

- **Pulse delay**: depending of the water appliance, the times of water uses are delayed to correspond to wastewater discharges (table 7).

5.1.2 GENERATION OF PHARMACEUTICALS LOADS

The model generates the pharmaceuticals loads produced by all types of population in the source (inhabitants, workers…). The persons that are consuming pharmaceuticals are randomly picked and then their metabolism and excretions pattern are calculated. Excretions are modelled as pulses linked to the toilet uses of the patient made when he/she is present in the catchment.

After consuming a pharmaceutical, the metabolizing and excretion processes may take more than one day. So, given a certain day, the pharmaceutical loads measured at the inlet of the WWTP are the result of pharmaceutical consumptions of the same day but also of the previous days. So, it is necessary to calculate the consumptions and excretions of pharmaceuticals of the days before the two days modelled. Inhabitants and workers are supposed to marginally change from one day to another. So, one must calculate as many days as the longest metabolizing and excretion processes that may happen. Bedded patients are not staying indefinitely in the hospital (chapter 4). Once they leave, a fraction of the pharmaceuticals that they consumed is discharged outside the hospital sewer network. So, one must calculate excretions according to the duration of hospitalization of the patients.

The model generates only one day of pharmaceutical consumption and the metabolizing and excretion processes associated (that can last multiple days). So, the model must be used as long as the metabolizing and excretion processes last or as many days as the bedded patients stay in the hospital.

Pharmaceuticals are sold with different dosages, forms and packages with different consumption patterns, posology and metabolizing processes. Thus, it is necessary to distinguish each pharmaceutical speciality at this stage. After human excretion, the loads produced by the consumption of the different specialities should be summed for each molecule.

The model includes four steps:

- **Masses of consumed pharmaceuticals**: determining the masses of consumed pharmaceuticals in one day by each population set.
- **Posology**: creating as many pharmaceutical intake patterns as necessary to cover the masses of consumed pharmaceuticals. As a result, this provides the number of patients in each population set and for each pharmaceutical.
- **Metabolism**: determining for each patient the metabolizing of the pharmaceutical taken until it is ready for excretion.
- **Excretion to the sewer network**: determining the excretion times and loads of the pharmaceutical and its selected metabolites according to the time-use pattern of the patient.

At the end of the four steps, the model provides a list of pharmaceuticals pulses with individual times and masses discharged that allows constructing pharmaceuticals loads time-series. The details of the steps are given in the next four sections.

5.1.2.1 MASSES OF CONSUMED PHARMACEUTICALS

For each population set in the catchment, the masses of consumed pharmaceuticals in one day are calculated as follows:

$$M_{i,j} = N_{i,j} \times random(P_{i,j})$$

With:
i: index of the pharmaceutical speciality (table 9)
j: index of the population set (1: household inhabitants, 2: workers and 3: bedded patients)
$M_{i,j}$: mass of pharmaceutical i consumed in one day by the population set j (mg/day)
$N_{i,j}$: number of persons in the population set j (capita) (table 9)
$random(x)$: return a random value from the probability distribution x
$P_{i,j}$: probability distribution of sales or distribution of pharmaceutical i for the population set j (mg/day/capita) (table 9)

Table 9: Origin of data used in the "Masses of consumed pharmaceuticals" step. The number of specialities is defined by the data on pharmaceuticals sales or distribution (chapter 4).

Population set	Number of persons	Pharmaceuticals probabilities data	Number of specialities
Household inhabitants	Derived from the number of households in the source N_{House} (5.1.1.1 Inhabitants of the household)	Corrected urban pharmaceuticals sales	188
Workers	Directly, the number of workers in the source N_{worker}	Corrected urban pharmaceuticals sales	177
Bedded patients	Directly, the number of hospital beds in the source N_{H-bed}	Corrected CHAL pharmaceuticals distributions	56

5.1.2.2 POSOLOGY

The previous step of the model does not provide the number of patients in each population set but only the mass of consumed pharmaceuticals. Thus, the model generates as many patients, each one with a different posology, as necessary to equal the mass of consumed pharmaceuticals.

A person consuming a given speciality is following a specific daily posology. This posology consists of a list of intakes each with different times, masses and durations. The number of intakes, their masses and durations are directly linked to the description of the posology by pharmacy literature (chapter 4). However, the description of the times of the intakes needs to be interpreted. Indeed, some specialities are consumed in relation to meals; some can be consumed at any time. Also, two intakes must be sufficiently distant in time to prevent overdose. In any case, the time-use pattern of each patient is predominant when determining the times of the intakes.

In the model, there are two ways to describe the posology. The choice to use one or another depends of its suitability to describe the recommended posology and the behavioural constraints of the patients. The two ways are:

- **Meal periods**: pharmaceutical intakes are defined in relation to meals. There are three possible meals: breakfast (B), lunch (L) and supper (S). The pharmaceuticals can be taken before (B), during (D) or after (A) any meal. This generates nine time periods (for example: BB, before breakfast; DL, during lunch; AS, after supper). Then for each time period a probability is determined. For example, the description "BB 50, DL 50" implies that it is as probable for the pharmaceutical to be taken before breakfast as it is during lunch.

- **Diffuse periods**: any of the following descriptions:
    1. Awake not out no meal: the speciality can be taken at any time given that the patient is awake, not out of his/her household (or out of the hospital for bedded patients) and not eating. It is essentially used for dermal application pharmaceuticals. Sometimes, pharmaceuticals are used to treat symptoms that aggravate thought the day (fatigue, headache…). In such cases, the description can be completed with "Pain increase".
    2. Awake not out meal high: the speciality can be taken at any time given that the patient is awake, not out of his/her household (or out of the hospital for bedded patients) but preferably during meal periods. The description can be completed with "Pain increase" (see above).

The posology description for all pharmaceutical specialities can be found in appendix 3.

Each new posology is generated as follows:

- **Number of intakes**: the number of intakes is randomly picked.

$$Nint = random_{int}(Nint_{i,min}, Nint_{i,max})$$

With:
$Nint$: number of intakes
$random_{int}(x, y)$: return a random integer between x and y both included
i: index of the pharmaceutical speciality
$Nint_{i,min}$, $Nint_{i,max}$: respectively the minimum and maximum numbers of intakes per day for the speciality i

- **Doses**: for each intake, the number of units taken is randomly picked. Multiplied by the dose of one unit of the speciality, it gives the mass of consumed speciality in each intake.

$$M_k = D_i \times randint(Nperint_{i,min}, Nperint_{i,max})$$

With:
k: index of the intake ($1 \leq k \leq Nint$)
$Nint$: number of intakes
M_k: mass of pharmaceutical consumed during intake k (mg)
i: index of the pharmaceutical speciality
D_i: dose of one unit of speciality i (mg)
$randint(x, y)$: return a random integer between x and y both included
$Nperint_{i,min}$, $Nperint_{i,max}$: respectively the minimum and maximum numbers of units that can be consumed in one intake for the speciality i

- **Durations**: Except for intravenous forms, the duration of each intake is assumed to be shorter than the time step of the simulation. Thus, the duration of each intake is set equal to one time step (60 s). For intravenous forms (especially at the hospital), the intake can last several minutes. The duration of each intake is randomly picked.

$$dur_k = random_{int}(dur_{i,min}, dur_{i,max})$$

With:
k: index of the intake ($1 \leq k \leq Nint$)
$Nint$: number of intakes
dur_k: duration of intake k (s)
$random_{int}(x, y)$: return a random integer between x and y both included
i: index of the pharmaceutical speciality
$dur_{i,min}$, $dur_{i,max}$: respectively the minimum and maximum durations for an intake of speciality i (s)

- **Duration between intakes**: for each intake, the duration with no intake is randomly picked.

$$\delta_k = random_{int}(\delta_{i,min}, \delta_{i,max})$$

With:

k: index of the intake ($1 \leq k \leq Nint$)

$Nint$: number of intakes

δ_k: duration with no intake before and after intake k (s)

$random_{int}(x, y)$: return a random integer between x and y both included

i: index of the pharmaceutical speciality

$\delta_{i,min}$, $\delta_{i,max}$: respectively the minimum and maximum durations with no intakes of speciality i

- **Time-use pattern**: patients from household inhabitants are linked randomly to a specific inhabitant, thus using its time-use pattern generated for wastewater flow generation (5.1.1.5 Time-use pattern of the inhabitants). Time-use patterns for workers and bedded patients are generated in the same way. Workers are assumed to be working adults. For bedded patients, time-use statistics are estimated from the wastewater flow analysis (chapter 6). The time of wake-up and going to sleep are assumed to be associated with the morning wastewater peak flow and low wastewater flow values in the evening (table 10).

  In addition to the three types of period previously defined (asleep, out of home and awake at home), nine periods are determined. They correspond to the three meals and surrounding times (before, during and after). For household inhabitants and workers, statistics on meal times and their durations are given by INSEE (2010). For bedded patients, meal times and durations are represented by uniform distributions (table 10). Before and after meals duration are arbitrarily set to 30 minutes.

Table 10: Time-use pattern parameters for bedded patients.

Parameter name		Uniform distribution	Average expected result
Wake-up time		440 ± 60 min	Wake-up at 7h20
Duration between waking up and:	Going to bed	840 ± 60 min	Going to bed at 21h20
	Breakfast	40 ± 15 min	Breakfast at 8h
	Lunch	310 ± 15 min	Lunch at 12h30
	Supper	640 ± 15 min	Supper at 18h
Duration of:	Breakfast	30 ± 15 min	30 min breakfast
	Lunch	30 ± 15 min	30 min lunch
	Supper	30 ± 15 min	30 min supper

- **Weighting**: time-use patterns are weighted to represent the probability to consume a speciality at any given time. This weighting process depends on the posology description:
    - **Meal periods posology**: for each time step in each period described in the posology, the assigned score is equal to:

$$S_h = \frac{\rho_h}{dur_h}$$

With:
h: index of the periods described in the posology
S_h: assigned score to every time step in the period h
ρ_h: probability to consume the speciality in period h
dur_h: duration of the period h (Δt)
Δt: time step of the model (60 s)

    - **Diffuse periods posology**: all the time step of the day are scored 0 by default.
        1. Awake not out no meal: each time step in the "awake at home" periods is scored 1. Time steps in meal periods are scored at 0.
        2. Awake not out meal high: each time step out of the "awake at home" periods is scored 1. Time steps in meal periods are scored at 3.

    If the description is completed with "Pain increase", each time step is multiplied by a factor:

$$F(t) = 2 + \cos(t + n)$$

With:
t: time (Δt)
Δt: time step of the model (60 s)
$F(t)$: weighting factor at time step t
n: temporal offset for the cosine wave (Δt), equal to 960 in order to reach maximum at 18h.

- **Times of intakes**: for each intake, a time of intake is randomly picked with the weighted time-use pattern. After each pick, the weighted time-use pattern is modified to assure that two intakes cannot be too close in time. Every time step that is less than the duration between intakes from the time of the intake is scored 0.

5.1.2.3 METABOLISM

Like posology, the metabolism is specific to each speciality of each molecule. However it does not depend on the population type. This step of the model transforms a posology pattern (times, masses and durations) into a flow that is stored in the human body until excretion (mainly urine or faeces). The model is derived from models of pharmacokinetic studies. It represents the human body by three boxes that can exchange pharmaceuticals loads.

A simple interpretation describes the most frequent pharmaceutical path in the human body. The three boxes represent respectively the gastro-intestinal system, the blood system and the bladder (or any organ that stores pharmaceuticals before excretions) (figure 31).

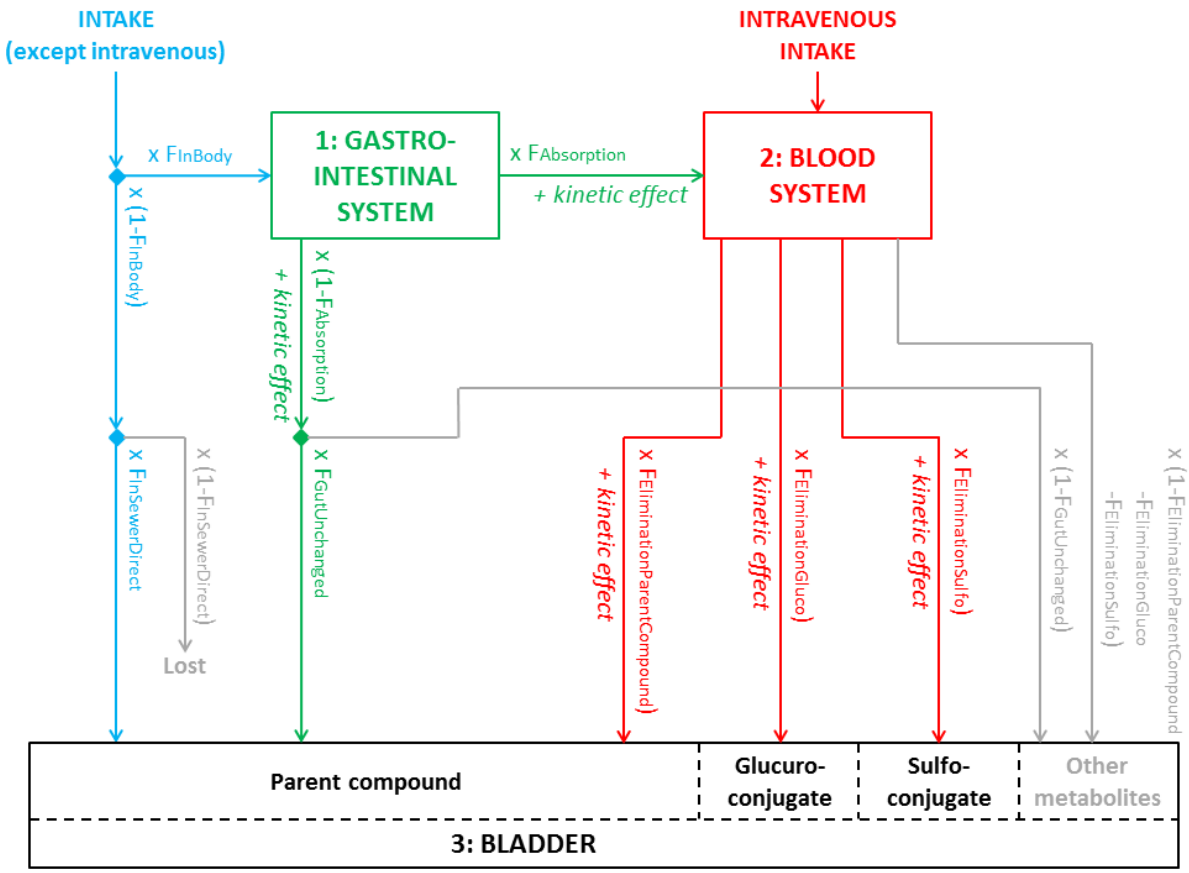


Figure 31: Metabolism diagram. Blue parts are relative to the intake process. Green parts are relative to the gastro-intestinal system. Red parts are relative to the blood system. Grey parts are relative to flux not studied by the model. Finally the black parts are relative to the bladder. Whatever is in the bladder is considered ready for excretion. In reality, pharmaceuticals can be stored in other organs before excretion (like for faeces). However excretion via urine in bladder is predominant in most cases. To remain simple, the blue flux not entering the body is stored in the bladder even if it is not the case in reality.

When consuming an orally taken pharmaceutical, a fraction of it (F_{InBody}) enters immediately the gastro-intestinal system. The fraction that does not enter the body is partially discharged in the sewer system ($F_{InSewerDirect}$). 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 $k_{absoprtion}$. If not metabolized, 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 an unchanged form and as metabolites. The kinetics is based on an exponential decay with a parameter $k_{elimination}$. In our case, only two types of metabolites are studied: glucuro-conjugates and sulfo-conjugates. The respective ratios of elimination for the parent compound, the glucuro-conjugates and the sulfo-conjugates are noted $F_{EliminationParentCompound}$, $F_{EliminationGluco}$ and $F_{EliminationSulfo}$.

In the case of an intravenous pharmaceutical, it enters directly the blood system then has the same fate as an orally taken one.

To summarize, the model has nine parameters: two of them control the kinetics ($k_{absoprtion}$ and $k_{elimination}$) and the seven others are ratios (F_{InBody}, $F_{InSewerDirect}$, $F_{Absorption}$, $F_{GutUnchanged}$, $F_{EliminationParentCompound}$, $F_{EliminationGluco}$ and $F_{EliminationSulfo}$).

The model includes the following steps:

- **Parameters**: the nine parameters are randomly taken from uniform distributions between their minimum and maximum possible values.
- **Intake profiles**: the intakes are transformed into time profiles. The "normal intakes" profile ($Int\ (t)$)) collects every speciality that is not an intravenous form. The "intravenous intakes" profile ($IVInt\ (t)$) collects intravenous intakes.
- **Metabolism**: the masses of pharmaceuticals and their glucuro and sulfo conjugates present in the three boxes are calculated for each time step with the following equations:

$$GP(t+\Delta t) = GP(t) \times \left(1 - k_{absorption}\right) + Int(t+\Delta t) \times F_{InBody}$$ *(exponential decay)* *(normal intake)*

$$BP(t+\Delta t) = BP(t) \times (1 - k_{elimination}) + GP(t) \times k_{absorption} \times F_{Absorption} + IVInt(t+\Delta t)$$ *(exponential decay)* *(absorbed fraction)* *(Intravenous intake)*

$$BlP_{PC}(t+\Delta t) = BlP_{PC}(t) + BP(t) \times k_{elimination} \times F_{EliminationParentCompound} + GP(t) \times k_{absorption} \times (1 - F_{Absorption}) \times F_{GutUnchanged} + Int(t+\Delta t) \times (1 - F_{InBody}) \times F_{InSewerDirect}$$ *(eliminated fraction)* *(un-absorbed fraction)* *(un-penetrated fraction)*

$$BlP_{GL}(t+\Delta t) = BlP_{GL}(t) + BP(t) \times k_{elimination} \times F_{EliminationGluco}$$ *(eliminated fraction)*

$$BlP_{SL}(t+\Delta t) = BlP_{SL}(t) + BP(t) \times k_{elimination} \times F_{EliminationSulfo}$$ *(eliminated fraction)*

With:
t: time (s)
Δt: time step of the model (60 s)
$GP(t)$: 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})
$Int(t)$: mass of consumed non-intravenous pharmaceutical at time t (mg)
F_i: fraction i (see above)
$BP(t)$: mass of pharmaceutical in the blood system at time t (mg)
$IVInt(t)$: mass of consumed intravenous pharmaceutical at time t (mg)
$BlP_{PC}(t)$: mass of unchanged pharmaceutical in the bladder at time t (mg)
$BlP_{GL}(t)$: mass of glucuro-conjugates in the bladder at time t (mg)
$BlP_{SL}(t)$: mass of sulfo-conjugates in the bladder at time t (mg)

The metabolic parameters of the 15 pharmaceuticals of the thesis are given in appendix 4.

5.1.2.4 EXCRETION TO THE SEWER NETWORK

The excretions are linked to toilet uses. Each time a patient goes to the toilet, he/she empties his/her bladder into the sewer network.

Toilet uses for patients who are household inhabitants are already calculated. Toilet uses for patients who are workers or bedded patients are generated with the time-use pattern created during the posology step and the weighting process and times picking described in section 5.1.1. However, for worker patients, the only toilet discharges kept are the ones happening during "out of home" periods.

5.1.3 HYPOTHESES AND CHOICES DISCUSSION

In order to properly model the sources of wastewater flow and pharmaceuticals loads, it is important to identify which populations generate them. In the model, only three types of populations are defined: household inhabitants, workers and bedded patients. In reality, it is possible to identify many more type of populations such as tourists, travelling workers, hospital visitors, hospital staff… Those populations types are not modelled because they are either negligible or not documented enough for modelling.

In reality, it is possible for one person to be more than one type. For example, an inhabitant of the source can work in it as well. However, for simplicity, the model assumes that one person can be categorized in one type only. This means that workers are all coming from outside the source and working inhabitants are working outside the source. This is why not all toilet flushes are considered (5.1.1.6 Times of the water uses and 5.1.2.4 Excretion to the sewer network).

5.1.3.1 WASTEWATER FLOW

The wastewater generator proposed only considers households inhabitants. The wastewater flows generated by workers or bedded patients are not modelled due to lack of data on the subject.

Concerning the composition of households, the model uses non-dependant statistics. This means that it neglects the potential correlation between the size of the household and the activity of its adults (working or not). Also, the model generates only a few type of household composition, neglecting more atypical situations.

Although the model is inspired by Elías-Maxil *et al.* (2014) works, it differs in some points. Mainly:

- Inhabitants are classified by their social status (working adult, non-working adult and children or students).
- There are five types of time-use pattern possible. This allows a better description of human behaviours. As presented in table 8, all time-use patterns are well represented in INSEE (2010). However, since only a few children or students participated in the study, the statistics on their time-use patterns are not well defined.
- Weighting the generated time-use pattern is done by giving score to each time-step depending of the activity of the person. The method used in Elías-Maxil *et al.* (2014) could not be applied because of the new types of time-use pattern defined.

The method to generate time-use patterns is relatively simple but has two main drawbacks. First, all the statistic distributions used are assumed to be independent. This means that the time-use pattern of one person is not influenced by its time of waking up. In reality, it is much more probable that all the parameters of a time-use pattern are inter-dependant. Secondly, and also as a result of the first point, the process is not fully robust. Indeed, it can generate time-use patterns that are overly constrained leading to absurd situations. For example,

a person state can change form “Away” to “At home” while being asleep. In such cases, the model generates a new time-use pattern for the person.

The same “overly constrained” effect can happen when picking the times of water demand, especially with the toilets uses. Indeed, after picking several toilet uses, the weighted time-use pattern can be null for any time-step.

5.1.3.2 PHARMACEUTICALS LOADS

The link between sales/distributions data and actual daily consumption is quite complicated. Sales/distributions data can be corrupted by stock problems, especially for the hospital distributions since the central pharmacy resupplies all the services that then distribute them to patients (chapter 6). All the pharmaceuticals sold are not consumed and the consumption of one box of pharmaceuticals is spread over time. Also, one box of pharmaceuticals can be used by more than one patient. The medication of patients can last several days, but it is difficult to estimate on a specific day how many patients are starting, continuing or stopping a treatment.

Thus, for the model, the raw sales/distributions data are treated (chapter 6) to minimize corruption from stock problems. Those treated data are assumed to represent the probability of pharmaceuticals consumption. By doing so, the model makes two hypotheses:

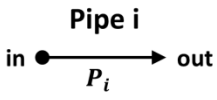
- Pharmaceuticals are bought and consumed at the same time (i.e. monthly sales transform in monthly consumptions). This choice mainly affects the variability in predicted consumptions. The shorter the time step is, the more variable the prediction is. One should choose the most detailed data available, but one should also keep in mind that data with short time steps are more vulnerable to artifacts, for example stock problems.
- Patients are only consuming pharmaceuticals for one day (i.e. on a specific day, all patients are new patients). It is a huge simplification of the reality, but it bears no effect since the following steps are quite linear.

The posology descriptions are meant to be simple, but determining those descriptions is rather difficult due to lack of data, especially for the intakes times. Also, determining the intakes times is sometimes not possible due to the “overly constrained” effect described above.

For the same reason as for posology description, determining the parameters values concerning the metabolism is difficult. This is because the goal of pharmacokinetic studies is not the same as this thesis. Also, the parameters are sometimes not well defined (“almost completely metabolized”, “approximately X % is excreted”…) (chapter 4).

5.2 MODEL FUNDAMENTAL ELEMENT: PIPE

Graphic symbol:



In: wastewater flow Q_{in} (m^3/s) and pharmaceuticals loads φ_{in} (g/s).

Out: wastewater flow Q_{out} (m^3/s) and pharmaceuticals loads φ_{out} (g/s).

Parameters: pipe length L (m), targeted spatial discretization length Δx_{target} (m), targeted weighting parameter α_{target} (dimensionless), targeted lag time K_{target} (s) and targeted delay δ_{target} (s).

Goal: model the behaviour of the wastewater flow and pharmaceuticals loads in a gravitational pipe.

5.2.1 WASTEWATER FLOW MODELLING

The main principle for the wastewater flow pipe model is to divide the pipe in shorter sub-pipes of a predetermined length and then to apply the Muskingum model (Mac Carthy, 1940) to each of them. This requires a set of 5 parameters (see above). Only the length of the pipe L is different for each pipe. The four others parameters are the same for all pipes. The targeted lag time K_{target} and the targeted delay δ_{target} of the pipe concern a pipe unit that is 100 m long.

The model follows the following steps:

- **Inflow**: the wastewater flow entering the pipe is equal to the sum of the wastewater flows of the upstream fundamental elements:

$$Q_{in}(t) = \sum_{j=1}^{J} Q_{upstream,j}(t)$$

  With:
  t: time (s)
  $Q_{in}(t)$: wastewater flow entering the pipe at time t (m^3/s)
  J: number of fundamental elements directly upstream of the pipe
  $Q_{upstream,j}(t)$: wastewater flow exiting the fundamental element j at time t (m^3/s)
- **Pipe discretization**: the pipe is divided into N sub-pipes, all with the same length Δx. N is set so that Δx is as close as possible to the targeted spatial discretization length Δx_{target}. It verifies the following equations:

$$L = N \times \Delta x$$

$$\left| \Delta x - \Delta x_{target} \right| < \left| \frac{N \pm 1}{L} - \Delta x_{target} \right|$$

  With:
  L: length of the pipe (m)
  N: number of sub-pipes
  Δx_{target}: targeted spatial discretization length (m), 200 m in the model (this value was chosen to ensure the coherence of the calculations, long and short pipes are calculated the same way).
  Δx: length of one sub-pipe (m)
- **Weighting coefficient**: the weighting coefficient α of each sub-pipe is equal to the targeted weighting parameter α_{target}. However, the weighting coefficient α of the first sup-pipe is equal to 0 if one of the fundamental elements directly upstream of the pipe is either a source or a pumping station.

- **Lag time**: the lag time K of each sub-pipe is scaled according to the length of the sub-pipes Δx:

$$K = \frac{K_{target}}{L_{K_{target}}} \times \Delta x$$

With:
K: lag time of each sub-pipe (s)
K_{target}: targeted lag time for a defined length $L_{K_{target}}$ (s)
$L_{K_{target}}$: pipe length associated to K_{target} (m), here equal to 100 m
Δx: length of one sub-pipe (m)

- **Muskingum model**: for each sub-pipe i the Muskingum model is applied. It is discretized as follows:

$$Q_i(t + \Delta t) = C_1 \times Q_{i-1}(t) + C_2 \times Q_{i-1}(t + \Delta t) + C_3 \times Q_i(t)$$
$$Q_0(t) = Q_{in}(t)$$
$$C_1 + C_2 + C_3 = 1$$
$$C_1 = \frac{\alpha}{1 - \alpha} \times C_3$$
$$C_2 = 1 - \frac{1}{1 - \alpha} \times C_3$$
$$C_3 = e^{\left(-\frac{\Delta t}{K \times (1-\alpha)}\right)}$$

With:
i: index of the sub-pipe ($1 \leq i \leq N$)
N: number of sub-pipes
t: time (s)
Δt: time step (s), equal to 60 seconds in the model
$Q_i(t)$: flow exiting the sub-pipe i at time t (m^3/s)
C_1, C_2 and C_3: intermediate calculus coefficients
α: weighting coefficient of the sub-pipe
K: lag time of the sub-pipe (s)
All wastewater flows are initially equal to 0.

- **Pipe delay**: the pipe delay δ is scaled according to the length of the pipe L, it is rounded to fit the time step of the model (*i.e.* 1 minute = 60 seconds):

$$\delta = Round\left(\frac{\delta_{target}}{L_{\delta_{target}} \times 60} \times L\right) \times 60$$

With:
δ: delay of the pipe (s)
δ_{target}: targeted delay of the pipe (s)
$L_{\delta_{target}}$: pipe length associated to δ_{target} (m), here equal to 100 m
L: length of the pipe (m)

- **Outflow**: the wastewater flow exiting the pipe is equal to the exiting flow of the last sub-pipe delayed by the pipe delay δ:

$$Q_{out}(t) = Q_N(t - \delta)$$

With:
t: time (s)
$Q_{out}(t)$: wastewater flow exiting the pipe at time t (m^3/s)
N: number of sub-pipes
δ: delay of the pipe (s)
$Q_N(t)$: flow exiting the last sub-pipe N at time t (m^3/s)
All wastewater flows are set equal to 0 at the beginning of each simulation of two consecutive days.

5.2.2 PHARMACEUTICALS LOADS MODELLING

The pharmaceutical loads follow the same modelling as the wastewater flow (see above). The same parameters are used.

5.2.3 HYPOTHESES AND CHOICES DISCUSSION

In order to model wastewater flow and pharmaceuticals loads in gravitational pipes, the Muskingum model was chosen. It is a conceptual model that is easy to use, it can be used as an approximation for dissolved pollutant transport, it does not require a lot of data (only the length of pipe) and it is easily calibrated. However, it neglects some aspects of water flow physics such as backflow effects and is not well suited to model singularities. The Muskingum model can be seen as a wave propagator with a lag time K and an weighting coefficient α.

Typically, it requires 4 parameters: time discretization duration Δt, length of the pipe L, lag time K and weighting coefficient α. Of course the length of the pipe L is determined by physical data. But the lag time K and the weighting coefficient α are not easily linked to data. The easiest way to determined them is by calibration with measured flows. This way the time discretization duration Δt needs to be equal to the flow measurements time step. In our case, the time discretization duration Δt is 60 seconds.

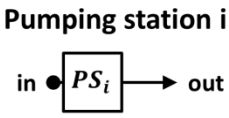
However, the lag time K and the weighting coefficient α depend on the length of the pipe L. So each pipe in the model would need an individual calibration. Since wastewater flow data is available only at the outlet of the catchment, such calibrations are not possible. Instead, the model divides each pipe in smaller pipes with similar length $\Delta_{x,target}$ and assumes that the physics of all the sub-pipes is roughly the same (same K and α), neglecting the different geometries, slopes and singularities of the pipes (see "**Pipe discretization**" step above). This way the lag time is defined for a determined length of pipe (100 m) and needs to be scaled to the actual length of each sub-pipe (see "**Lag time**" step above).

Mathematically, the Muskingum model introduces no delay in the flow, but in reality it takes time for wastewater to travel the length of the pipe. In this regard, a delay parameter is introduced. Rather than applying it to each sub-pipe it is applied for each pipe (see "**Outflow**" step above). To keep it simple, the applied delay parameter δ is always a round number of time discretization duration Δt and, like the lag time parameter K, it is defined for a determined length of pipe (100 m) and need to be scaled to the actual length of each pipe (see "**Pipe delay**" step above).

Finally, another mathematical problem of the Muskingum model is possible negative outflow values in certain circumstances (extremely rapid flow fluctuations, null or near-null flow values…). Such conditions are probable in this model, especially downstream a source element (pulse discharges) or a pumping station element. To avoid negative outflow values, the weighting coefficient α is set to 0 in sub-pipes that are directly downstream of a source element or a pumping station element (see "**Weighting coefficient**" step above).

5.3 MODEL FUNDAMENTAL ELEMENT: PUMPING STATION

Graphic symbol:



In: wastewater flow and pharmaceuticals loads (one set or more).

Out: wastewater flow and pharmaceuticals loads.

Parameters: number of pumps N_{pump}, maximum capacity of the pumps C_i (m^3/s), start volume threshold of the pumps $V_{on,i}$ (m^3) and stop volume threshold of the pumps $V_{off,i}$ (m^3).

Goal: model the behaviour of the wastewater flow and pharmaceutical loads in a pumping chamber and its downstream pressurized pipe.

5.3.1 WASTEWATER FLOW MODELLING

The model for the wastewater flow pumping station is a simple model based on the volume of wastewater stored in the pumping station. Each pumping station has its own set of parameters determined by data of the actual sewer network.

At the beginning of each simulation of two consecutive days, the pumping station is assumed to be empty and all pumps are off. Then for each time step the model includes the following steps:

- **Inflow**: the wastewater flow entering the pumping station is equal to the sum of the wastewater flows of the fundamental elements directly upstream:

$$Q_{in}(t) = \sum_{j=1}^{J} Q_{upstream,j}(t)$$

With:
t: time (s)
$Q_{in}(t)$: wastewater flow entering the pumping station at time t (m^3/s)
J: number of fundamental elements directly upstream of the pumping station
$Q_{upstream,j}(t)$: wastewater flow exiting the fundamental element j at time t (m^3/s)

- **Pumps flow**: the wastewater flow of each pump is determined by the pump state (on or off) and its previous wastewater flow. If the pump is powered but has not reached its maximum capacity, then its flow is increased by 1/60 of its maximum capacity (section 5.3.3). If the pump is not powered but its flow is strictly positive, then its flow is decreased by 1/15 of its maximum capacity (section 5.3.3). In any other case, the flow of the pump does not change.

$$\boldsymbol{if}\ P_i(t) = \text{"on" and } q_i(t) < C_i\ \boldsymbol{then}\ q_i(t + \Delta t) = q(t) + \frac{C_i}{60}$$
$$\boldsymbol{if}\ P_i(t) = \text{"off" and } q_i(t) > 0\ \boldsymbol{then}\ q_i(t + \Delta t) = q_i(t) - \frac{C_i}{15}$$
$$\boldsymbol{else}\ q_i(t + \Delta t) = q_i(t)$$

  With:
  N_{pump}: number of pumps
  i: index of the pump ($1 \leq i \leq N_{pump}$)
  t: time (s)
  $P_i(t)$: state of the pump i at time t (either “on” or “off”)
  $q_i(t)$: wastewater flow of the pump i at time t (m^3/s)
  C_i: maximum capacity of the pump i (m^3/s)
  Δt: time step (s), equal to 60 seconds in the model
- **Outflow**: the wastewater flow exiting the pumping station is equal to the sum of the wastewater flows of all pumps:

$$Q_{out}(t) = \sum_{i=1}^{N_{pump}} q_i(t)$$

  With:
  t: time (s)
  $Q_{out}(t)$: wastewater flow exiting the pumping station at time t (m^3/s)
  N_{pump}: number of pumps
  $q_i(t)$: wastewater flow of the pump i at time t (m^3/s)
- **Stored volume**: the stored volume of wastewater in the pumping station is the balance between what was previously stored in the pumping station, what enters and what exits the pumping station:

$$V_{stored}(t + \Delta t) = V_{stored}(t) + \Delta t \times (Q_{in}(t + \Delta t) - Q_{out}(t + \Delta t))$$

  With:
  t: time (s)
  Δt: time step (s), equal to 60 seconds in the model
  $V_{stored}(t)$: stored volume of wastewater in the pumping station at time t (m^3)
  $Q_{in}(t)$: wastewater flow entering the pumping station at time t (m^3/s)
  $Q_{out}(t)$: wastewater flow exiting the pumping station at time t (m^3/s)

- **Pumps state**: the status of each pump is determined according to the stored volume of wastewater in the pumping station, the start and stop volume thresholds of the pumps and the previous state of the pumps. If the pump is not powered and the stored volume of wastewater is greater than the start volume threshold of the pump, then the pump is started. If the pump is powered and the stored volume of wastewater is smaller than the stop volume threshold of the pump, then the pump is stopped. In any other case, the pump state does not change.

$$\boldsymbol{if}\ P_i(t) = \text{"off" and } V_{stored}(t+\Delta t) > V_{on,i}\ \boldsymbol{then}\ P_i(t+\Delta t) = \text{"}on\text{"}$$
$$\boldsymbol{if}\ P_i(t) = \text{"on" and } V_{stored}(t+\Delta t) < V_{off,i}\ \boldsymbol{then}\ P_i(t+\Delta t) = \text{"off"}$$
$$\boldsymbol{else}\ P_i(t+\Delta t) = P_i(t)$$

With:
i: index of the pump ($1 \leq i \leq N_{pump}$)
N_{pump}: number of pumps
t: time (s)
$P_i(t)$: state of the pump i at time t (either “on” or “off”)
Δt: time step (s), equal to 60 seconds in the model
$V_{stored}(t)$: stored volume of wastewater in the pumping station at time t (m^3)
$V_{on,i}$: start volume threshold of the pump i (m^3)
$V_{off,i}$: stop volume threshold of the pump i (m^3)

5.3.2 PHARMACEUTICALS LOADS MODELLING

The pharmaceutical loads model of the pumping station is based upon the hypothesis that the concentration of pharmaceutical is homogenous within the pumping station. It uses the results of the wastewater flow model of the pumping station. Then for each time step the model consists of the following steps:

- **Loads entering**: the pharmaceuticals loads entering the pumping station are equal to the sum of the pharmaceutical loads of the fundamental elements directly upstream:

$$\varphi_{in}(t) = \sum_{j=1}^{J} \varphi_{upstream,j}(t)$$

With:
t: time (s)
$\varphi_{in}(t)$: pharmaceutical loads entering the pumping station at time t (g/s)
J: number of fundamental elements directly upstream of the pumping station
$\varphi_{upstream,j}(t)$: pharmaceutical loads exiting the fundamental element j at time t (g/s)

- **Loads exiting**: the pharmaceutical loads exiting the pumping station are proportional to the volume exiting the pumping station.

$$\varphi_{out}(t+\Delta t) = Q_{out}(t) \times \frac{M_{stored}(t)}{V_{stored}(t)}$$

- **Stored loads**: the stored loads of pharmaceutical in the pumping station is the balance between what was previously stored in the pumping station, what enters and what exits the pumping station:

$$M_{stored}(t+\Delta t) = M_{stored}(t) + \Delta t \times (\varphi_{in}(t+\Delta t) - \varphi_{out}(t+\Delta t))$$

With:
t: time (s)
Δt: time step (s), equal to 60 seconds in the model
$\varphi_{out}(t)$: pharmaceutical loads exiting the pumping station at time t (ng/s)
$Q_{out}(t)$: wastewater flow exiting the pumping station at time t (m^3/s)
$M_{stored}(t)$: stored loads of pharmaceutical in the pumping station at time t (ng)
$V_{stored}(t)$: stored volume of wastewater in the pumping station at time t (m^3)

5.3.3 HYPOTHESES AND CHOICES DISCUSSION

In order to keep the model simple but realistic a few hypothesis are made.

In reality each pump is controlled by a set of two height detectors: one bottom set point that stops the pump when it is powered and one high set point that starts the pump when it is not powered. The water level inside the pumping chamber depends on the inflow and outflow, but also on the geometry of the pumping chamber. Their basic geometry is a vertical cylinder. But the relation between the stored wastewater volume and its height inside the chamber is complicated by irregularities in the construction of the chamber and the presence of diverse appliances or solid waste. However, the model assumes that all pumping chambers are perfect vertical cylinders, implying that the stored wastewater volume in the pumping chamber is a linear function of its height. Knowing the theoretical diameter of the pumping chamber and the height thresholds of the pumps, one can determined start and stop volume thresholds for each pump.

In reality, when a pump is turned on, it does not reach its maximum capacity instantaneously. It is due to the inertia of the pump and to the pre-existing pressure inside the downstream pressurized pipe that is always full of wastewater since it is equipped with anti-backflow valves. The model assumes a linear progression of the pump flow after it is started or stopped (figure 32 and "**Pumps flow**" step above).

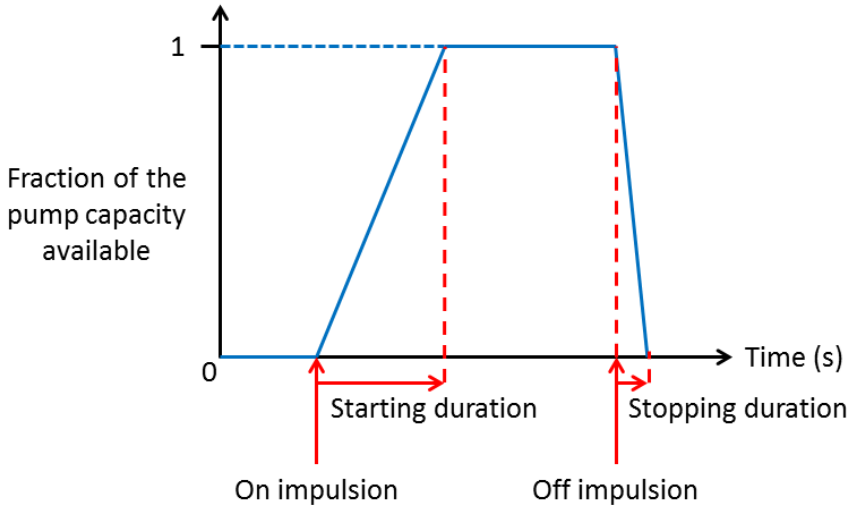


Figure 32: Starting and stopping pattern of the pumps. The starting and stopping duration are respectively set equal to 60 and 15 seconds. It was derived from on-site observations.

Regarding pharmaceuticals loads in the pumping station, the model assumes that the concentration of pharmaceutical is always homogenous within the pumping chamber (see "**Loads exiting**" step above).

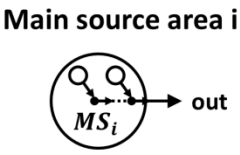
5.4 STRUCTURE OF THE MODEL

5.4.1 MAIN SOURCE AREA MODEL

Data on the urban catchment are often regrouped by city. 18 household areas can be identified. In most cases, those areas are spread over large surface with extensive sewer network. Thus, using those areas directly as source elements in the model would be an over-simplification of the reality as it would not represent the complexity of the system. The same difficulty applies to the hospital. Rooms are spread on a complex and large sewer network within the hospital. To consider that all the rooms are at the same point would be an over-simplification.

However, there is not much data to model this level of complexity. That is why the "Main source area" model is proposed. It is a generic assembling of fundamental elements (sources and pipes) that spreads the discharges in order to represent the complexity of the sources. It requires two additional parameters for the source fundamental element: the average length of pipes between the household outlet and the associated standard deviation.

Graphic symbol:



In: -

Out: wastewater flow and pharmaceutical loads.

Parameters: number of households N_{house}, number of workers N_{worker}, number of hospital beds N_{H-bed} present in the main source area, average length of sewers between discharge points and the outlet of the area $\bar{L}$ (m) and standard deviation associated to this distribution $\sigma(L)$ (m).

Goal: to generate the wastewater flow and pharmaceuticals loads of all population types inside a main source area.

5.4.1.1 GENERATION OF THE MAIN SOURCE AREA

The main source area model arbitrarily consists of 20 consecutives pipes with 20 sources, one at each pipe input (figure 33). Households, workers or hospital beds are distributed in the 20 sources.

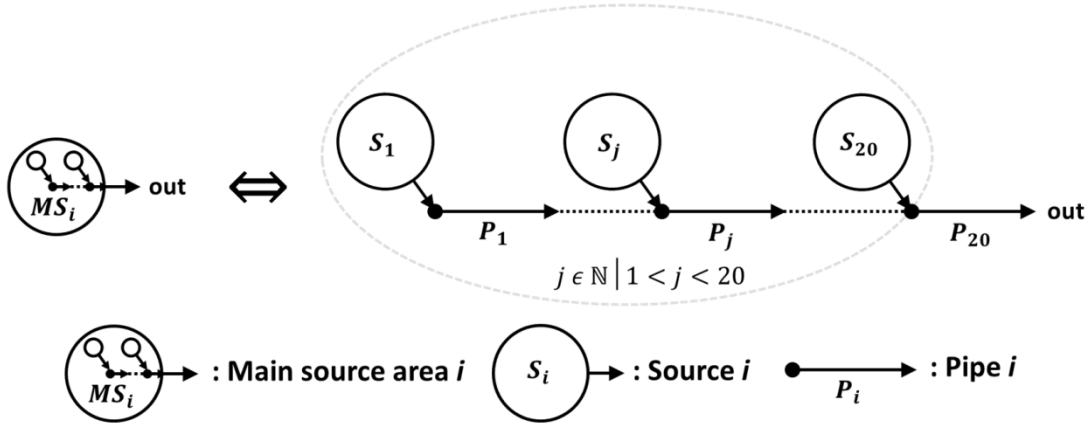


Figure 33: Main source area structure.

To generate a main source area, one must follow the following steps:

- **Lengths**: each household, worker and hospital bed is affected with a length of pipe necessary to reach the output of the main area source. Those lengths are randomly picked following a lognormal distribution of parameters μ and σ.

  $$l_i = random_{lognorm}(\log(\bar{L}), \log(1 + \frac{\sigma(L)}{\bar{L}}))$$

  With:
  i: index of the household or worker or hospital bed
  l_i: length of pipe to the outlet of the main source area for the household, worker or hospital bed i (m)
  $random_{lognorm}(\mu, \sigma)$: return a random value with a lognormal distribution of parameters μ and σ
  $\log(x)$: return the natural logarithm of the strictly positive real number x
  $\bar{L}$: average length of sewers between the discharge points and the outlet of the area (m)
  $\sigma(L)$: standard deviation of the length of sewers between the discharge points and the outlet of the area (m)
- **Last pipe**: the length of the last pipe, the one directly linked to the outlet of the main source area is set equal to the smallest length randomly picked on the previous step (no discharges point is directly connected to the outlet).

  $$L_{20} = \min(l)$$

  With:
  L_{20}: length of the 20th pipe of the main source area (m)
  $\min(d)$: return the smallest value of a list of values d
  l: list of all the lengths picked for households, worker and hospital beds on the previous step (m)

- **Other pipes**: the length of each of the 19 remaining pipes is equal to the difference between the largest and the smallest length randomly picked on the previous step divided by 20.

$$L_n = \frac{\max(l) - \min(l)}{20}$$

With:

n: index of the pipe ($1 \leq n \leq 19$)

L_n: length of the nth pipe of the main source area (m)

$\max(d)$: return the largest value of a list of values d

$\min(d)$: return the smallest value of a list of values d

l: list of all the lengths picked for households, worker and hospital beds on the previous step (m)

- **Sources**: the 20 sources are linked to the 20 inputs of the 20 pipes. Their number of households, workers and hospital beds is determined by the length of pipe to the outlet of the main source area.

$$\boldsymbol{if}\ l_i \neq \max(l)\ \boldsymbol{then}\ j = floor\left(\frac{l_i - L_{20}}{L_{1\rightarrow 19}}\right) + 1$$

$$\boldsymbol{else}\ j = 20$$

With:

i: index of the household or worker or hospital bed

l_i: length of pipe to the outlet of the main source area for the household, worker or hospital bed i (m)

$\max(d)$: return the largest value of a list of values d

l: list of all the lengths picked for households, worker and hospital beds on the previous step (m)

j: index of the source that contain the household, worker or hospital bed i

$floor(x)$: return the greatest integer smaller or equal to the real number x

L_{20}: length of the 20th pipe of the main source area (m)

$L_{1\rightarrow 19}$: length of the pipes 1 to 19 of the main source area (m)

5.4.1.2 HYPOTHESES AND CHOICES DISCUSSION

The current structure of the main source area was chosen mainly to allow different wastewater travel times. This way, wastewater discharged at the same time in two different households reaches the WWTP at different times.

To keep the model as simple as possible, the amount of pipes and sources is set at 20. It provides enough complexity for the present case, but keeps computation needs low. Another approach was considered but not kept. It consisted of determining the number of pipes and sources according to the average length of sewers between discharge points and the outlet of the area $\bar{L}$, the standard deviation associated to this distribution $\sigma(L)$ and the targeted spatial discretization length Δx_{target} of the pipe element.

As the model does not take into account transformations of the pharmaceuticals loads in the sewer system and as the Muskingum model used for the pipe is linear, it is not worth proposing a more complex structure for the main source area, such as a tree structure in comparison to a series of consecutive pipes.

Estimating the average length of sewers between the discharge points and the outlet of the area $\bar{L}$ and the standard deviation associated to this distribution $\sigma(L)$ is done by studying the map of the sewer network of the catchment.

The lognormal distribution of the lengths of sewers between the discharge points and the outlet of the area is chosen because it guaranties positive values.

5.4.2 URBAN SITE

5.4.2.1 STRUCTURE

The structure of the urban catchment model is composed of 18 main source areas, 27 pipes and 8 pumping stations. A diagram of the elements connections is given in figure 34. Details of the different elements can be found in appendix 5. Figure 35 is a representation of the correspondence between the urban catchment and its modelled version.

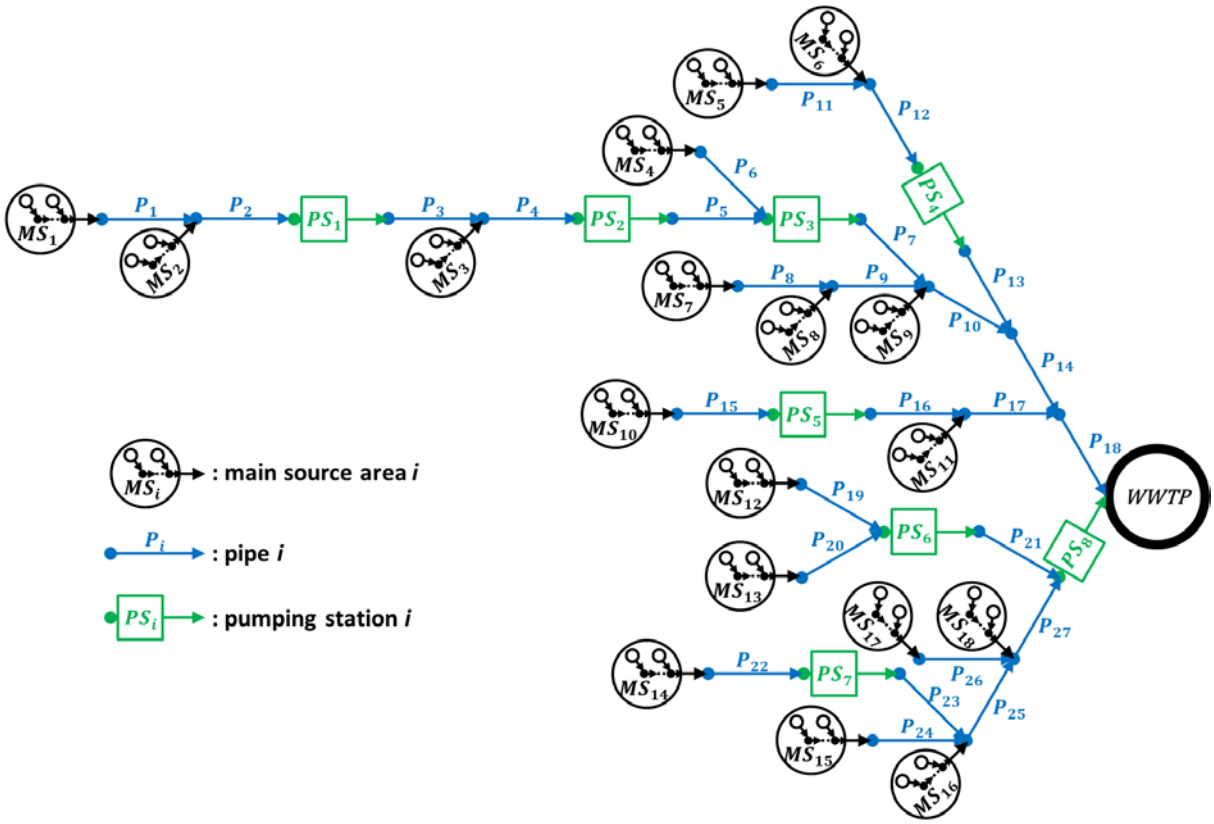


Figure 34: Structure of the urban catchment model.

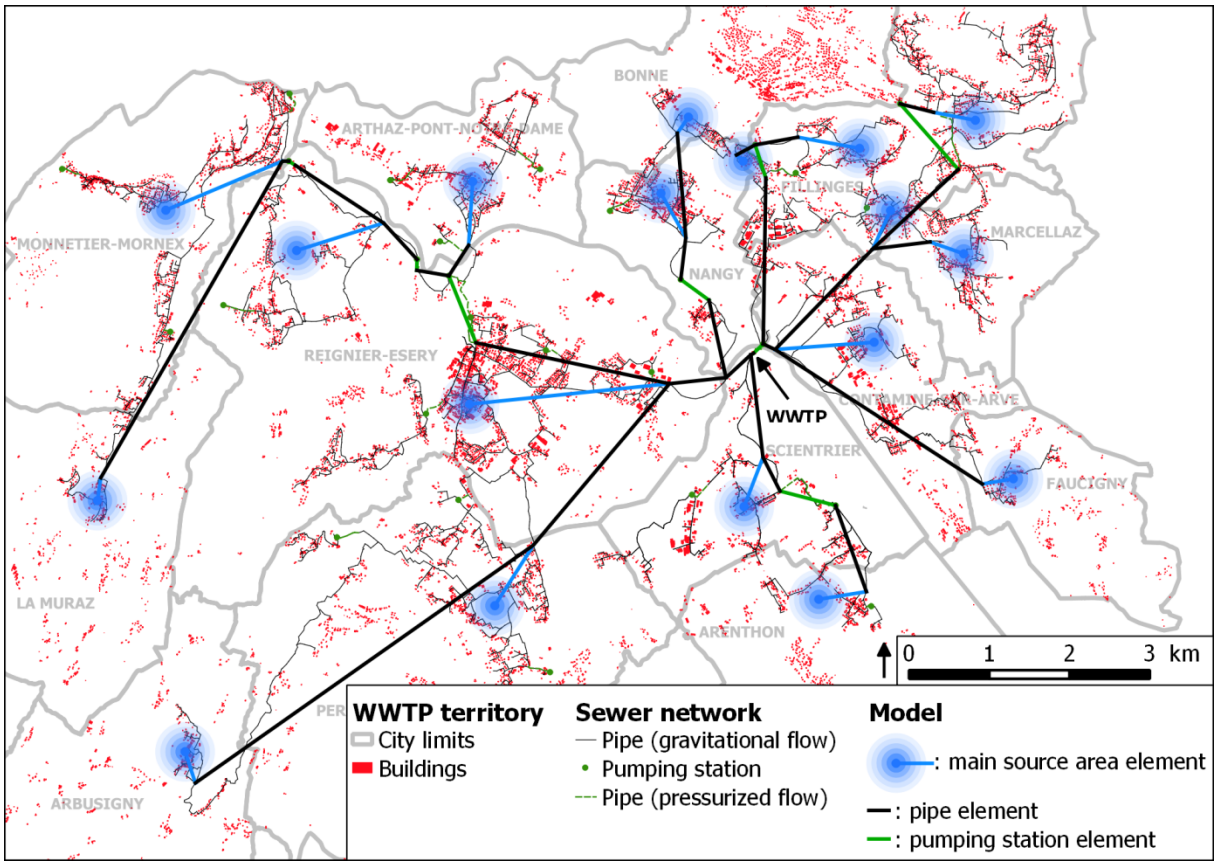


Figure 35: Location of the structure of the urban catchment model (From RDA74, 2010).

5.4.2.2 HYPOTHESES AND CHOICES DISCUSSION

The construction of the structure of the urban catchment model is driven by the definition of the main source areas. They are defined according to the available data. Looking at the sewer network and buildings map of the catchment (figure 35), it is possible to identify many clusters of buildings. However, determining precisely the number of households, workers or hospital beds present in them is not currently possible. That is why the main source area of the structure represents either a whole city or an important identified part of it. The main source area elements in the structure contain household inhabitants and workers.

The wastewater generator only considers households inhabitants. This means that any wastewater that is not from domestic origin is neglected by the model. It is a serious issue for both sites. Indeed, data shows that there is a non-negligible fraction of non-domestic non-parasitic wastewater in the urban catchment (chapter 4). However, such type of wastewater is difficult to model since it represents various kinds of activity with specific wastewater discharges patterns. To address the problem, a methodology is proposed in section 5.5.1.

5.4.3 CHAL HOSPITAL

5.4.3.1 STRUCTURE

The structure of the CHAL hospital model is composed of 1 main source area and 1 pipe. A diagram of the elements connections is proposed in figure 36. Details of the different elements can be found in appendix 6.

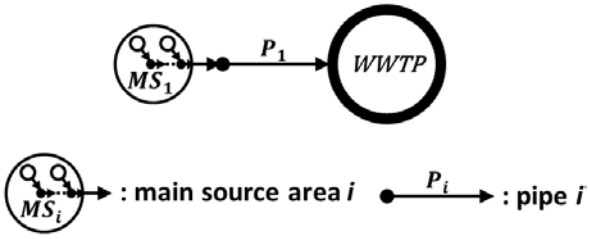


Figure 36: Structure of the model of the CHAL network.

5.4.3.2 HYPOTHESES AND CHOICES DISCUSSION

The structure of the hospital network model is very simple.

Indeed, the hospital is modelled as a simplified and indivisible unit regardless of all the different units of the hospital and of all the different types of population present in the hospital. Only bedded patients are considered, neglecting ambulatory patients, visitors and staff members. Staff members were not assumed to be the average worker that the model generates. Indeed, hospitals are 24 h facilities with a non-negligible fraction of night workers. As a result, no wastewater flow is generated as such by the model in the CHAL hospital.

The real sewer network is composed of a single pipe and a single pumping station. The pipe is present in the modelled structure, but the pumping station is not. Indeed, to run the pumping station element model, it is necessary to have a wastewater inflow to determine the stored volume of wastewater and so the pumps activities. Thus, the pumping station is neglected in the model.

For the same reason, it is not possible to calibrate this structure in this context. As an alternative, it is proposed to apply the calibrated parameters of the urban catchment model to the pipes of the hospital network model.

5.5 CALIBRATION AND VERIFICATION METHODS

The model is analysed in two steps, by first looking at the wastewater flow and then at the pharmaceuticals loads.

Nine model parameters need to be calibrated. They are the six scores associated to "awake at home (transitions)" periods in the time-use pattern weighting process (5.1.1.6 Times of the water uses) and three parameters used in the pipe fundamental element model (5.2.1 Wastewater flow modelling). Their primary effect is on wastewater discharges and transport. Thus, it was decided to first calibrate and validate the model only with its wastewater components, and in a second time, to compare the model results regarding pharmaceuticals loads to measurements.

5.5.1 CALIBRATION AND VERIFICATION METHODS FOR THE WASTEWATER FLOW

Since the hospital network model generates no wastewater flow, calibration and verification are only done for the urban catchment model. Out of the 129 wastewater flow measurements of two consecutive days identified (chapter 6), two thirds (86) and one third (43) are respectively assigned for calibration and verification. Each of the 129 time series is analyzed to determine its parasitic water baseline and smoothed with a 30 minutes mobile mean to get the average dynamics of the wastewater flow (chapter 6).

The calibration is done in two steps, after which a corrective model is added and, finally, it is validated. Measured and modelled time series are always compared with the Nash-Sutcliffe model efficiency coefficient (NSE) (Nash and Sutcliffe, 1970). The NSE ranges from $-\infty$ to 1. 1 is the perfect score and 0 means that the model is equivalent to the average value. It is common to say that models with NSE score over 0.5 are good (Moriasi *et al.*, 2007). It is calculated as follows:

$$NSE = 1 - \frac{\sum_{t=1}^{T}\left(Q_{measured}(t) - Q_{modelled}(t)\right)^2}{\sum_{t=1}^{T}(Q_{measured}(t) - \overline{Q_{measured}})^2} = f_{NSE}(Q_{measured}; Q_{modelled}; P)$$

With:
t: time ($t \in P$)
P: time period on which the NSE is calculated
$Q_{measured}(t)$: measured flow a time t (m^3/s)
$Q_{modelled}(t)$: modelled flow a time t (m^3/s)
$\overline{Q_{measured}}$: average measured flow a time t (m^3/s)
$f_{NSE}(x; y; P)$: return the NSE score of the measured time series x and modelled time series y for the time period P

The calibration and verification process consists of the following steps:

- **Pipe parameters calibration**: three parameters of the pipe fundamental element are calibrated: targeted weighting parameter α_{target}, targeted lag time K_{target} and targeted delay δ_{target}. 10 000 sets of the three parameters are generated using a Latin Hypercube Sampling (LHS) method (McKay *et al.*, 1979). The six "Awake at home (transitions)" period weighting parameters are equal to two. 30 stochastic repetitions of the urban catchment model are run for each parameter set. This provides 300 000 (10 000 sets time 30 stochastic repetitions) modelled wastewater flow time series of two consecutive days. The best parameter set is determined using the method described in appendix 7 with:
    - 300 000 modelled wastewater flow time series
    - 86 measured wastewater flow time series dedicated to calibration
    - Values from 6 h to 10 h and from 20 h to 6 h as period of calibration

- **"Awake at home (transitions)" weighting parameters calibration**: the six "Awake at home (transitions)" period weighting parameters are calibrated using the same methodology as the previous point but the calibration period is extended. The best parameter set is determined using the method described in appendix 7 with:
    - 300 000 modelled wastewater flow time series
    - 86 measured wastewater flow time series dedicated to calibration
    - Values from 6 h to 8 h and from 22 h to 6 h as period of calibration
- **Non-parasitic non-domestic wastewater modelling (NPND model)**: a simple empirical statistic model is generated to compensate for possible underestimated wastewater flow. The idea is to randomly picked the contribution of NPND wastewater from a normal distribution which the parameters are derived from the difference between the measured and modelled wastewater flow:

$$Q_{NPND}(t) = \max[\![0; random_{norm}\{Av[Q_{diff,1\to N_{Dates}}(t)]; Std[Q_{diff,1\to N_{Dates}}(t)]\}]\!]$$

$$Q_{diff,k}(t) = \max[\![0; Q_{Smoothed\ Measured,k}(t) - (\overline{Q_{Smoothed\ Modelled,I}(t)} + PWB_k(t))]\!]$$

With:

t: time (Δt)

Δt: time step of the simulation (60 s)

$Q_{NPND}(t)$: non-parasitic non domestic wastewater flow at time t (m^3/s)

$max[\![x, y]\!]$: return the maximum value between x and y

$random_{norm}\{\mu; \sigma\}$: return a random value with a normal distribution of parameter μ and σ

$Av[X]$: average of the list of values X

$Std[X]$: standard deviation of the list of values X

k: index of the measured time series ($1 \leq k \leq 86$ calibration dates)

$Q_{diff,k}(t)$: possible underestimated wastewater flow for date k at time t (m^3/s)

$Q_{Smoothed\ Measured,k}(t)$: smoothed measured time series of date k at time t (m^3/s)

$\overline{Q_{Smoothed\ Modelled}(t)}$: average of 30 stochastic smoothed modelled time series generated with the calibrated parameters at time t (m^3/s)

$PWB_k(t)$: parasitic water baseline of date k at time t (m^3/s)

- **Verification**: The urban catchment model with calibrated parameters and the NPND model are run for 100 stochastic repetitions. Then NSE scores are calculated for the 36 smoothed measured wastewater flow time series dedicated to verification and the 100 stochastic repetitions of the model:

$$NSE_{k,j} = f_{NSE}(Q_{Smoothed\ Measured,k}; Q_{Smoothed\ Modelled,j} + Q_{NPND} + PWB_k; P_{Sampling})$$

With:

k: index of the measured time series ($1 \leq k \leq 43$ verification dates)

j: index of the stochastic repetition ($1 \leq i \leq 100$)

$NSE_{k,j}$: NSE score for measured date k and stochastic repetition j

$f_{NSE}(x; y; P)$: return the NSE score of the measured time series x and modelled time series y for the time period P

$Q_{Smoothed\ Measured,k}$: smoothed measured wastewater flow of date k (m^3/s)

$Q_{Smoothed\ Modelled,j}$: smoothed modelled wastewater flow of stochastic repetition j (m^3/s)

Q_{NPND}: non-parasitic non domestic wastewater flow (m^3/s)

PWB_k: parasitic water baseline of date k (m^3/s)

$P_{Sampling}$: time period of sampling during the pharmaceuticals daily loads measurement campaigns, 8h to 8h (chapter 4)

The 4 300 NSE scores are then analysed to determine the validity of the proposed model.

For the two calibration steps, the number of parameter sets and stochastic repetitions are chosen as a compromise between precision of screening and stochastic variability and computational duration.

The calibration is made in two steps to keep the computational duration manageable. For the same number n of values tested for each parameter, it requires fewer computations to explore three then six parameters rather than 9 parameters directly ($\forall\, n \in \mathbb{N} \mid n \geq 2 \;\Rightarrow\; n^3 + n^6 < n^9$). This two steps calibration is possible because the three parameters for the pipe fundamental element and the six "Awake at home (transitions)" period weighting parameters have different effects on the model.

The first three parameters modify the velocity at which the wastewater flow travels along the pipes. The main goal of the first calibration is to ensure that the wastewater flow enters the WWTP at the right time. For this reason, the calibration period is focused on the morning increase (6 h to 8 h), the evening decrease and the night levels (22 h to 6 h) of wastewater flow.

The six other parameters have an impact on the levels of wastewater flow. The goal of this second calibration is to ensure that the relative heights of the wastewater flow peaks are correct. For this reason, the calibration period is focused on the morning increase and peak (6 h to 10 h), the evening peak and decrease and the night levels (20 h to 6 h) of wastewater flow.

Both calibration periods do not cover the diurnal hours (10 h to 20 h). This means that the model can deviate from the measurements during this period. However, as described in chapter 4, the urban catchment is expected to generate wastewater flow that are neither from domestic origin nor parasitic in nature. This additional wastewater flow is expected to happen during diurnal hours. To compensate this non-parasitic non-domestic wastewater flow that is not modelled, the NPND model is added.

5.5.2 VERIFICATION METHODS OF THE PHARMACEUTICAL LOADS

A thousand of simulations are run for both sites. The results of the model are compared in two different manners with two sets of data. First, pharmaceuticals loads are summed over a 24 h period to obtain daily loads that are then compared to the measured daily loads. Both the average value and the dispersion of observations are taken into account. Also, metabolites loads are added to their parent compounds to verify the hypothesis that some of them can be transformed back to the parent compound in wastewater.

Then, hourly loads are studied. The goodness of fit is calculated with a modified version of the NSE coefficient on normalized pharmaceutical profiles. This way the focus is set on the shape of the profile and not its level.

PART 3: RESULTS AND DISCUSSION

This part is divided in two chapters.

In chapter 6, all the collected data are analyzed. This includes pharmaceutical sales and distribution data, measured wastewater flows and pharmaceuticals loads.

In chapter 7, the results of the model are analyzed for both sites.

CHAPTER 6: MONITORING RESULTS

Three types of data were collected for the two sites: pharmaceuticals sales or distributions, wastewater flows and pharmaceuticals loads at the inlet of the WWTP. In sections 6.1, 6.2 and 6.3, they are presented and analyzed in the above order, by first focusing on the urban catchment and then on the CHAL hospital. As the analytical logics and tools used are the same for both sites, repetitions can occur in the text. A comparison of the two sites is proposed only for the analysis of pharmaceuticals loads (section 6.3.3).

Finally, in section 6.4, the link between pharmaceuticals sales or distributions and loads is analyzed.

6.1 PHARMACEUTICALS SALES AND DISTRIBUTION DATA

The main reason to use pharmaceuticals sales and distribution data is to try to represent the consumption of the population regarding both its magnitude and dynamics.

6.1.1 URBAN SITE

Pharmaceuticals sales for the urban catchment were obtained over 2.5 years on a monthly basis on two scales (chapter 4): a small one targeting the six pharmacies of the Bellecombe catchment (30 015 expected inhabitants) and a wider one representing the whole Haute-Savoie area (793 342 expected inhabitants). All time series were checked for anomalies before their analysis (negative values or suspicious outliers). No anomaly was found.

First a comparison of the two data sets is made investigate the magnitudes and dynamics of pharmaceutical consumption. Then a new set of pharmaceutical sales time series is proposed. Finally, various observations are made concerning the pharmaceuticals sales in the urban catchment.

Global comparison

For both datasets, the mass sales of each month were summed for each speciality and were then divided by the number of days of the period (2.5 years) and by the number of expected inhabitants being supplied, thus giving the total mass sold per capita per day for all the specialities.

When comparing the two datasets, one can expect random deviations as the consumption of pharmaceuticals is not necessarily spatially homogenous (figure 37). First, 21 of the 188 specialities are not sold in Bellecombe but they are in Haute-Savoie. This is because they only concern low sales volumes. They are not taken into account in regard to the following analysis. For the 167 remaining specialities, the ratios between Bellecombe and Haute-Savoie range from 0.03 to 13.6 but 136 of them (81 %) are below 1 even for specialities that represent most of the molecule sales. This “systematic” deviation is not explainable by spatial heterogeneity as both Bellecombe and Haute-Savoie are large enough and representative of the population age and household composition distributions. The ratios can also be influenced by the expected number of inhabitants supplied for each dataset. For Haute-Savoie, this number is considered correct since it is a very large area with good census data. However, for Bellecombe, this number was constructed by assuming that the 6 targeted pharmacies supplied exclusively and completely the Bellecombe area. Assuming that this last number is biased one can propose a correction factor F_{corr} that is the weighted average of the ratios:

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

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

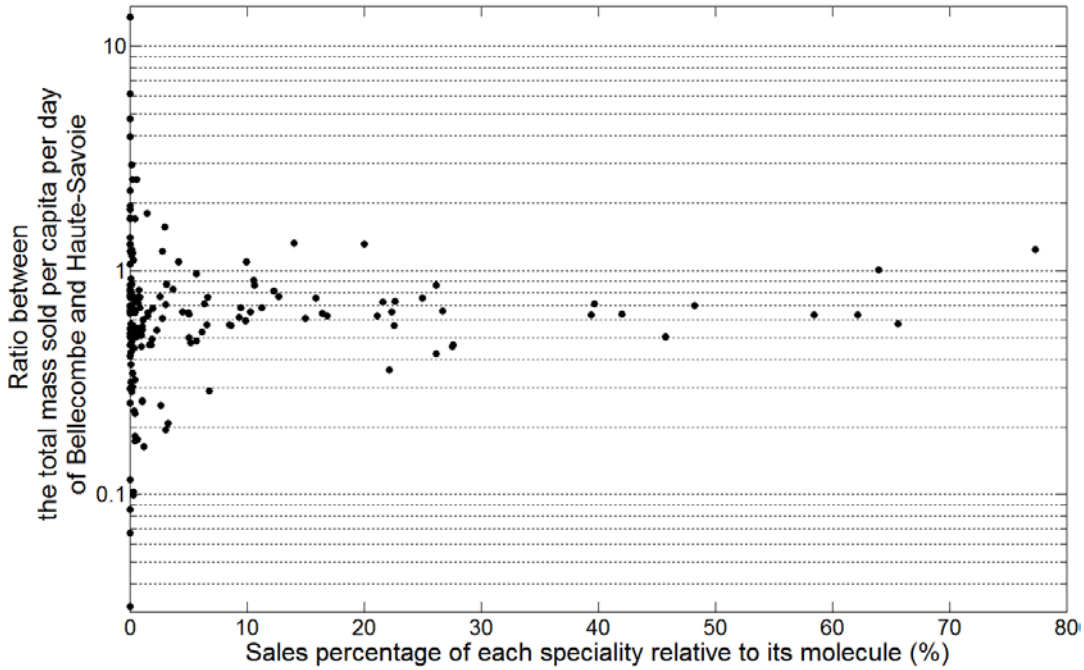


Figure 37: Ratios of all the specialties between the total mass sold per capita per day of Bellecombe and Haute-Savoie. The Y axis is logarithmic.

To evaluate the validity of this correction factor, one can calculate the coefficient of determination R^2 of the linear function $M_B = F_{corr} \times M_H$ (figure 38). It was found to be equal to 0.998. In comparison, a $M_B = M_H$ line gives a R^2 of 0.372, and a classic linear regression by the least squares method gives a R^2 of 0.987. As a consequence, F_{corr} was chosen as a global correction factor.

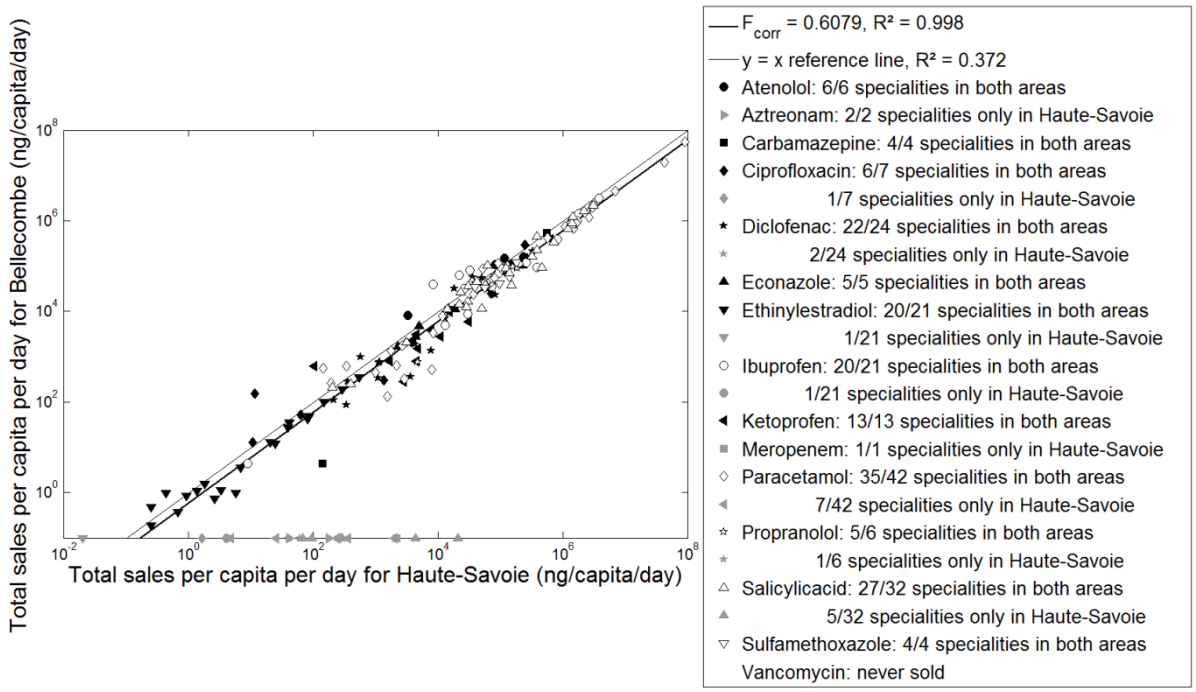


Figure 38: Comparison of sales between Bellecombe and Haute-Savoie. Some specialities are not sold in both areas, in which case they are displayed with plain grey symbols on the X axis and were not taken into account to calculate the correction factor.

Dynamics comparison

The comparison of the two time series was made under the assumption that both time series (Bellecombe and Haute-Savoie) have the same profile but different variability. Indeed, due to its smaller population sample, the one from Bellecombe would be more variable.

To verify this assumption, two steps were followed: first the variability levels were checked and compared, and secondly, the profile similarity was assessed. The analysis is carried out on normalized time series (time series divided by their average), in order to compare only the shapes of the curves rather than their absolute values. Also, to avoid artifacts from low sales specialities, the time series are grouped by molecule and location, thus giving 2 x 15 time series.

To evaluate the noise level in each time series, it is proposed to calculate the average local amplitudes of sales (mean of the absolute differences between two consecutive values). The idea was that a greater value would imply greater short term variations that could be interpreted as "noise". The results are presented in table 11.

The average local amplitudes are always greater for Bellecombe than for Haute-Savoie, that would tend to confirm that the time series of Bellecombe show more fluctuation and variability compared to Haute-Savoie. The ratios of the average local amplitudes between Bellecombe and Haute-Savoie are, in consequence, always greater than 1. One could have predicted that the ratios are proportional to the level of consumption of the molecule, but it is not the case, as the numbers of DDD sold per day in Haute-Savoie indicate. However, the molecules with a ratio under 2 are all buyable without prescription (ANSM, 2015). The consumption of those molecules is thus already smoothed at the Bellecombe scale. This could indicate that those molecules are bought in a different pattern than more regulated ones. Indeed they are all used to treat pain and fever, and those conditions affect everybody quite regularly (headache, cold, fatigue…).

Table 11: Comparison of the average local amplitudes for each molecule between Haute-Savoie and Bellecombe

Molecule	Average local amplitudes for the normalized time series		Ratio Bellecombe / Haute-Savoie	Average number of DDD sold in one day in Haute-Savoie
	Haute-Savoie	Bellecombe		
Atenolol	0.04	0.15	3.86	6 071
Aztreonam				
Carbamazepine	0.05	0.2	4.32	669
Ciprofloxacin	0.1	0.34	3.49	247
Diclofenac	0.05	0.09	1.87	9 487
Econazole	0.07	0.16	2.31	857
Ethinylestradiol	0.04	0.1	2.66	40 702
Ibuprofen	0.1	0.15	1.44	9 310
Ketoprofen	0.05	0.13	2.6	7 807
Meropenem				
Paracetamol	0.07	0.08	1.1	39 725
Propranolol	0.04	0.19	4.99	1 963
Salicylic acid	0.07	0.09	1.3	3 583
Sulfamethoxazole	0.1	0.26	2.47	144
Vancomycin				

To evaluate the trend similarity between the two sites, the Mean Absolute Percentage Errors (MAPE) are calculated on time series normalized and smoothed by means of a mobile mean over 5 months. The smoothing process goal is to reduce the noise of each time series as much as possible in order to focus the analysis on the shape of the curve. The MAPE definition is:

$$MAPE = \frac{100}{n} \times \sum_{i=1}^{n} \left| \frac{R_i - C_i}{R_i} \right|$$

With:
n: the number of points in the time series
R_i: the value of the i^{th} point of the reference time series
C_i: the value of the i^{th} point of the tested time series

As the MAPEs take one time series as a reference, MAPEs are calculated once with Haute-Savoie as a reference and once with Bellecombe. The results are presented in table 12.

Table 12: Mean absolute percentage error results between Bellecombe and Haute-Savoie.

Molecule	Mean absolute percentage error (MAPE)				Average number of DDDs sold in one day in Bellecombe
	smoothed time series with, as reference,		not smoothed time series with, as reference,		
	Haute-Savoie	Bellecombe	Haute-Savoie	Bellecombe	
Atenolol	2.49	2.48	7.62	7.78	215
Aztreonam					
Carbamazepine	4.38	4.35	11.22	11.37	21
Ciprofloxacin	6.94	6.98	18.07	18.48	10
Diclofenac	6.72	6.89	8.43	8.76	239
Econazole	8.67	8.72	12.35	12.63	20
Ethinylestradiol	2.76	2.75	5.9	6.2	985
Ibuprofen	2.49	2.52	5.5	5.61	258
Ketoprofen	5.39	5.35	8.65	8.69	185
Meropenem					
Paracetamol	2.43	2.45	4.12	4.22	879
Propranolol	6.27	6.25	12.5	12.72	46
Salicylic acid	1.41	1.42	4.03	4.05	93
Sulfamethoxazole	18.64	18.68	26.14	31.12	3
Vancomycin					
Average	5.7	5.7	10.4	11	
Average (without sulfamethoxazole)	4.5	4.6	8.9	9.1	

The MAPEs do not change much depending on the reference (less than 1 % difference, except for Sulfamethoxazole concerning not smoothed time series). Except for Sulfamethoxazole, the MAPEs are never greater than 10 % for the smoothed time series and average 4.5 %. This indicates that the time series for Haute-Savoie and Bellecombe share the same shape. Obviously, with not smoothed time series, the MAPEs are greater (on average 2 times greater). This is in accordance to the variability analysis done previously.

The case of Sulfamethoxazole stands apart. Its MAPE for smoothed time series show the highest value (18.6 %). However, one can notice that it represents the smallest number of DDDs averagely sold in one day in Haute-Savoie (144 DDDs) and Bellecombe (3 DDDs). Thus it not surprising that the shapes of the two time series do not match really well.

In conclusion, it is assumed that sales from Bellecombe follow the same trend as the ones from Haute-Savoie, but they are "noisier" due to the smaller population sample.

The molecules can be divided in two sets depending on the ratio of the noise levels of Bellecombe over the ones of Haute-Savoie (table 11). Molecules with a ratio below 2 are not significantly noisier in Bellecombe. This means that their sales are already smoothed at the scale of Bellecombe. Both sets of molecules are illustrated with three examples in figure 39. Sulfamethoxazole is difficult to analyse since it is seldom sold. Its time series are presented in figure 39.

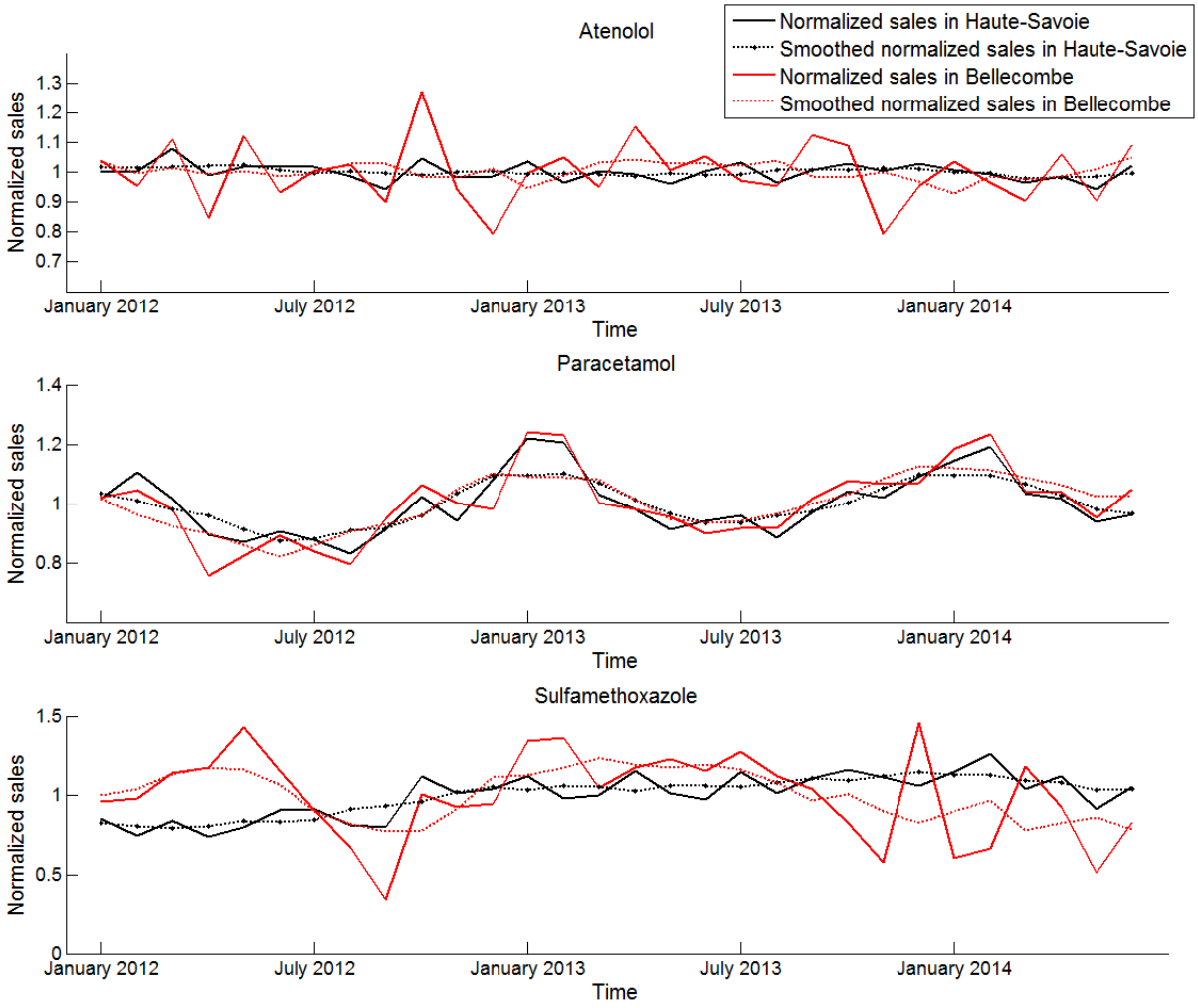


Figure 39: Three examples of sales time series. Atenolol is an example of molecules which is significantly noisier in Bellecombe. Paracetamol is an example of molecules which is not significantly noisier in Bellecombe. Sulfamethoxazole is the single molecule which is extremely noisier in Bellecombe.

A new set of pharmaceuticals sales time series

As a consequence of the above analysis of data, the corrected urban pharmaceuticals sales time series set is established to be used further in this section and for modelling. It is constructed by dividing each time series of the Bellecombe set by a correction factor $F_{corr} = 0.6079$. This way each time series is as variable as possible and adjusted to the right level. There are more uncertainties in estimating the number of customers for six pharmacies rather than a whole region with 223 pharmacies (French Chamber of Pharmacists, 2017). Thus, the magnitudes of the sales per capita for the Bellecombe area are less accurate than the ones for the Haute-Savoie area.

Molecule versus specialities

Each molecule is sold as a certain number of specialities. The 15 molecules in SIPIBEL are represented by 188 specialities. However, these specialities are not equally distributed amongst the different molecules. Excluding Aztreonam, Meropenem and Vancomycin that are never sold in Bellecombe, the average number of specialities per molecule is 14.4 ranging from 4 for Carbamazepine and Sulfamethoxazole to 42 for Paracetamol (table 13). Also, for one molecule, its different specialities are not sold equally (table 13). The most sold speciality of each molecule represents at least 24 % of the total mass sold for the molecule and 50 % on average. 90 % of the total mass sold of each molecule is represented on average by only four specialities.

Table 13: Relative importance for the ten most represented specialities in Bellecombe of each molecule for the corrected urban pharmaceuticals sales time series. Aztreonam and Meropenem are never sold. Vancomycin is not available, thus has no speciality.

Molecule	Average mass sold (mg/day)	Number of specialities	Ten most represented specialities in descending order of masses sold (%)									
			1	2	3	4	5	6	7	8	9	10
Atenolol	26 563	6	30	28	20	20	2	0				
Aztreonam	0	2										
Carbamazepine	34 082	4	79	15	6	0						
Ciprofloxacin	15 975	7	92	8	0	0	0	0	0			
Diclofenac	39 330	24	26	19	9	8	7	7	7	5	4	4
Econazole	2 646	5	61	21	9	5	3					
Ethinylestradiol	40	21	42	23	12	6	5	4	3	2	2	0
Ibuprofen	510 363	21	31	21	15	14	9	4	1	1	1	1
Ketoprofen	30 468	13	63	17	16	2	1	1	1	1	0	0
Meropenem	0	1										
Paracetamol	4 345 642	42	63	22	5	2	1	1	1	1	1	1
Propranolol	12 166	6	40	37	18	5	0	0				
Salicylic acid	458 302	32	24	18	13	10	9	7	5	4	3	2
Sulfamethoxazole	11 390	4	53	18	15	14						
Vancomycin	0	0										
Average representation (%)			50	21	11	7	3	2	2	1	1	1
Minimum cumulated representation (%)			24	42	54	62	69	76	83	87	92	93
Average cumulated representation (%)			50	71	82	90	93	95	96	97	98	99
Maximum cumulated representation (%)			92	100	100	100	100	100	100	100	100	100

Molecule and pharmaceuticals forms

Pharmaceuticals are sold under different forms. They can be classified by the way they enter the human body. The main forms are oral, intravenous, dermal, ophthalmic, urogenital and rectal. These forms have a great impact on the metabolism of the molecules. Thus they have a great impact on excreted loads. That's why they need to be identified. Table 14 summarizes the distributions of the forms. Most of the molecules are predominantly sold as oral forms (8 out the 12 molecules actually sold). Diclofenac and Ketoprofen are divided between oral and dermal forms (respectively 47 % and 82 % of oral forms). Only Econazole is never sold as oral forms but as dermal forms (70 %) and urogenital forms. Intravenous forms are never sold for the considered molecules.

Table 14: Relative importance of the different forms of pharmaceuticals for the corrected urban pharmaceuticals sales time series.

Molecule	Average mass sold (mg/day)	Oral (%)	Intravenous (%)	Dermal (%)	Other (ophthalmic, urogenital, rectal...) (%)
Atenolol	26 563	100	0	0	0
Aztreonam	0				
Carbamazepine	34 082	100	0	0	0
Ciprofloxacin	15 975	100	0	0	0
Diclofenac	39 330	47	0	53	0
Econazole	2 646	0	0	70	30
Ethinylestradiol	40	100	0	0	0
Ibuprofen	510 363	99	0	1	0
Ketoprofen	30 468	82	0	17	1
Meropenem	0				
Paracetamol	4 345 642	100	0	0	0
Propranolol	12 166	100	0	0	0
Salicylic acid	458 302	100	0	0	0
Sulfamethoxazole	11 390	100	0	0	0
Vancomycin	0				

Mass sold versus potential number of patients

Ranking the molecules according to the mass that are sold is important. Indeed, a molecule that is massively consumed has more chance to reach the environment later. With this ranking system, one can divide the molecules in 4 sets (table 15):

- **High sales, over 10 mg per day per capita, 3 molecules**: Paracetamol (145), Ibuprofen (17) and Salicylic acid (15).
- **Medium sales, between 0.1 and 1.5 mg per day per capita, 7 molecules**: Diclofenac (1.31), Carbamazepine (1.14), Ketoprofen (1.02), Atenolol (0.88), Ciprofloxacin (0.53), Propranolol (0.41) and Sulfamethoxazole (0.38).
- **Low sales, under 0.1 mg per day per capita, 2 molecules**: Econazole (0.09) and Ethinylestradiol (0.001).
- **No sales, 3 molecules**: Aztreonam, Meropenem and Vancomycin.

Table 15: Mass and number of DDD sold for the corrected urban pharmaceuticals sales time series.

Molecule	Average mass sold		Average number of DDD sold		Rank according to	
	(mg/day)	(mg/day /capita)	(DDD/day)	(DDD/day /10 000 capita)	the mass sold	the DDD sold
Atenolol	26 563	0.88	354	118	7	5
Aztreonam	0	0	0	0		
Carbamazepine	34 082	1.14	34	11	5	9
Ciprofloxacin	15 975	0.53	16	5	8	11
Diclofenac	39 330	1.31	393	131	4	4
Econazole	2 646	0.09	33	11	11	10
Ethinylestradiol	40	0.001	1 620	540	12	1
Ibuprofen	510 363	17.00	425	142	2	3
Ketoprofen	30 468	1.02	305	102	6	6
Meropenem	0	0	0	0		
Paracetamol	4 345 642	145	1 449	483	1	2
Propranolol	12 166	0.41	76	25	9	8
Salicylic acid	458 302	15.27	153	51	3	7
Sulfamethoxazole	11 390	0.38	6	2	10	12
Vancomycin	0	0	0	0		

However, for modelling purposes, it is also important to rank the molecules according to the number of DDD sold. It allows roughly estimating the average number of patients consuming a molecule per day. Indeed, a molecule consumed by a huge number of patients will be easier to model since the randomness of the consumption will be smoothed. With this ranking, one can divide the molecules in 4 sets (table 15):

- **High sales, over 400 DDD per 10 000 capita per day, 2 molecules**: Ethinylestradiol (540) and Paracetamol (483).
- **Medium sales, between 50 and 150 DDD per 10 000 capita per day, 5 molecules**: Ibuprofen (142), Diclofenac (131), Atenolol (118), Ketoprofen (102) and Salicylic acid (51).
- **Low sales, under 30 DDD per 10 000 capita per day, 5 molecules**: Propranolol (25), Carbamazepine (11), Econazole (11), Ciprofloxacin (5) and Sulfamethoxazole (2).
- **No sales, 3 molecules**: Aztreonam, Meropenem and Vancomycin.

The two rankings provide different insights in the molecules studied. The most stunning difference is observed for Ethinylestradiol that moves from last place (12) for mass ranking to first place for DDD ranking. This is because it is widely used but at very low doses.

General trends and seasonality

It is not realistic to perform a complete analysis of the general trend and potential seasonality of pharmaceuticals sales with only a little more than 2 years of data. Nevertheless, both general trends and potential seasonality have been studied for the 15 molecules on two consecutive years of data (2012 and 2013). Results for the general trend analysis are shown in table 16. Between 2012 and 2013, the variation of the sales of pharmaceuticals ranges from -6 to +17 %. However, it is important to consider the number of potential patients those sales represent. Indeed, a +11 % variation for Paracetamol that provides roughly 1 450 DDD per day does not have the same importance as a +17 % variation for Econazole that provides roughly 30 DDD per day.

Table 16: Global trend analysis for the corrected urban pharmaceuticals sales time series.

Molecule name	Average sales for the year starting in January				Variation	
	2012		2013			
	(mg/day)	(DDD/day)	(mg/day)	(DDD/day)	(mg/day)	(%)
Atenolol	26 459	353	26 764	357	305	1
Aztreonam	0	0	0	0	0	0
Carbamazepine	34 539	35	34 950	35	411	1
Ciprofloxacin	16 066	16	16 777	17	711	4
Diclofenac	38 452	385	39 805	398	1 353	4
Econazole	2 349	29	2 751	34	402	17
Ethinylestradiol	42	1 673	40	1 615	- 1	- 4
Ibuprofen	474 719	396	532 781	444	58 062	12
Ketoprofen	30 526	305	30 638	306	113	0
Meropenem	0	0	0	0	0	0
Paracetamol	4 033 499	1 344	4 472 478	1 491	438 978	11
Propranolol	12 601	79	11 835	74	- 767	- 6
Salicylic acid	466 112	155	462 114	154	- 3 998	- 1
Sulfamethoxazole	11 070	6	12 922	6	1 852	17
Vancomycin	0	0	0	0	0	0

To investigate the potential seasonality of the molecules sales, it is proposed to detect sets of consecutive monthly values all above or under the annual average every year. Molecules that present both at least one high and one low season are considered seasonal. Table 17 shows the results of this analysis. Only three molecules present a clear seasonal behaviour with a high season in cold periods (autumn and winter) and a low season in warm periods (spring and summer). Figure 40 shows the sales evolution for the 3 seasonal molecules. Sales evolutions for all the molecules are presented in appendix 8.

Table 17: Seasonality analysis for the corrected urban pharmaceuticals sales time series.

Molecule	High season	Low season
Atenolol		
Aztreonam		
Carbamazepine		
Ciprofloxacin		
Diclofenac		
Econazole		
Ethinylestradiol		
Ibuprofen	January to February	April to August
Ketoprofen		
Meropenem		
Paracetamol	October to February	April to August
Propranolol		
Salicylic acid	January to February	April to July
Sulfamethoxazole		
Vancomycin		

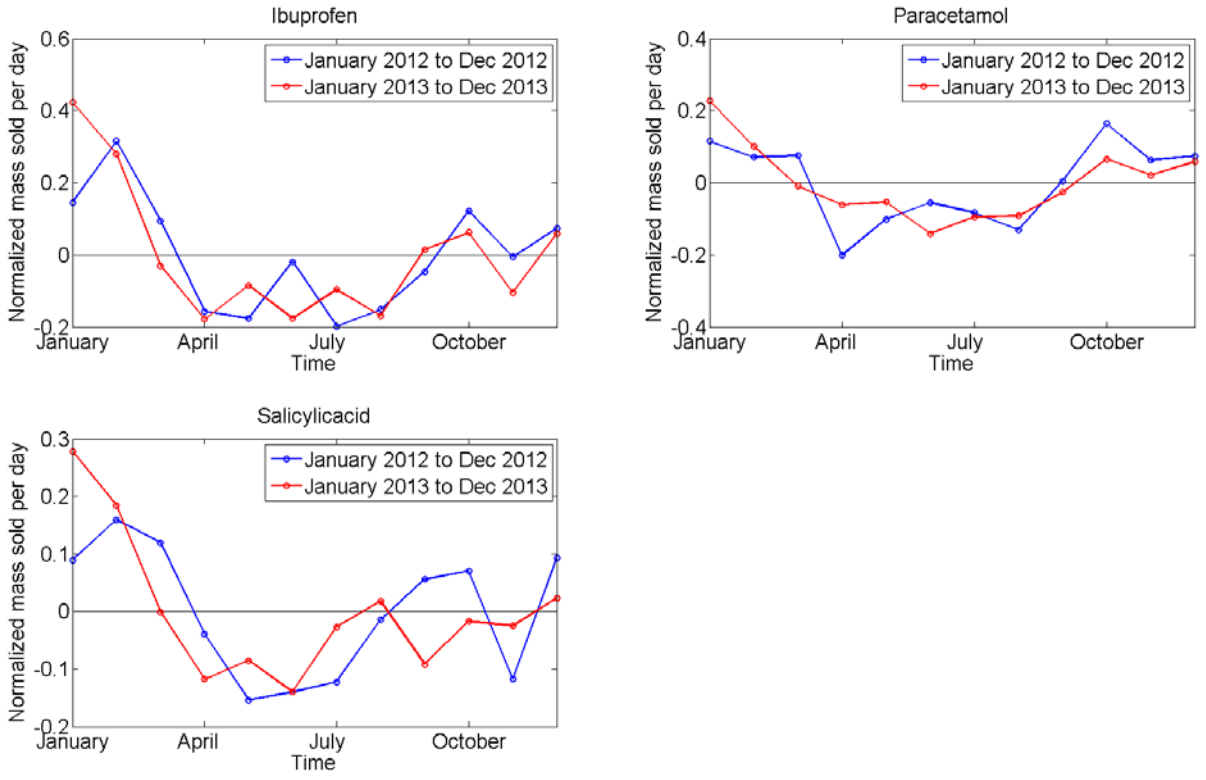


Figure 40: Sales evolution for the three molecules with seasonal component for the corrected urban pharmaceuticals sales time series.

6.1.2 CHAL HOSPITAL

For the CHAL hospital, pharmaceuticals distribution data were collected at the central pharmacy of the hospital (chapter 4). These data are supposed to represent the distribution of pharmaceuticals to the different services supplying bedded patients. Three time scales of analysis were investigated: daily, weekly and monthly.

First the presence of anomalies in the distributions is pointed out. As a consequence, a new set of time series is proposed. Finally, various observations are made concerning the pharmaceuticals distributions in the CHAL hospital.

Anomalies in the raw time series

Pharmaceuticals distributions data are not directly linked to the actual consumption of the patients in the hospital. They are hugely impacted by the management of stocks between the central pharmacy and the different services. As a result, some dynamics in the distribution data can be seen as anomalies for modelling the consumption of patients. Thus, these anomalies need to be analysed, in order to treat them before they can credibly represent the consumption of pharmaceuticals.

In our context, an anomaly is everything that significantly makes the distribution data of pharmaceuticals different than the actual consumption of the pharmaceuticals in the hospital. For each of the three investigated temporal scales, anomalies have been detected.

Negative and suspiciously high values have been detected for many specialities on each temporal scale. Suspiciously high values are assumed to be the ones that are outside ± 3 standard deviations from the average interval (assuming the distribution of pharmaceuticals follow a normal law this interval should cover 99.7 % of the values). The results are summarized in table 18. Collecting daily distributions was very time consuming, so only a few days corresponding to sampling campaigns were collected. Thus, their comparison with weekly and monthly distributions is difficult. However, focusing on the weekly and monthly distributions, one can see that there are more anomalies, both negatives and high values, than the weekly distributions. This is because monthly distributions are naturally smoothed. Regardless of the temporal scale considered, more than 40 % of the specialities contain more than 1 % of negative values. Also, respectively 58.9 % and 30.4 % of the specialities contain more than 1 % of outliers for the weekly and monthly distributions.

Table 18: Summary of the negative and suspiciously high values detection for the hospital pharmaceuticals distributions data. The percentage of outliers is calculated without the negative values.

	Daily scale 120 points		Weekly scale 138 points		Monthly scale 32 points	
	<0 (%)	Outliers (%)	<0 (%)	Outliers (%)	<0 (%)	Outliers (%)
Minimum	0	0	0	0	0	0
Average	2.1	2.5	3.6	1.4	2.6	1
Max	12.5	6.7	12.3	3.1	15.6	6.7
Specialities > 1% (%)	55.4	83.9	66.1	58.9	41.1	30.4

Moreover, the daily distributions present two other kinds of anomalies. First, a pattern of distribution can be highlighted. Indeed, as shown in table 19, there are seldom distributions of pharmaceuticals during the weekend days. The average number of units for all specialities distributed per day is significantly lower on Saturdays and Sundays, respectively 80 and 31 units per day (Mondays, Tuesdays and Fridays average 2 632 units per day). Also, the percentage of Saturdays and Sundays without any distribution are high, respectively 22.2 % and 25 % (Mondays, Tuesdays and Fridays are at 0 %). Data from the Wednesdays and Thursdays are not analysed since they were only recorded respectively 4 and 3 times (chapter 4).

Table 19: Daily pharmaceuticals distributions for the hospital, pattern detection.

Day	Occurrence		Units distributed for all the specialities		
			Average	Days with no distribution	
	Number	%	(units/day)	Number	%
Monday	27	23	2 416	0	0
Tuesday	27	23	2 999	0	0
Wednesday	4	3	680	0	0
Thursday	3	3	2 447	0	0
Friday	28	23	2 481	0	0
Saturday	27	23	80	6	22.2
Sunday	4	3	31	1	25
Total	120	100			

The daily distributions also highlight that pharmaceuticals leave the central pharmacy by batch, even if the database consider the units separated from each other and not regrouped in boxes. This phenomenon has been noticed for 15 specialities.

The 4 types of anomalies are illustrated in figure 41. The Diclofenac speciality presents some major negative outliers for all temporal scales and also some "suspiciously high" values. The Paracetamol speciality is always dispensed by multiples of 10 (0, 10 and 20 units at a time) for the daily distributions. It logically appears as 1.43 units per day on the weekly distributions (10 units divided by 7 days is equal to 1.43).

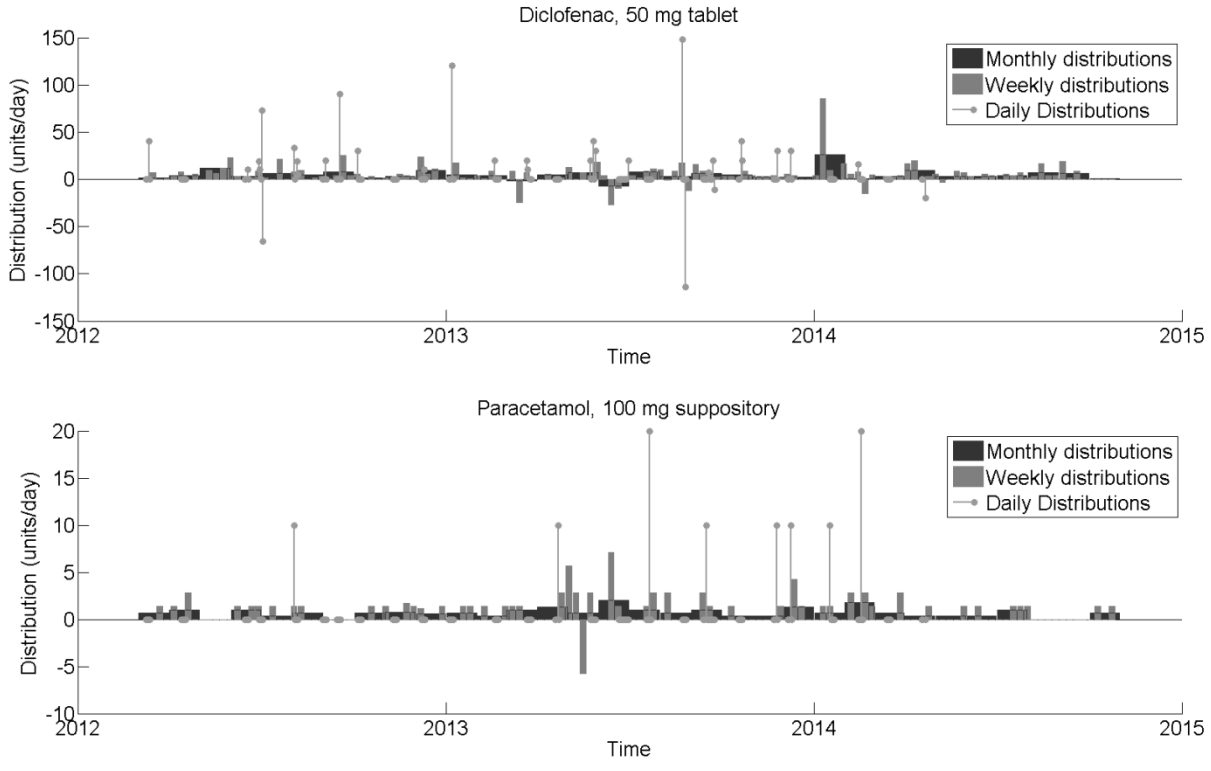


Figure 41: Examples of "anomalies" found in the pharmaceuticals distributions time series at the CHAL hospital.

A new set of pharmaceuticals distributions time series

The corrected CHAL pharmaceuticals distributions time series set is defined to be used for modelling. It is based on the weekly distributions of the central pharmacy. Raw daily distributions were rejected because they are too much disturbed by stock management in the hospital. Weekly distributions were chosen over monthly distributions because they include more variability. Each time series is treated as follows:

- Negative values are removed.
- Values that are more than 3 standard deviations away from the mean are removed.
- Gaps in the two previous steps are filled linearly.
- A mobile mean of 3 weeks is applied to smooth the time series. This spreads the batch distribution effect of the central pharmacy and acknowledges the fact that the central pharmacy resupply services pharmacies that consume pharmaceuticals at different times.

It is this set of corrected time series that is analysed further in this section.

Molecules versus specialities

Each molecule is distributed as a certain number of specialities. The 15 molecules of SIPIBEL are represented by 56 specialities. However, these specialities are not equally distributed amongst the different molecules. Excluding Aztreonam and Ethinylestradiol that are never distributed in this hospital, the average number of specialities per molecule is 4.3 ranging from 1 for Ibuprofen, Meropenem and Vancomycin to 17 for Paracetamol (table 20). Also, for one molecule, its different specialities are not distributed equally (table 20). The most distributed speciality of each molecule represents of at least 37 % of the total mass distributed for the molecule and 68 % on average. 90 % of the total mass distributed of each molecule is covered in average by only three specialities.

Table 20: Relative importance for the ten most represented specialities of each molecule for the corrected CHAL pharmaceuticals distributions time series.

Molecule	Average mass distributed (mg/day)	Number of specialities	Ten most represented specialities in descending order of masses distributed (%)									
			1	2	3	4	5	6	7	8	9	10
Atenolol	1 204	3	55	45	0							
Aztreonam		0										
Carbamazepine	2 175	3	38	34	28							
Ciprofloxacin	3 597	4	91	6	4	0						
Diclofenac	1 741	3	76	15	10							
Econazole	1 129	5	54	24	13	8	1					
Ethinylestradiol		0										
Ibuprofen	16 408	1	100									
Ketoprofen	6 519	5	37	33	30	1	0					
Meropenem	894	1	100									
Paracetamol	588 225	17	58	13	11	10	3	2	2	0	0	0
Propranolol	723	3	72	28								
Salicylic acid	18 547	7	38	25	21	7	5	2	2			
Sulfamethoxazole	7 801	3	66	34	0							
Vancomycin	5 064	1	100									
Average representation (%)			68	20	9	2	1	0	0	0	0	0
Minimum cumulated representation (%)			37	63	83	91	95	97	99	100	100	100
Average cumulated representation (%)			68	88	97	99	99	100	100	100	100	100
Maximum cumulated representation (%)			100	100	100	100	100	100	100	100	100	100

Molecules and pharmaceuticals forms

Table 21 summarizes the distributions of the pharmaceuticals forms. Oral and intravenous forms are the most represented ones. Respectively, 10 and 7 out of the 13 molecules actually distributed have oral forms and intravenous forms. Diclofenac is divided between oral and dermal forms (24 % of oral forms). Econazole is divided between dermal and urogenital forms (92 % of dermal forms).

Table 21: Relative importance of the different forms of pharmaceuticals for the corrected CHAL pharmaceuticals distributions time series.

Molecule	Average mass distributed (mg/day)	Oral (%)	Intravenous (%)	Dermal (%)	Other (ophthalmic, urogenital, rectal...) (%)
Atenolol	1 204	100	0	0	0
Aztreonam	0				
Carbamazepine	2 175	100	0	0	0
Ciprofloxacin	3 597	91	9	0	0
Diclofenac	1 741	24	0	76	0
Econazole	1 129	0	0	92	8
Ethinylestradiol	0				
Ibuprofen	16 408	100	0	0	0
Ketoprofen	6 519	66	33	0	1
Meropenem	894	0	100	0	0
Paracetamol	588 225	88	11	0	0
Propranolol	723	100	0	0	0
Salicylic acid	18 547	93	7	0	0
Sulfamethoxazole	7 801	66	34	0	0
Vancomycin	5 064	0	100	0	0

Mass distributed versus potential number of patients

One can divide the molecules in 4 sets according to the average mass distributed (table 22):

- **Very high distributions, over 1000 mg per day per bed, 1 molecule**: Paracetamol (1 307.2).
- **Medium distributions, between 10 and 50 mg per day per bed, 5 molecules**: Salicylic acid (41.2), Ibuprofen (36.5), Sulfamethoxazole (17.3), Ketoprofen (14.5) and Vancomycin (11.3).
- **Low distributions, under 0.1 mg per day per bed, 7 molecules**: Ciprofloxacin (8), Carbamazepine (4.8), Diclofenac (3.9), Atenolol (2.7), Econazole (2.5), Meropenem (2) and Propranolol (1.6).
- **No distributions, 2 molecules**: Aztreonam and Ethinylestradiol.

Table 22: Mass and number of DDD distributed for the corrected CHAL pharmaceuticals distributions time series.

Molecule	Average mass distributed		Average number of DDD distributed		Rank according to	
	for CHAL (mg/day)	(mg/day /bed)	for CHAL (DDD/day)	(DDD/day /1 000 beds)	the mass distributed	the DDD distributed
Atenolol	1 204	2.7	16	36	10	4
Aztreonam		0				
Carbamazepine	2 175	4.8	2	4	8	12
Ciprofloxacin	3 597	8	4	9	7	9
Diclofenac	1 741	3.9	17	39	9	3
Econazole	1 129	2.5	14	31	11	5
Ethinylestradiol		0				
Ibuprofen	16 408	36.5	14	31	3	6
Ketoprofen	6 519	14.5	65	144	5	2
Meropenem	894	2	0.4	1	12	13
Paracetamol	588 225	1 307	196	436	1	1
Propranolol	723	1.6	5	11	13	8
Salicylic acid	18 547	41.2	6	13	2	7
Sulfamethoxazole	7 801	17.3	4	9	4	10
Vancomycin	5 064	11.3	3	7	6	11

One can divide the molecules in 4 sets according to the number of DDD distributed (table 22):

- **High distributions, over 100 DDD per 1 000 beds per day, 2 molecules**: Paracetamol (436) and Ketoprofen (144).
- **Medium distributions, between 10 and 100 DDD per 1 000 beds per day, 6 molecules**: Diclofenac (39), Atenolol (36), Econazole (31), Ibuprofen (31), Salicylic acid (13) and Propranolol (11).
- **Low distributions, under 10 DDD per 1 000 beds per day, 5 molecules**: Sulfamethoxazole (9), Ciprofloxacin (9), Vancomycin (7), Carbamazepine (4) and Meropenem (1).
- **No distributions, 2 molecules**: Aztreonam and Ethinylestradiol.

General trends and seasonality

Both general trends and potential seasonality have been studied for the 15 molecules on two consecutive years of data (April 2012 to March 2014) (table 23). Between April 2012 and March 2014, the variation of the distributions of pharmaceuticals ranges from -7 to +367 %. However, it is important to consider the number of potential patients those distributions represent. Indeed, a +11 % variation for Paracetamol that provides roughly 200 DDD per day does not have the same importance as a +367 % variation for Meropenem that provides roughly 1 DDD per day.

Table 23: Global trend analysis for the corrected CHAL pharmaceuticals distributions time series.

Molecule	Average distributions for the year starting in April				Average variation	
	2012		2013			
	(mg/day)	(DDD/day)	(mg/day)	(DDD/day)	(mg/day)	(%)
Atenolol	1 188	16	1 259	17	71	6
Aztreonam	0	0	0	0	0	0
Carbamazepine	1 504	2	2 700	3	1 196	80
Ciprofloxacin	3 354	3	3 320	3	- 34	- 1
Diclofenac	1 687	17	1 712	17	26	2
Econazole	1 060	13	1 175	15	116	11
Ethinylestradiol	0	0	0	0	0	0
Ibuprofen	12 126	10	18 502	15	6 376	53
Ketoprofen	6 808	68	6 472	65	- 336	- 5
Meropenem	272	0	1 267	1	996	367
Paracetamol	542 808	181	604 609	202	61 801	11
Propranolol	672	4	702	4	30	4
Salicylic acid	16 988	6	19 490	6	2 502	15
Sulfamethoxazole	7 215	4	7 829	4	614	9
Vancomycin	5 201	3	4 861	2	- 340	- 7

Table 24 shows the results of the seasonality analysis. Only two molecules present a clear seasonal behaviour with a high season in cold periods (autumn and winter) and a low season in warm periods (spring and summer). Figure 42 shows the distributions evolution for the 2 seasonal molecules. Distributions evolutions for all the molecules are presented in appendix 9.

Table 24: Seasonality analysis for the corrected CHAL pharmaceuticals distributions time series.

Molecule	High season	Low season
Atenolol		
Aztreonam		
Carbamazepine		
Ciprofloxacin		
Diclofenac		
Econazole		
Ethinylestradiol		
Ibuprofen	January to March	June to September
Ketoprofen		
Meropenem		
Paracetamol	January to March	June to September
Propranolol		
Salicylic acid		
Sulfamethoxazole		
Vancomycin		

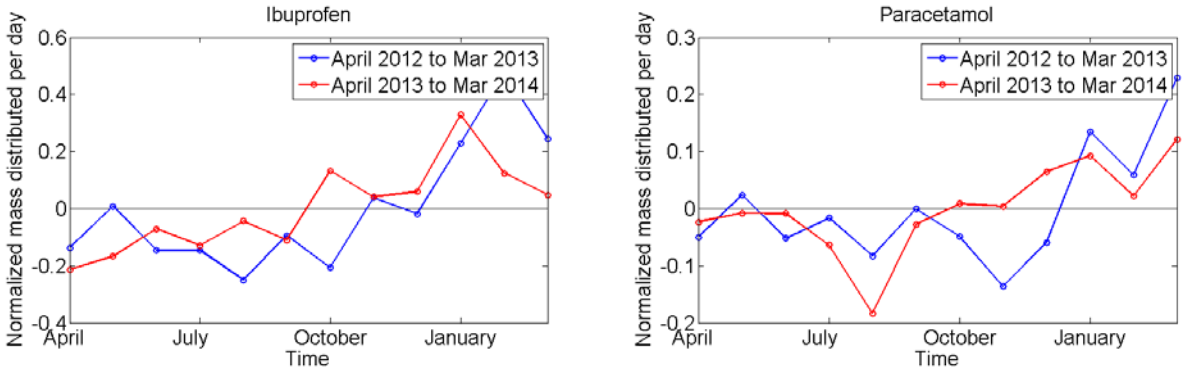


Figure 42: Distributions evolution for the molecules with seasonal component for the corrected CHAL pharmaceuticals distributions time series.

6.2 WASTEWATER FLOWS OF THE SITES

The wastewater flows of the two sites are analysed in this section. They both present gaps (unrecorded values). The first step of the analysis consists to detect the gaps and filling them. Then daily flows and intraday dynamics are explored. Finally, further uses of the time series in this study are explained.

6.2.1 URBAN SITE

Gaps detection

Out of the 1 052 640 minutes (731 days) covered by the records (chapter 4), 66 719 minutes were not saved (6 % of the duration). They are divided in 339 gaps which duration ranges from 1 to 60 474 minutes. Most of the gaps are short: 85 % of the gaps are less than or equal to 10 minutes. Only 3.5 % of the gaps are more than 1 hour long. Figure 43 shows the time distribution of the gaps for the recorded 2 years. A simple linear function was used to fill the gaps. The precise cause of missing data is not known, but it is surely linked to malfunctions monitoring system, either the measurement apparatus or the data transmission or banking.

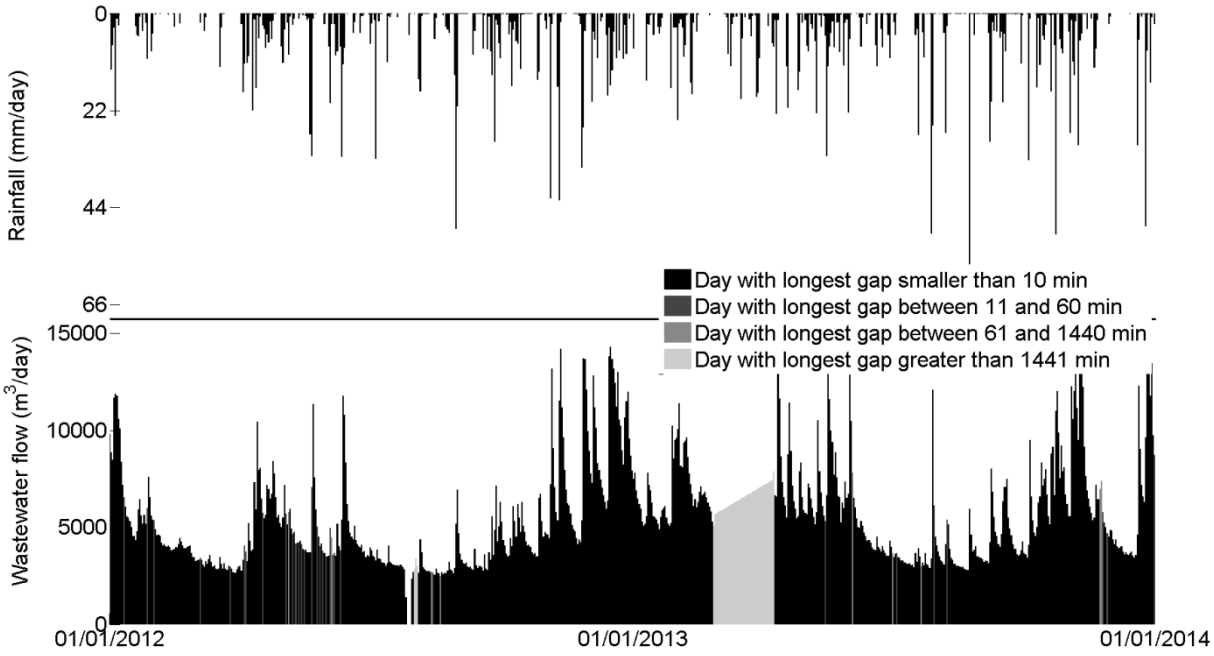


Figure 43: Bellecombe WWTP daily inflows and rainfall in 2012 and 2013.

Daily flows

The daily flows are very variable (from 2 352 to 14 400 m^3 per day). A comparison with the recorded rain events on the catchment tends to indicate that the network is actually draining a significant amount of parasitic water (figure 43). Indeed, the Pearson product-moment correlation coefficient between the increase of flow from one day to another (excluding the days with smaller daily flow than the previous day) and the rainfall of the same day, the day before and 2 days earlier are respectively 0.30, 0.72 and 0.09. This means that the increases of the daily wastewater flow are correlated to the rainfall of the same day and the day before. In addition, the daily flows are slowly decreasing after wet weather days. As it is highly improbable for pharmaceutical products to come from rain and runoff, it is important to identify and quantify the parasitic water flow for dry weather days.

A simple method is proposed. Assuming that the evolution of the parasitic water flow is slow (evolution over several days, except for wet weather days) and that the flow of the “non-parasitic” wastewater is lowest during

night time (0 to 7 h), it is possible to build a “parasitic water baseline” by detecting the minimum flow of each night of the time series and linearly linked them. To account for the presence of “non-parasitic” wastewater during night time, 0.15 m^3/min are subtracted for each minute from the “parasitic water baseline”. It corresponds to roughly one toilet flush per inhabitant per night and some non-domestic wastewater flow spread over the 7 hours of night time (it represents 3 % of the expected production of wastewater by the Bellecombe catchment). The results for the wastewater time series of Bellecombe are shown in figure 44.

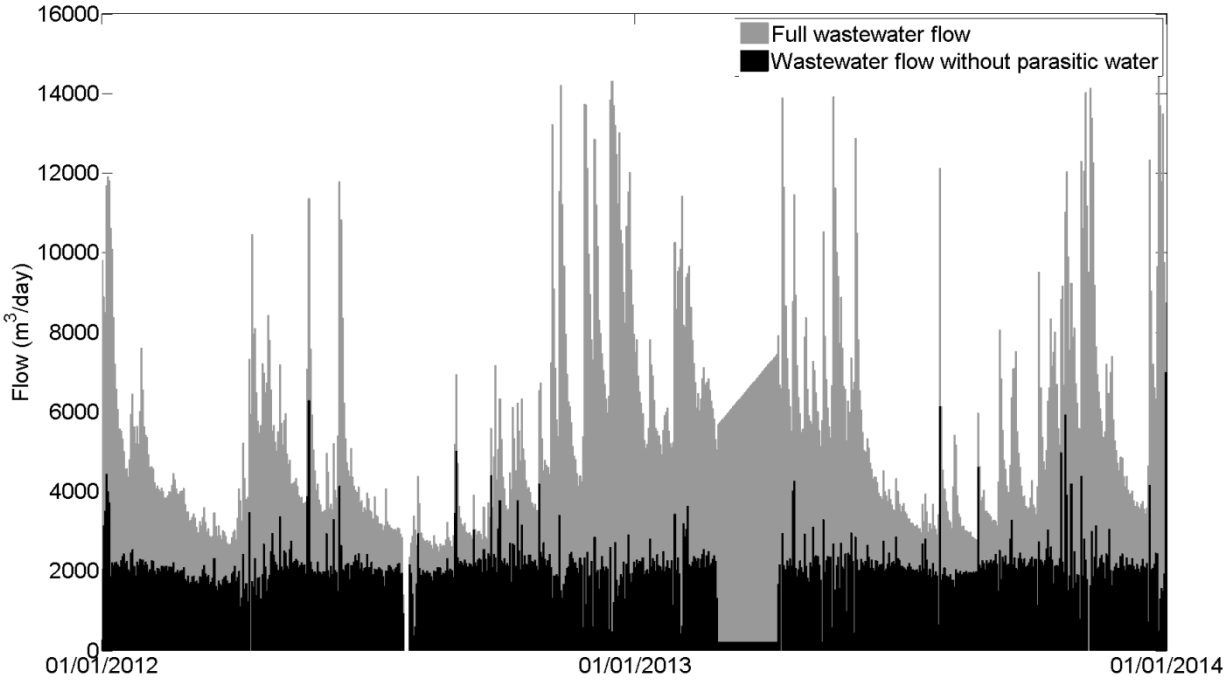


Figure 44: Daily parasitic water at the inlet of the Bellecombe WWTP for the 2 recorded years.

Subtracting the infiltration baseline from the wastewater flow time series, and only considering days with no long gaps in data (longest gap <10 min) and with dry weather from the day before to the day after (rainfall <0.5 mm for the three days), the daily flows are analysed (figure 45). For the 211 remaining days, the average daily flow is 2 088 m^3/day with a standard deviation of 179 m^3/day. Week days and weekend days shows similar patterns with, on average, 4 % more wastewater during weekend days.

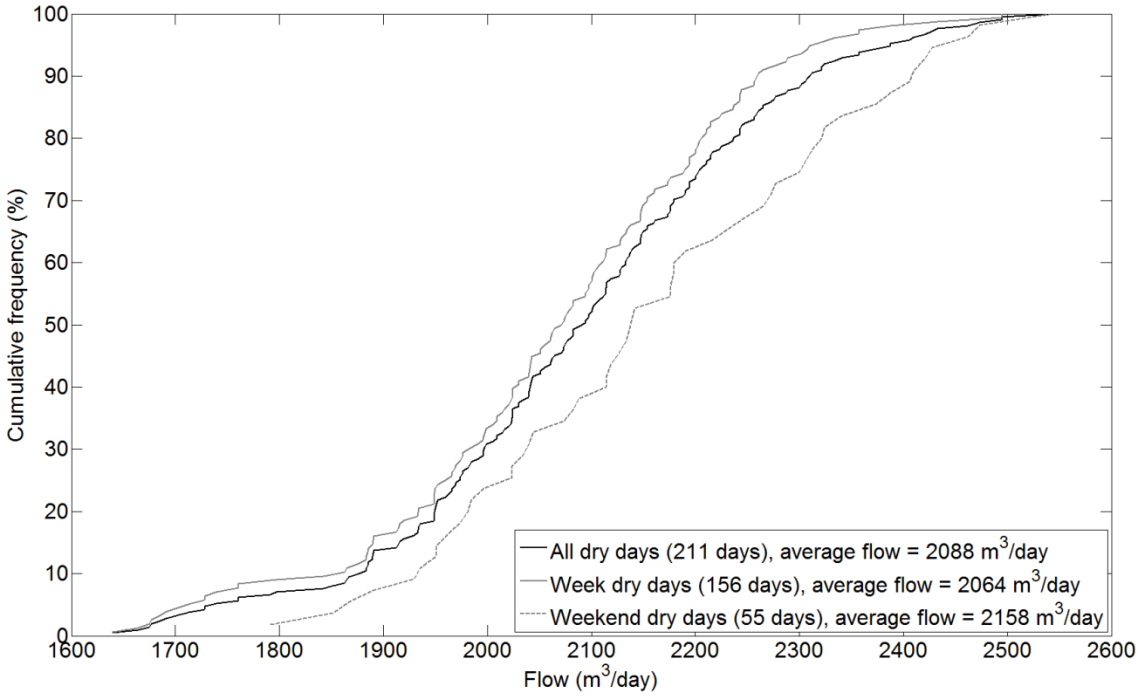


Figure 45: Distribution of the daily wastewater flows of the Bellecombe catchment.

Flow dynamics

Looking at an infra-day scale, the main characteristic of the wastewater flow is the rapid and important fluctuations of the flow (example in figure 46). These are the result of the pumping stations in the sewer network. They make the analysis of the wastewater flow dynamics difficult. To overcome this difficulty and get the average dynamics of the wastewater flow, a 30 minutes mobile mean was applied to the whole time series to smooth the fluctuations caused by pumping stations.

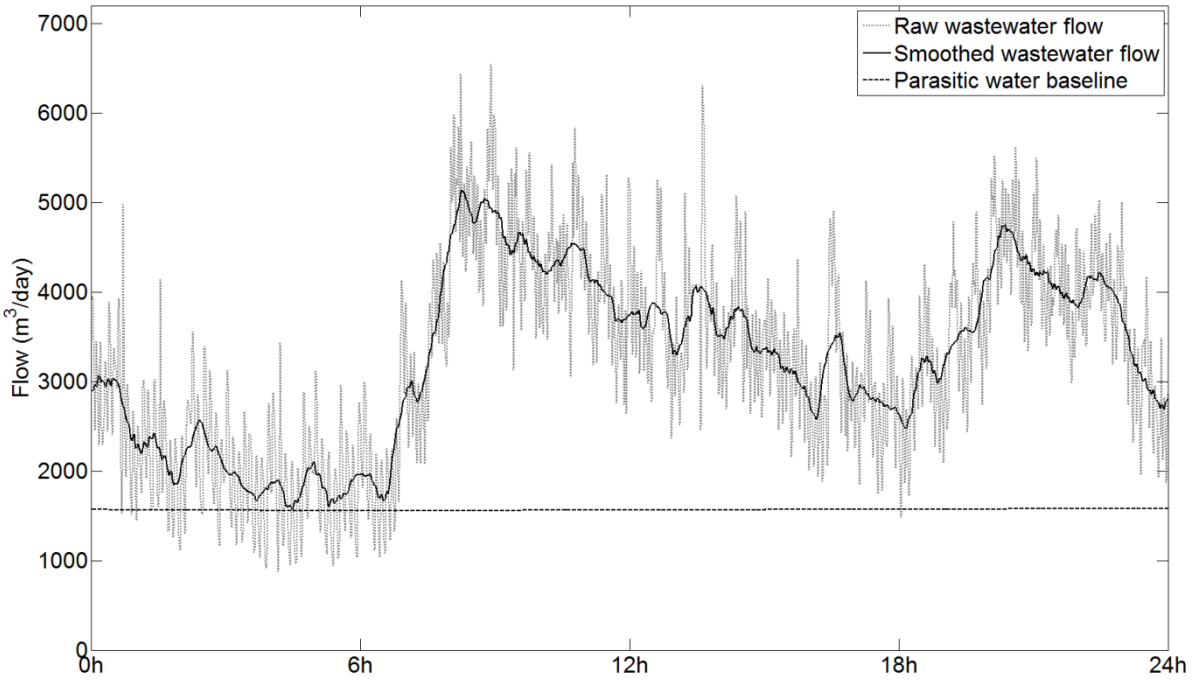


Figure 46: One day of the Bellecombe raw wastewater flows time series.

Considering the smoothed time series, subtracting the infiltration baseline and only keeping days with no long gaps in data (longest gap <10 min) and with dry weather from the day before to the day after (rainfall <0.5 mm for the three days), the infra-day dynamics of the wastewater flow of the Bellecombe catchment is analyzed. The Nash-Sutcliffe Efficiency coefficient is used even if it is not a model, in order to highlight similar or dissimilar dynamics patterns (table 25).

Wastewater flows of week dry days are similar. Indeed, the average NSE of the wastewater flows of week dry days with, as reference time series, the average wastewater flow of week dry days is equal to 0.86. Likewise, the wastewater flows of weekend dry days are similar (NSE of 0.90). However, different dynamics are observed between week and weekend dry days. Indeed, the average NSE of the wastewater flows of week (respectively weekend) dry days with, as reference time series, the average wastewater flow of weekend (respectively week) dry days is equal to 0.55 (respectively 0.36). Representations of both wastewater flows of week and weekend dry days are shown in figure 47.

Table 25: Nash-Sutcliffe efficiency coefficient (NSE) of the wastewater flows at the inlet of the Bellecombe WWTP.

Time series as "modelled" data	Time series as "measured" data	Average NSE (standard deviation)
Wastewater flows of week days	Average wastewater flow of week days	0.86 (0.15)
	Average wastewater flow of weekend days	0.55 (0.19)
Wastewater flows of weekend days	Average wastewater flow of week days	0.36 (0.23)
	Average wastewater flow of weekend days	0.90 (0.05)

Wastewater flows of week and weekend dry days share the same basic shape consisting of low flows during the night followed by a rapid increase in the morning and a local minimum flow at the end of the afternoon followed by an evening peak. The main difference concern the morning flows since the rapid increase of the flow are happening at different times and reach different levels (approximately 2 hours later and 860 m^3/day more during weekend days). After that the flows seems to slowly catch up until the evening peak that is reached almost at the same time (1 hour sooner during weekend days) with the same level (≈ 3 300 m^3/day).

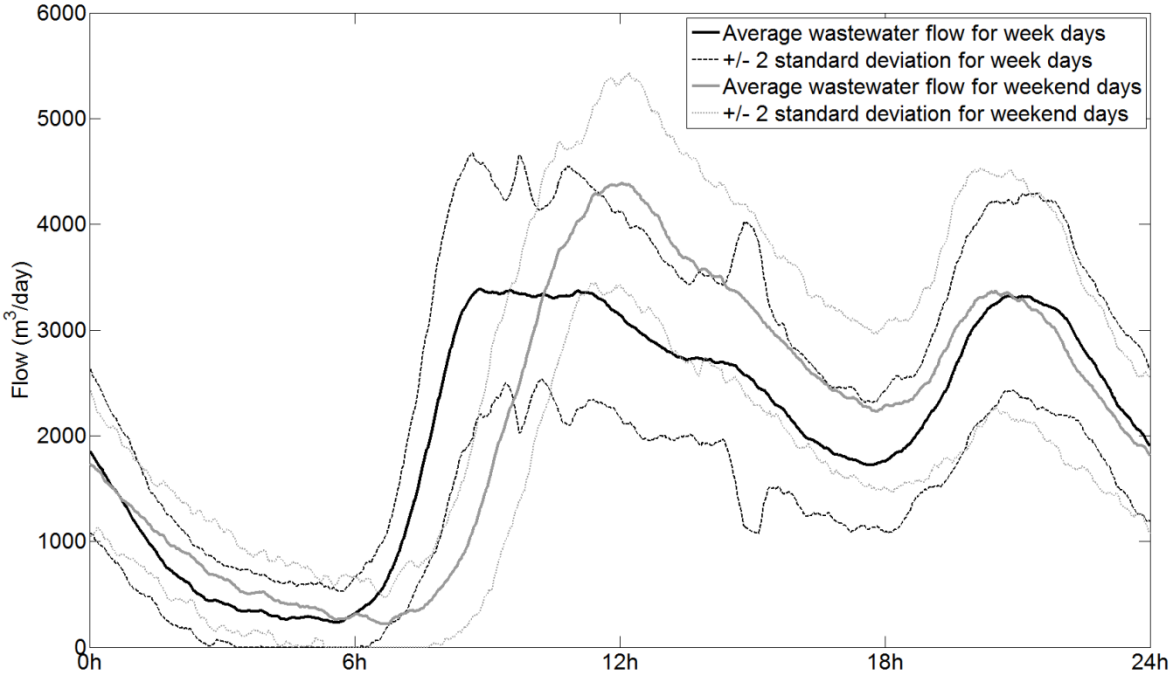


Figure 47: Dynamics of the wastewater flow for the Bellecombe catchment. For week and weekend dry days, the lowest flow happening during night time is approximately equal to 290 m^3/day. For week and weekend dry days, the morning increase respectively starts approximately at 6 h 30 and 8 h 30, ends approximately at 8 h and 12 h and reaches 3 460 m^3/day and 4 320 m^3/day. Evening peaks of 3 310 m^3/day are reached at 21 h for week dry days and 20 h for weekend dry days.

Further uses

Wastewater flows of the Bellecombe catchment are used for two purposes:

- Pharmaceuticals loads calculation: for each sampling campaign the actual daily flow is measured directly at the WWTP.
- Calibration and verification of the hydraulic part of the model. As the model simulates wastewater flow during dry weather periods for week days, not all days of the 2012/2013 time series are suitable for calibration or verification of the model. Only periods of two consecutive days are kept. They must not contain gaps in data longer than 10 min during the sampling period (8 h to 8 h), rainfall must be below 0.5 mm and neither day must be weekend days. This provides 129 sets of periods of 2 consecutive days.

6.2.2 CHAL HOSPITAL

Gaps detection

Out of the 527 040 minutes (366 days) covered by the records (chapter 4), 53 594 minutes were not valid (10 % of the duration). They are divided in 2099 gaps which duration ranges from 1 to 49 049 minutes. Most of the gaps are short. 83.7 % of the gaps are less than or equal to 10 minutes. Only 3.8 % of the gaps are more than 1 hour long. Figure 48 shows the dispersion of the gaps for the recorded year. A simple linear function was used to fill the gaps.

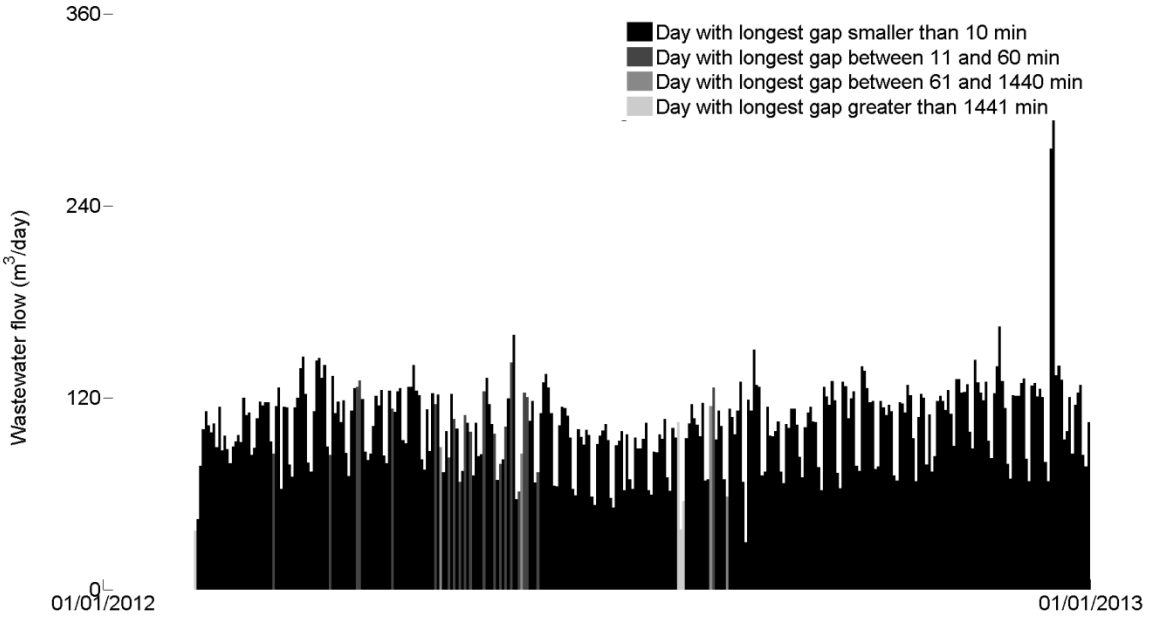


Figure 48: CHAL hospital daily flows in 2012. Two days at the end of 2012 have exceptionally high daily flow without known explanation.

Daily flows

Only considering days with no long gaps in data (longest gap <10 min), the daily flows are analysed (figure 49). For the 297 remaining days, the average daily flow is 103 m^3/day with a standard deviation of 22 m^3/day. Week and weekend days show distinct daily flows with, on average, 32 % less wastewater during weekend days. This could be related to the planning of both medical activities and cleaning maintenance at the hospital.

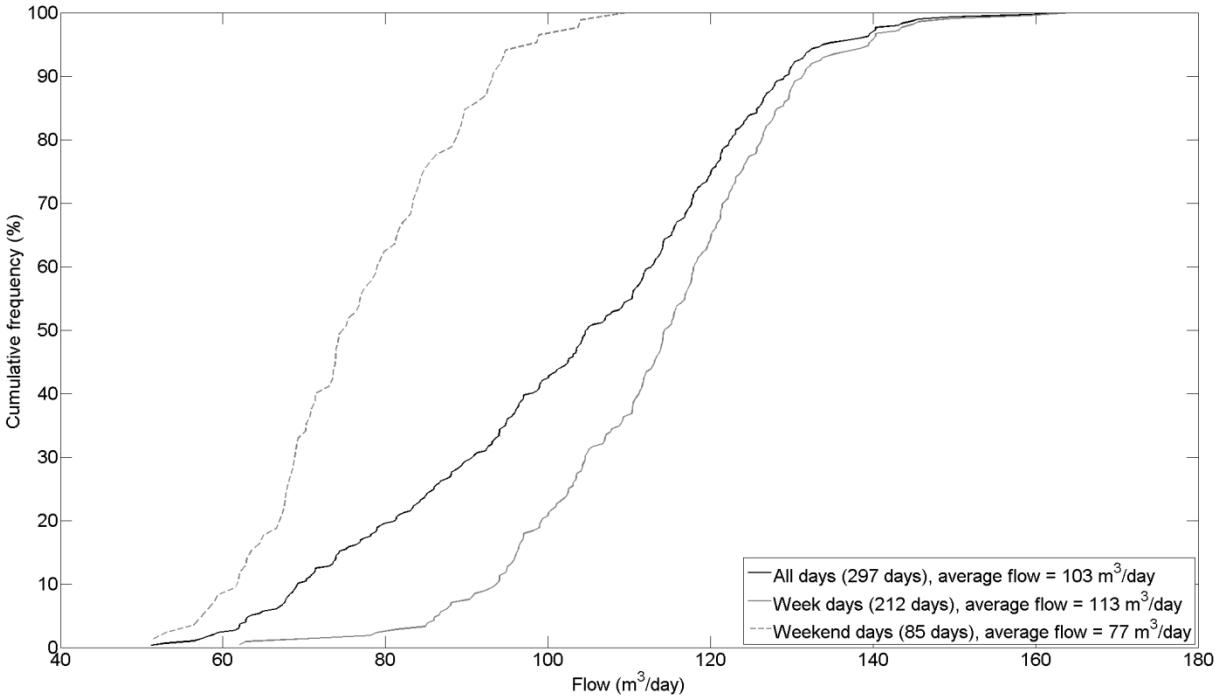


Figure 49: Distribution of the daily wastewater flows of the CHAL hospital.

Flow dynamics

Like the Bellecombe catchment, the main characteristic of the CHAL wastewater flow at an infra-day scale is the rapid and important variations of the flow (example in figure 50). These are the result of the pumping station located just upstream the WWTP that collects all the wastewater from the CHAL. To simplify the analysis and get the average dynamics of the wastewater flow, a 60 minutes mobile mean was applied to the whole time series.

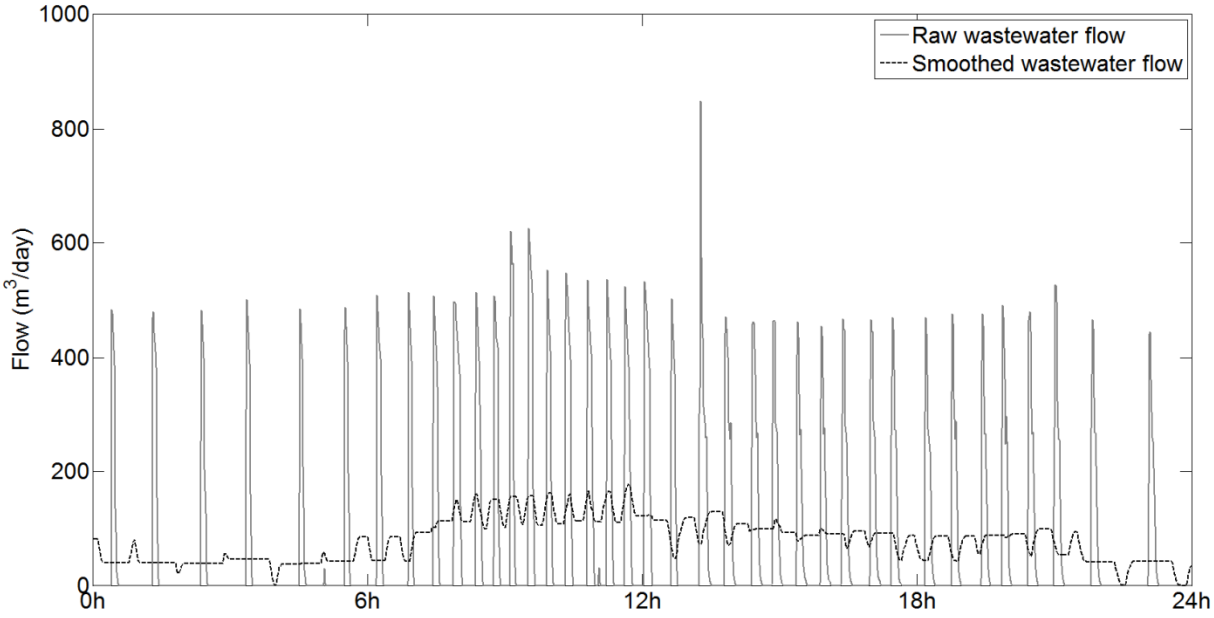


Figure 50: One day of the CHAL raw wastewater flow time series.

Considering the smoothed time series and only keeping days with no long gaps in data (longest gap <10 min), the infra-day dynamics of the wastewater flow of the CHAL hospital is analyzed. The Nash-Sutcliffe Efficiency coefficient is used even if it is not a model, in order to highlight similar or dissimilar dynamics patterns (table 26).

Wastewater flows of week dry days are similar. Indeed, the average NSE of the wastewater flows of week dry days with, as reference time series, the average wastewater flow of week dry days is equal to 0.67. Likewise, the wastewater flows of weekend dry days are similar (NSE of 0.43). However, different dynamics are observed between week and weekend dry days. Indeed, the average NSE of the wastewater flows of week (respectively weekend) dry days with, as reference time series, the average wastewater flow of weekend (respectively week) dry days is equal to -2.39 (respectively 0.28). Representations of both wastewater flows of week and weekend dry days are shown in figure 51.

Table 26: Nash-Sutcliffe efficiency coefficient (NSE) of the wastewater flows of CHAL hospital.

Time series as "modelled" data	Time series as "measured" data	Average NSE (standard deviation)
Wastewater flows of week days	Average wastewater flow of week days	0.67 (0.38)
	Average wastewater flow of weekend days	-2.39 (2.43)
Wastewater flows of weekend days	Average wastewater flow of week days	0.28 (0.24)
	Average wastewater flow of weekend days	0.43 (0.52)

Wastewater flows of week and weekend days share the same basic shape consisting of low flows during the night followed by an increase in the morning that happens at the same time for both week and weekend days but reaches different levels (approximately 60 m^3/day less during weekend days). After that the flow seems to slowly catch up until a small evening peak that is reached at the same time with almost the same level.

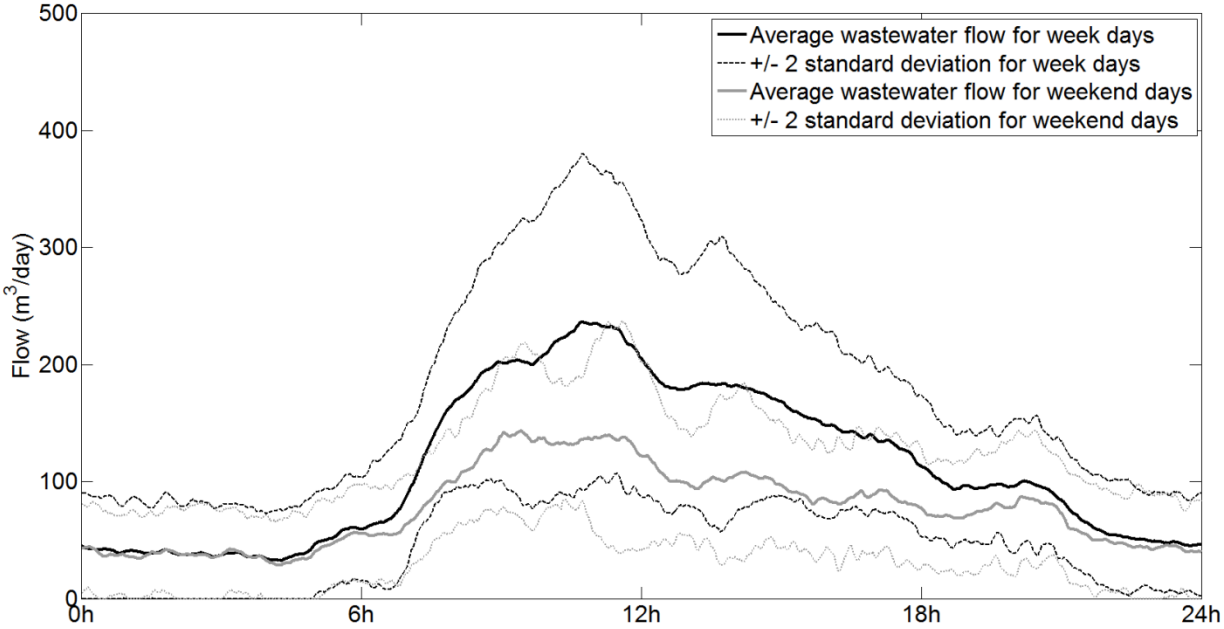


Figure 51: Dynamics of the wastewater flow for the CHAL hospital. For week and weekend days, the lowest flow happening during night time is approximately equal to 43 m^3/day. For week and weekend days, the morning increase starts approximately at 7 h, ends approximately at 9 h and reaches respectively 216 m^3/day and 144 m^3/day.

Further uses

Wastewater flows of the CHAL hospital are used only for pharmaceuticals loads calculation. For each sampling campaign the actual daily flow is measured directly at the WWTP.

6.3 PHARMACEUTICALS LOADS AT THE WWTP

For both sites, the study is focused on pharmaceuticals loads rather than concentrations. For the urban catchment, it is mainly because the daily volume of wastewater is strongly influenced by the rain events via infiltration (section 6.2.1) and because these parasitic waters are assumed to be not significantly contaminated by pharmaceuticals. For the CHAL hospital, the fact that the proposed model does not predict the wastewater flow makes it impossible to predict pharmaceuticals concentrations and thus to allow the comparison of concentrations.

As seen in chapter 4, all the samples are rated according to their quality. In this chapter, only "correct" quality samples are considered for analysis. Exceptionally, "uncertain" quality samples are analyzed if there are not enough "correct" quality samples available for the same type of analysis. In such cases, the "uncertain" quality samples are compared to "correct" quality samples from another type of campaign.

Sometimes pharmaceuticals cannot be detected or quantified. Indeed the analytical method has a limit of detection (LoD) and a limit of quantification (LoQ) for each molecule. In such cases, the actual concentration, and thus the load, of the pharmaceutical cannot be known exactly but can be represented as intervals. The concentration of a pharmaceutical is one of the three possibilities: between 0 and LoD, between LoD and LoQ, or its actual measured value.

Measurement is always done with uncertainties. Uncertainties can be of different nature and created at different stages of the measurement process. Evaluating uncertainties can be difficult. In our case, uncertainties of the analytical methods are known (95 % confidence interval). Estimating the uncertainties of the sampling method is possible by comparison to other studies but remains complex. Estimating the uncertainties of the sampling strategy is much more complex (Ort *et al.*, 2010b). As a result, only the uncertainties of the analytical method are taken into account in the following analysis.

Pharmaceuticals loads are analyzed the same way for the two sites. It consists of four steps corresponding to the 4 types of campaigns (chapter 4): "24 h particulate", "24 h", "24 x 1 h" and "7 x 24 h" campaigns. Since the analysis is focused on loads, the wastewater flow values were checked before to ensure that each campaign represents the "normal" conditions of the catchment (section 6.2) in both daily volume and dynamics. However it is not described here.

Finally, in section 6.3.3, a comparison of the two sites is proposed.

6.3.1 URBAN SITE

Dissolved versus particulate phases

Seven samples of "24 h particulate" campaigns with "correct quality" ratings were analyzed to determine the load of pharmaceuticals in both dissolved and particulate phases. However, out of the 15 studied molecules 4 were not analyzed by choice: Aztreonam, Ciprofloxacin, Meropenem and Vancomycin. Since pharmaceuticals are not always detected or quantified at the same time in the same sample in both phases, intervals of possible values are computed using LoD and LoQ.

Concentrations of pharmaceuticals in the particulate phase are provided as a fraction of the mass of Total Suspended Solid (TSS). It is necessary to convert them in order to compare the dissolved and particulate phases:

$$\varphi_{particulate} = \frac{C_{solid}}{10^{-9}} \times TSS \times V$$

With:
$\varphi_{particulate}$: daily particulate pharmaceutical load (mg/day)
C_{solid}: fraction of pharmaceutical in the particulate phase (µg/kg)
TSS: total suspended solids (mg/L)
V: daily volume of wastewater (L/day)

The particulate pharmaceutical fraction of the total pharmaceutical load ($F_{particulate}$) is then calculated as follow:

$$F_{particulate} = \frac{\varphi_{particulate}}{\varphi_{particulate} + \varphi_{dissolved}}$$

With:
$\varphi_{particulate}$: daily particulate pharmaceutical load (mg/day)
$\varphi_{dissolved}$: daily dissolved pharmaceutical load (mg/day)

Results are shown in table 27 and figure 52.

Table 27: Dissolved and particulate phases ratios of the 15 pharmaceuticals for the urban catchment.

Molecule	Dissolved phase		Particulate phase			Number of samples quantified in both phases
	Detected	Quantified	Detected	Quantified	Average fraction of the total load (standard deviation) (%)	
Atenolol	7/7	7/7	6/7	5/7	2.9 (2) to 3 (1.8)	5
Aztreonam						
Carbamazepine	7/7	7/7	7/7	6/7	6.7 (4.8) to 6.8 (4.7)	6
Ciprofloxacin						
Diclofenac	7/7	7/7	1/7	1/7	1.1 (2.7) to 1.4 (2.6)	1
Econazole	2/7	1/7	7/7	2/7	81.7 (14.5) to 96.9 (7.4)	0
Ethinylestradiol	0	0	2/7	2/7	28.6 (45.2) to 100 (0)	0
Ibuprofen	7/7	7/7	7/7	4/7	1 (0.8) to 1.1 (0.7)	4
Ketoprofen	7/7	7/7	7/7	5/7	2.2 (1.6) to 2.3 (1.4)	5
Meropenem						
Paracetamol	7/7	7/7	1/7	0/7	0 (0) to 0 (0)	0
Propranolol	7/7	7/7	7/7	5/7	14 (10) to 14.3 (9.6)	5
Salicylic acid	7/7	6/7	7/7	6/7	23.4 (36.7) to 24.2 (38)	5
Sulfamethoxazole	7/7	7/7	1/7	0/7	0.2 (0.5) to 1.4 (1)	0
Vancomycin						

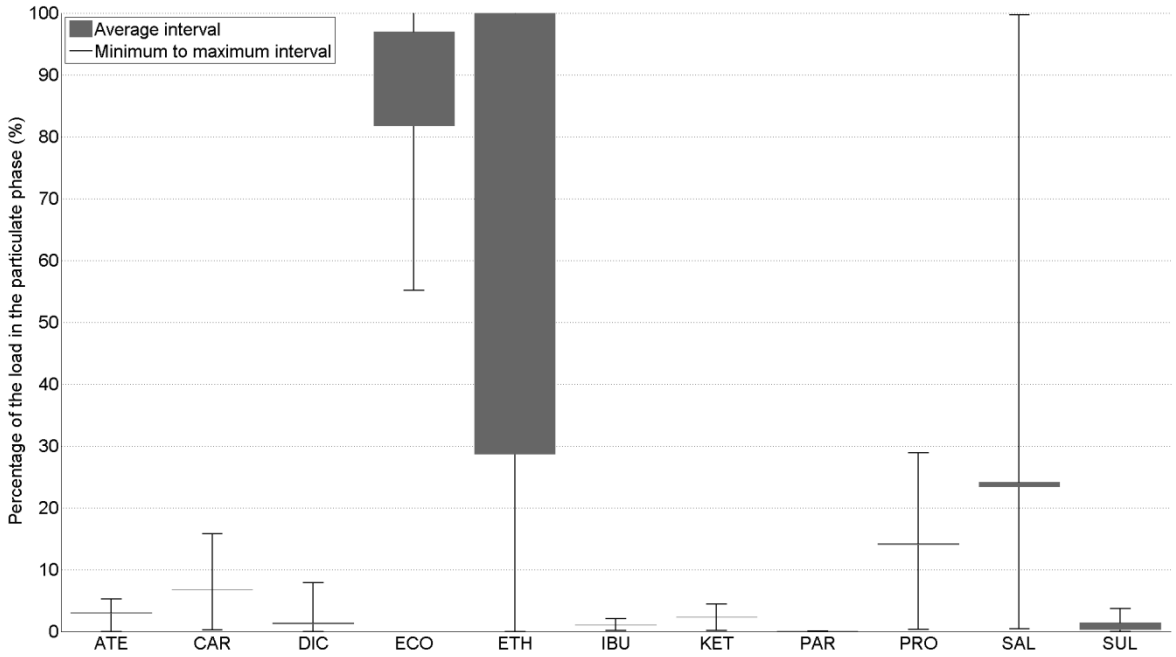


Figure 52: Percentage of pharmaceuticals measured in the particulate phase for the urban catchment.

According to those results, the molecules can be split in three groups:

- **Atenolol, Carbamazepine, Diclofenac, Ibuprofen, Ketoprofen, Paracetamol and Sulfamethoxazole**: they are always quantified in the dissolved phase. They are averagely over 90 % in the dissolved phase with a small range of variations (standard deviation below 5 %). This means that it is reasonable to only measure those pharmaceuticals in the dissolved phase. It is also possible to consider those ratios and to correct the loads modelled later to represent only the pharmaceuticals in the dissolved phase. In this regard, Paracetamol is remarkable as it is almost completely in the dissolved phase.
- **Propranolol and Salicylic acid**: most of the times, they are quantified in the dissolved phase. Their average particulate percentages are important (respectively ≈14 and ≈24 %) with an important range of variations (standard deviation over 10 %). This means that it is hard to predict the total pharmaceutical load, knowing only the dissolved load. Comparison between the measured and modelled daily dissolved loads should be made carefully.
- **Econazole and Ethinylestradiol**: they are almost never quantified in both phases. As a result, the partition between dissolved and particulate phases is not well known (extended range for the possible value of the average partition and important standard deviations).

Dissolved daily concentrations and loads

Twenty samples of "24 h" campaigns with "correct quality" ratings were analyzed. A first look at the loads revealed that in some samples, suspiciously high values occur (appendix 10). Those values are considered to be sampling or analytical artifacts due to the difficulty to sample pharmaceuticals products (Ort *et al.*, 2010b). In the following analysis, values that are more than 2.5 standard deviations away from the average are excluded. Results are shown in table 28 and figure 53.

Table 28: Dissolved daily pharmaceuticals concentrations and loads in the urban catchment.

Molecule	Outlier campaigns	Detected	Quantified	Average concentration (standard deviation) (ng/L)	Concentrations range in literature (ng/L)	Average daily load (standard deviation) (mg/day)	Analytical uncertainties (%)
Atenolol	1	19/19	19/19	2 533 (826)	30 - 33 100	9 578 (2 319)	3
Aztreonam	0	0/20	0/20	0 (0) to 8 (0)	-	0 (0) to 32 (8)	-
Carbamazepine	1	19/19	19/19	648 (268)	40 - 3 780	2 422 (639)	4
Ciprofloxacin	2	7/18	0/18	1 (2) to 16 (16)	8 - 3 700	6 (7) to 65 (68)	27
Diclofenac	1	19/19	19/19	818 (297)	160 - 94 200	3 030 (780)	16
Econazole	1	3/19	0/19	0 (0) to 1 (0)	-	0 (0) to 2 (1)	27
Ethinylestradiol	0	0/20	0/20	0 (0) to 0 (0)	1 - 3	0 (0) to 2 (0)	-
Ibuprofen	0	20/20	20/20	8 813 (3 124)	4 - 603 000	33 043 (8 387)	20
Ketoprofen	0	20/20	20/20	1 423 (552)	4 - 8 560	5 376 (1 488)	7
Meropenem	0	0/20	0/20	0 (0) to 8 (0)	-	0 (0) to 32 (8)	-
Paracetamol	2	18/18	18/18	146 619 (48 804)	130 - 569 000	564 429 (192 844)	30
Propranolol	2	18/18	18/18	464 (213)	50 - 290	1 683 (487)	5
Salicylic acid	0	20/20	19/20	28 727 (19085) to 28 727 (19084)	580 - 63 700	102 395 (56 093) to 102 398 (56 087)	35
Sulfamethoxazole	1	19/19	19/19	453 (277)	3 - 2 800	1 709 (917)	25
Vancomycin	0	1/20	0/20	0 (2) to 10 (9)	41 - 664	2 (7) to 41 (39)	-

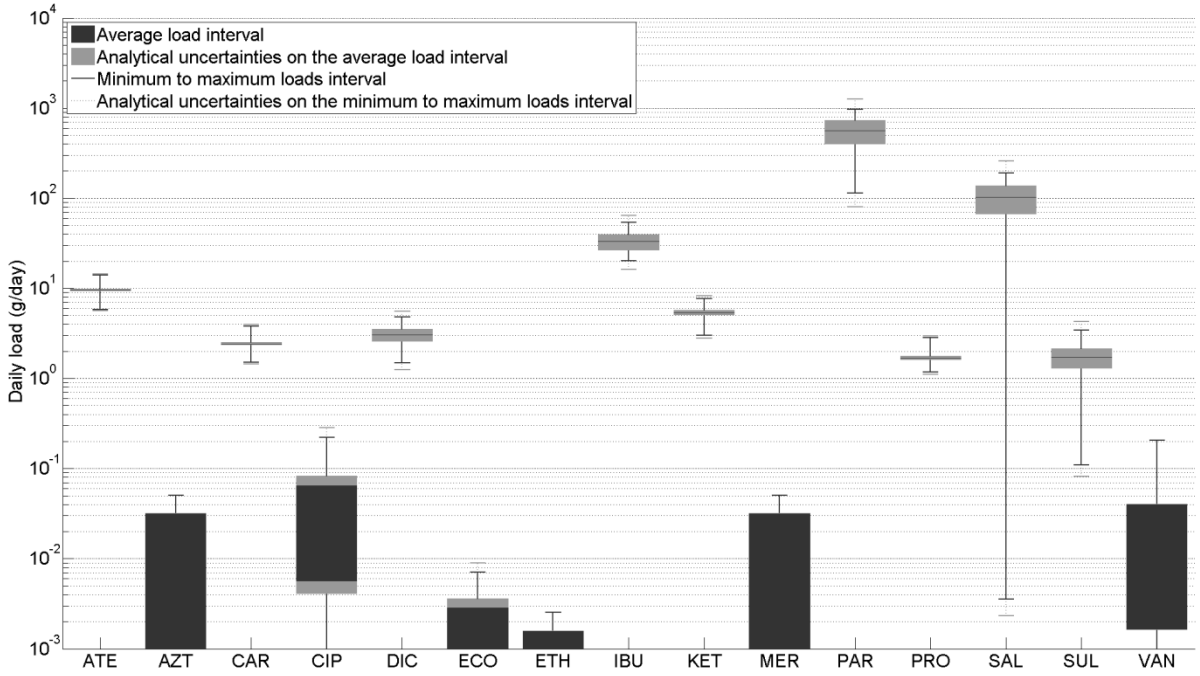


Figure 53: Dissolved daily pharmaceuticals loads in the urban catchment.

It is possible to group the different molecules according to their average daily load levels:

- **Less than 0.1 g/day: Aztreonam, Ciprofloxacin, Econazole, Ethinylestradiol, Meropenem and Vancomycin.** They are never or sometimes detected but never quantified. Thus, their range of daily concentration often correspond to the interval 0 to LOD.
- **Between 1 and 10 g/day: Atenolol, Carbamazepine, Diclofenac, Ketoprofen, Propranolol and Sulfamethoxazole.** They are always quantified.
- **Higher than 10 g/day: Ibuprofen, Paracetamol and Salicylic acid.** Except once for Salicylic acid that is detected but not quantified, they are always quantified. Even though they are grouped here, it is important to point out the very high values for Paracetamol that is respectively 5.5 and 17 times higher than Salicylic acid and Ibuprofen.

Concerning the quantified molecules (> 1 g/day), it is important to note that the dispersions of the daily loads are quite high since their average standard deviation is always greater than 24 % of their average values. Most are within the 24 to 34 % interval, but Sulfamethoxazole and Salicylic acid are respectively at 54 and 55 %. Both molecules have some of their campaigns with suspiciously low daily loads.

The twenty campaigns took place between August 2013 and October 2015. The variability of the molecules loads have not been analysed because there are too few samples on a too short period of time. However, some molecules are strongly suspected of demonstrating a seasonal pattern (appendix 10).

Regarding the concentrations of the molecules, they appear to be in range of the values reported by other studies, except for Propranolol which average measured concentration is approximately 1.6 times greater than the upper boundaries of reported concentrations. Comparing concentrations is not really a good idea since it can be affected by many factors (presence of parasitic waters diluting the load…). A good comparison could be to express daily load per inhabitants. However, it is seldom possible to compute such values from literature data.

Dissolved hourly loads

Four “24 x 1 h” campaigns were made. This is obviously far too less data to make any reliable analysis and all the following results are to be considered accordingly. It is also important to note that sometimes an hourly load is missing in a time series. This can be the result of many things such as: a lost sample, a sample of not “correct” quality or an unreliable flow measurement… An analysis is proposed anyway.

First, it was verified that the pharmaceuticals loads of the “24 x 1 h” campaigns were summing up to be in the range of the “24 h” campaigns. The results are presented in figure 54. For every molecule, each time a “24 x 1 h” campaign has a reconstructed daily loads lower or greater than the minimum and maximum daily loads measured in the “24 h” campaigns, it is considered to be “out of range” and is discarded in the next analysis. Except for two molecules, all four campaigns are kept. Ciprofloxacin has one campaign with a higher reconstructed daily load, and Propranolol has two campaigns with lower reconstructed daily loads.

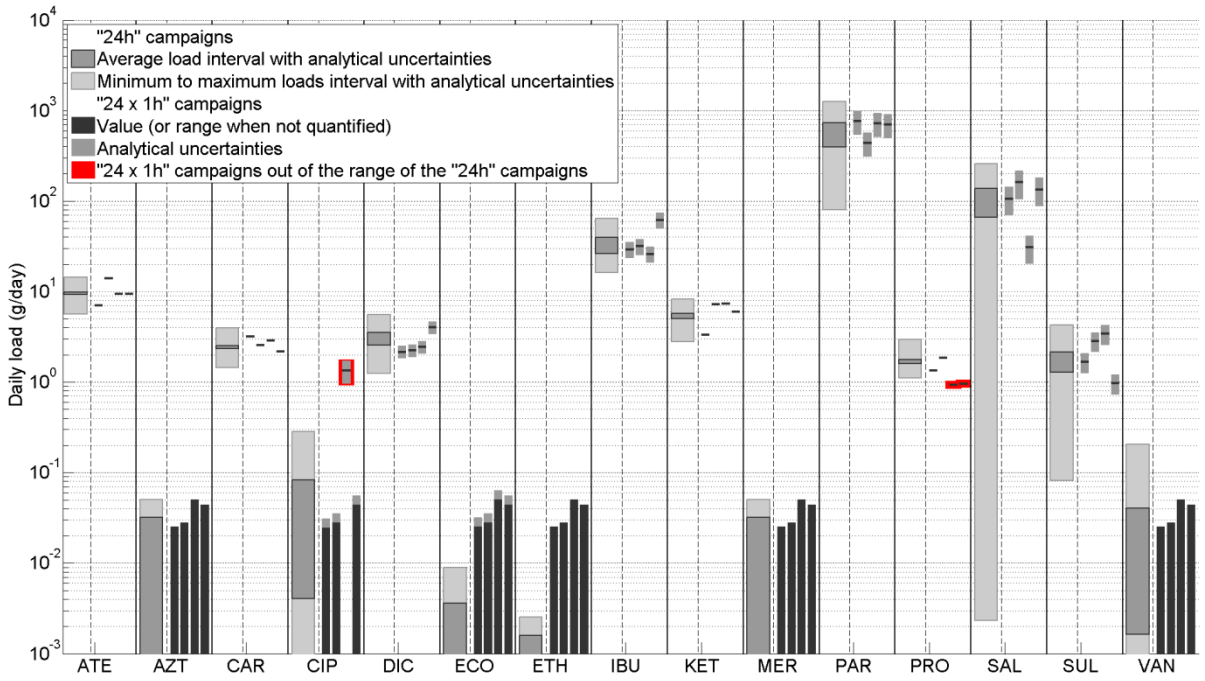


Figure 54: Comparison of the daily loads of the "24 x 1 h" campaigns with the ones of the "24 h" campaigns in the urban catchment.

The next step checks if the hourly loads time series of one pharmaceutical are alike from one campaign to another. In other words, it checks if one molecule has a repetitive dynamics. In order to do so, the time series are normalized with their average value. Then their Nash-Sutcliffe efficiency coefficient (NSE) score is calculated with the median normalized time series of the molecule as the reference time series. Finally, the median NSE score is kept. Results are shown in table 29. Using the median rather than the average is a way to minimize the importance of isolated high hourly loads.

Table 29: Repeatability of the dynamics of the pharmaceuticals hourly loads for the urban catchment.

Molecule	Number of "in range" campaigns	For the "in range" campaigns				
		Average reconstructed daily load (standard deviation) (mg/day)	Total number of missing hourly loads	Median NSE with, as reference,		
				The median normalized hourly loads	The normalized wastewater flow with the infiltration baseline	The normalized wastewater flow without the infiltration baseline
Atenolol	4/4	9 939 (2 870)	2	0.51	- 1.18	0.19
Aztreonam	4/4	0 (0) to 37 (12)	2	-	-	-
Carbamazepine	4/4	2 703 (436)	2	- 5.69	-	-
Ciprofloxacin	3/4	0 (0) to 32 (10)	3	-	-	-
Diclofenac	4/4	2 715 (878)	2	0.08	-	-
Econazole	4/4	0 (0) to 37 (12)	2	-	-	-
Ethinylestradiol	4/4	0 (0) to 37 (12)	2	-	-	-
Ibuprofen	4/4	37 167 (16 537)	2	0.67	0.1	0.5
Ketoprofen	4/4	5 979 (1 888)	2	0.57	- 1.14	0.37
Meropenem	4/4	0 (0) to 37 (12)	2	-	-	-
Paracetamol	4/4	658 415 (148 518)	3	0.75	- 0.66	0.39
Propranolol	2/4	1 600 (357)	0	0.59	- 0.68	0.08
Salicylic acid	4/4	108 076 (56 183)	4	0.55	- 2.87	- 0.07
Sulfamethoxazole	4/4	2 224 (1 108)	2	- 0.52	-	-
Vancomycin	4/4	0 (0) to 37 (12)	2	-	-	-

According to the results, the molecules can be divided in three groups:

- **No observed dynamics: Aztreonam, Ciprofloxacin, Econazole, Ethinylestradiol, Meropenem and Vancomycin.** As they are seldom detected or quantified, it is not possible to analyse their dynamics.
- **Repeatable dynamics: Atenolol, Ibuprofen, Ketoprofen, Paracetamol, Propranolol and Salicylic acid.** They have a median NSE score of at least 0.5. As an example, figure 55 illustrates the case of Ibuprofen. All the time series are shown in appendix 11.

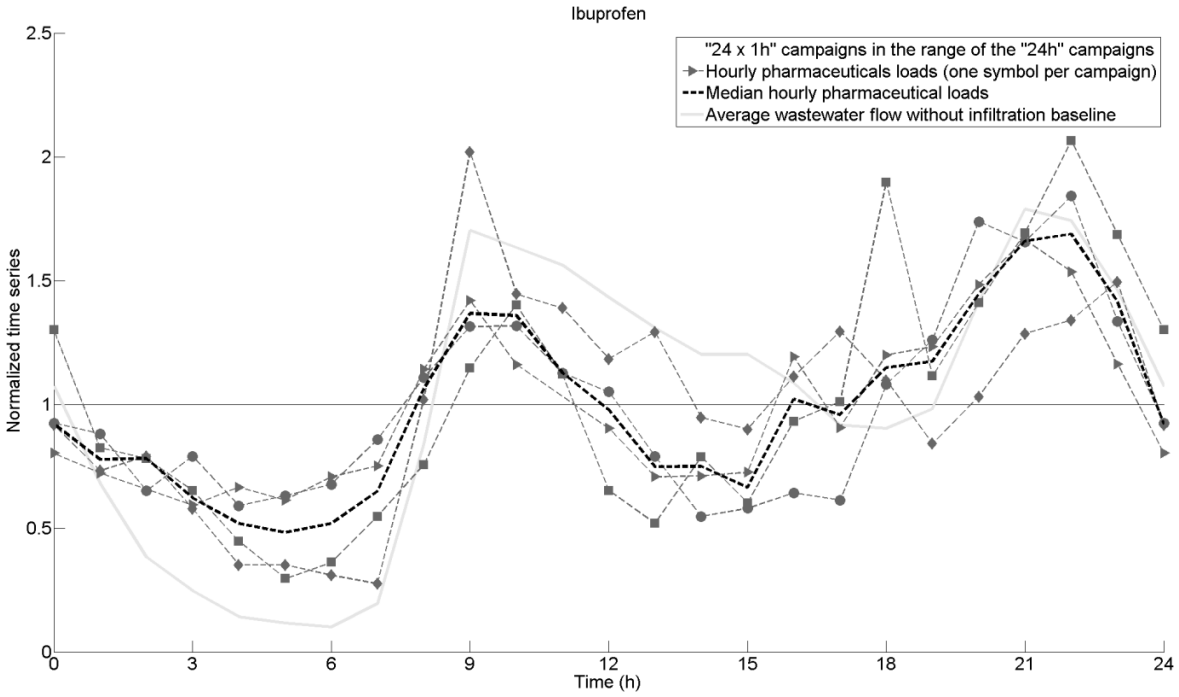


Figure 55: Hourly loads time series of Ibuprofen in the urban catchment.

- **Chaotic dynamics: Carbamazepine, Diclofenac and Sulfamethoxazole.** Their median NSE score is never higher than 0.08. Carbamazepine and Sulfamethoxazole have both very low median NSE score (respectively -5.69 and -0.52). They are both seldom consumed (section 6.1, respectively 4.3 and 0.7 DDD/day/10 000 capita). At the scale of the urban catchment, it means that the dynamics of the hourly loads of these molecules are very sensitive to a few patients and their consumption and time-use pattern. This can lead to isolated peak loads. Figure 56 illustrates this effect in the case of Carbamazepine. All three isolated peak loads are from a different "24 x 1 h" campaigns. The case of Diclofenac is even more difficult to interpret and is not shown here.

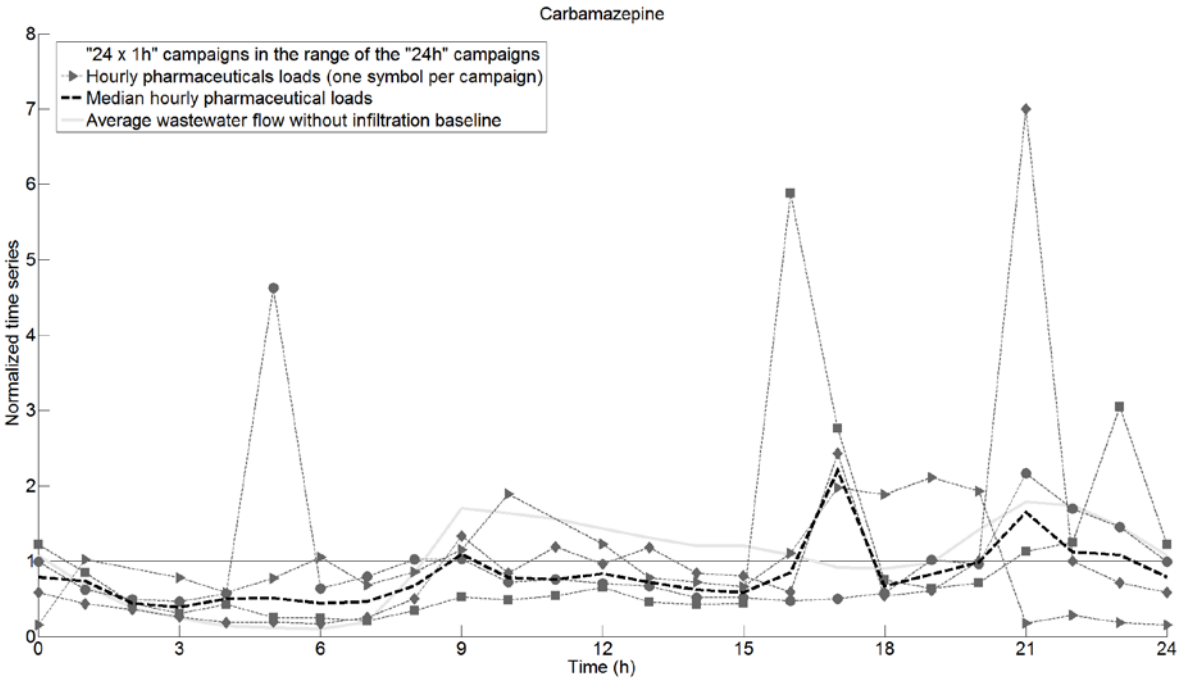


Figure 56: Hourly loads time series of Carbamazepine in the urban catchment.

For the molecules with repeatable dynamics, the goal of the next analysis is to check if the pharmaceuticals hourly loads share the same dynamics as the wastewater flow.

Both wastewater flow with and without the infiltration baseline (section 6.2) are tested. The results shown in table 29 indicate that dynamics of wastewater flow and pharmaceuticals are not similar. The discharge of pharmaceuticals has its own dynamics that is not directly related to the discharge of wastewater. However, the wastewater flow without the infiltration baseline has better scores than the one with it. This was expected since it is assumed that, for pharmaceuticals, the main route to wastewater is via human consumption and excretion and not infiltration of rain.

The last analysis checks if the dynamics of the different molecules are alike. In order to do so, the median normalized loads time series of each molecule is tested by the NSE score with as reference the median normalized loads time series of every other molecule. For each pair of molecule this provides two NSE scores. Assuming that two molecules share the same dynamics when their NSE scores are higher than 0.5, it is possible to draw a connection graph (figure 57).

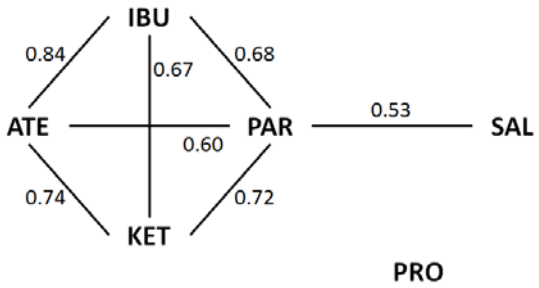


Figure 57: Map of molecules with similar hourly loads dynamics for the urban catchment. Only the smallest NSE score is indicated.

Atenolol, Ibuprofen, Ketoprofen and Paracetamol seem to share the same dynamics. Paracetamol and Salicylic acid are also alike. However, Propranolol stands aside.

Dissolved daily loads through the week

Three "7 x 24 h" campaigns were made. However, the quality of the samples have mostly been rated "uncertain" (19/21 samples) due to the fact that the protocol to clean the sample containers has not been followed. This lead to suspicious measurements when compared to the daily pharmaceuticals loads measured in the "24 h" campaigns. Anyway, results are presented in table 30 and appendix 12. Considering the analytical uncertainties and the variability of the pharmaceuticals loads measured in the "24 h" campaigns, no dynamics in the pharmaceuticals loads during the week was observed.

Table 30: Daily pharmaceutical loads of the urban catchment for the "7 x 24 h" campaigns.

Molecule	Median NSE with as reference the median normalized daily loads	Average daily load (standard deviation) (g/day) "7 x 24 h" campaigns							"24 h" campaigns
		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	
Atenolol	0.51	8.7 (1.4)	9 (1.6)	10.1 (2.9)	12.9 (3.3)	10 (1.6)	10 (2.7)	9.6 (2.5)	9.6 (2.3)
Aztreonam	-	-	-	-	-	-	-	-	-
Carbamazepine	-29.2	2.5 (0.5)	3.4 (2.5)	4 (2.5)	3.5 (2.7)	2.8 (0.5)	2.8 (0.8)	2.2 (0.3)	2.4 (0.6)
Ciprofloxacin	-1.13	-	-	-	-	-	-	-	-
Diclofenac	-2.39	2.8 (1.2)	2.5 (1)	3.8 (0.7)	4.1 (1.9)	2.8 (0.6)	2.9 (0.8)	3 (1.3)	3.0 (0.8)
Econazole	-	-	-	-	-	-	-	-	-
Ethinylestradiol	-	-	-	-	-	-	-	-	-
Ibuprofen	-0.19	35.4 (7.2)	31.6 (4.4)	47.9 (26.8)	51.9 (15.6)	32 (8.1)	47.2 (6.6)	48.4 (13.1)	33.0 (8.4)
Ketoprofen	-7.96	5.1 (1.8)	5.3 (1.8)	5.4 (2)	6 (1.3)	5.8 (2.2)	6.2 (2.2)	5.7 (2.7)	5.4 (1.5)
Meropenem	-	-	-	-	-	-	-	-	-
Paracetamol	0.29	606 (73.4)	617.7 (6.4)	593.4 (27)	694.3 (128.9)	621.7 (24.2)	667.2 (49)	740.9 (57.5)	564.4 (192.8)
Propranolol	-2.24	1.4 (0.2)	1.4 (0.4)	2.2 (0.8)	5.2 (5.3)	1.5 (0.4)	1.6 (0.4)	1.6 (0.4)	1.7 (0.5)
Salicylic acid	0.58	58.9 (51.4)	42.7 (50.6)	62.6 (58.1)	57.9 (50)	58.1 (57.1)	73.5 (63)	102.7 (77.4)	102.4 (56.1)
Sulfamethoxazole	-1.46	1.3 (0.4)	1.4 (0.7)	1.5 (0.5)	2 (0.4)	1.6 (0.5)	2 (0.6)	1.8 (0.7)	1.7 (0.9)
Vancomycin	-	-	-	-	-	-	-	-	-

6.3.2 CHAL HOSPITAL

Dissolved versus particulate phases

Seven samples of "24 h particulate" campaigns with "correct quality" ratings are analyzed to evaluate the load of pharmaceuticals present in both the dissolved and particulate phases. However, out of the 15 studied molecules 4 were not analyzed by choice: Aztreonam, Ciprofloxacin, Meropenem and Vancomycin. Since pharmaceuticals are not always detected or quantified at the same time in the same sample in both phases, intervals of possible values are computed. Results are shown in table 31 and figure 58.

Table 31: Dissolved and particulate phases ratios of the 15 pharmaceuticals in the CHAL hospital.

Molecule	Dissolved phase		Particulate phase			Number of samples quantified in both phases
	Detected	Quantified	Detected	Quantified	Average fraction of the total load (standard deviation) (%)	
Atenolol	7/7	7/7	3/7	2/7	0.3 (0.4) to 0.6 (0.4)	2
Aztreonam						
Carbamazepine	7/7	7/7	7/7	4/7	1.9 (1.4) to 2.4 (1.2)	4
Ciprofloxacin						
Diclofenac	7/7	7/7	0/7	0/7	0 (0) to 1 (0.8)	0
Econazole	3/7	2/7	7/7	4/7	86.2 (17.1) to 98.1 (4.4)	2
Ethinylestradiol	0/7	0/7	0/7	0/7	0 (0) to 100 (0)	0
Ibuprofen	7/7	7/7	7/7	6/7	1.6 (0.8) to 1.6 (0.8)	6
Ketoprofen	7/7	7/7	7/7	7/7	1.7 (0.4)	7
Meropenem						
Paracetamol	7/7	7/7	6/7	5/7	0.2 (0.2) to 0.2 (0.2)	5
Propranolol	7/7	7/7	7/7	6/7	13.7 (11.3) to 13.8 (11.3)	6
Salicylic acid	7/7	7/7	6/7	6/7	2.9 (3.2) to 2.9 (3.2)	6
Sulfamethoxazole	7/7	7/7	6/7	5/7	1.2 (0.9) to 1.3 (0.8)	5
Vancomycin						

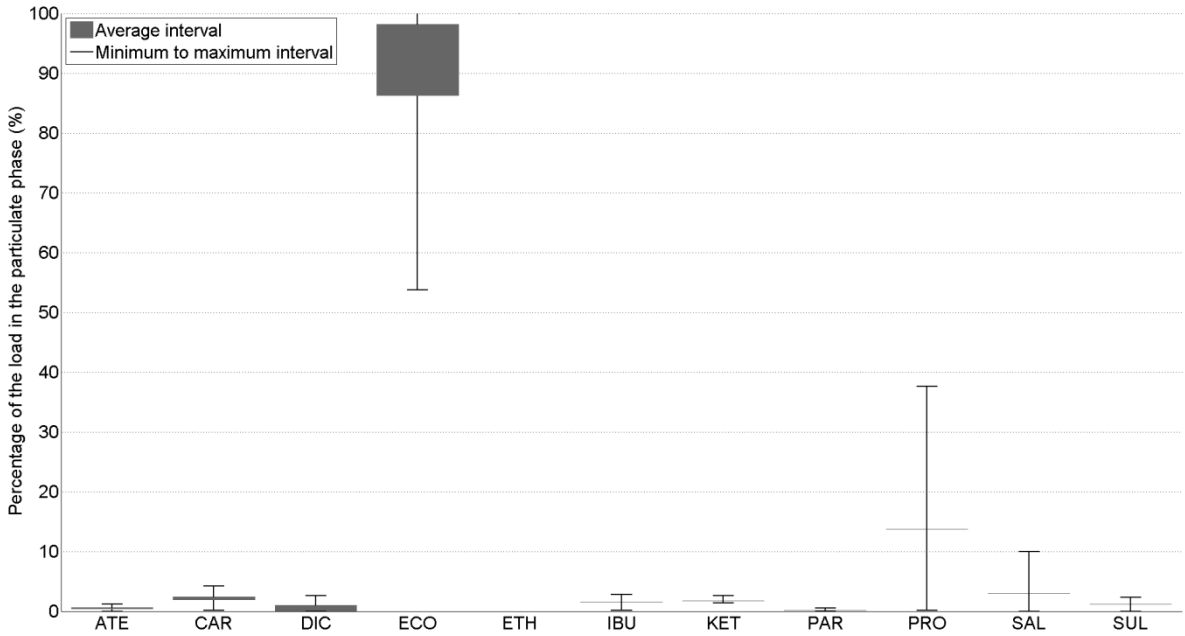


Figure 58: Percentage of pharmaceuticals measured in the particulate phase for the CHAL hospital.

According to those results, all the molecules share the same behavior except three:

- **Atenolol, Carbamazepine, Diclofenac, Ibuprofen, Ketoprofen, Paracetamol, Salicylic acid and Sulfamethoxazole**: they are always quantified in the dissolved phase. They are averagely over 97 % in the dissolved phase with a small range of variations (standard deviation below 5 %). This means that it is reasonable to measure those pharmaceuticals only in the dissolved phase. Also it is possible to consider those ratios and to correct the loads modelled later on to represent only the pharmaceuticals in the dissolved phase.
- **Econazole**: it is almost never quantified in both phases. As a result, the partition between dissolved and particulate phases is not well known (extended range for the possible value of the average partition and important standard deviations).
- **Ethinylestradiol**: it is never quantified nor detected in both phases. As a result, the partition between dissolved and particulate phases is unknown.
- **Propranolol**: most of the times, it is quantified in both phases. Its average particulate percentage is significant (≈14 %) with an important range of variation (standard deviation over 10 %). This means that it is hard to predict the total pharmaceutical load, knowing only the dissolved load. Comparison between the daily dissolved loads measured and the daily loads modelled should be made carefully.

Dissolved daily concentrations and loads

Twenty-four samples of “24 h” campaigns with “correct quality” ratings were analyzed. A first look at the loads reveals that in some samples, suspiciously high values can occur (appendix 13). Those values are considered to be sampling artifacts due to the difficulty to sample pharmaceuticals products (Ort *et al.*, 2010b). In the following analysis, values that are more than 2.5 standard deviations away from the average are excluded. Results are shown in table 32 and figure 59.

Table 32: Dissolved daily pharmaceuticals measured concentrations and loads in the CHAL hospital.

Molecule	Outlier campaigns	Detected	Quantified	Average concentration (standard deviation) (ng/L)	Concentrations range in literature (ng/L)	Average daily load (standard deviation) (mg/day)	Analytical uncertainties (%)
Atenolol	3	21/21	21/21	2 553 (869)	595 - 5 800	477 (204)	3
Aztreonam	0	0/24	0/24	0 (0) to 8 (0)	-	0 (0) to 1 (0)	-
Carbamazepine	2	22/22	22/22	368 (423)	123 - 1 123	67 (75)	4
Ciprofloxacin	1	23/23	23/23	23 845 (16 702)	457 - 101 000	4 635 (3 948)	27
Diclofenac	2	22/22	22/22	339 (194)	46 - 2 737	59 (31)	16
Econazole	1	4/23	1/23	0 (0) to 1 (0)	-	0 (0) to 0 (0)	27
Ethinylestradiol	0	0/24	0/24	0 (0) to 0 (0)	32 - 432	0 (0) to 0 (0)	-
Ibuprofen	2	22/22	22/22	6 885 (1 943)	119 - 19 770	1 204 (285)	20
Ketoprofen	2	22/22	22/22	9 385 (2 156)	10 - 1 100	1 665 (475)	7
Meropenem	0	0/24	0/24	0 (0) to 8 (0)	-	0 (0) to 1 (0)	-
Paracetamol	3	21/21	21/21	886 733 (224 801)	2 500 - 329 852	153 881 (32 959)	30
Propranolol	1	23/23	23/23	621 (444)	18 - 15 500	113 (83)	5
Salicylic acid	1	23/23	23/23	20 377 (10 291)	383 - 2 817	3 704 (2 026)	35
Sulfamethoxazole	3	21/21	21/21	5 885 (5 567)	191 - 12 800	991 (835)	25
Vancomycin	2	22/22	22/22	719 (499)	-	128 (95)	50

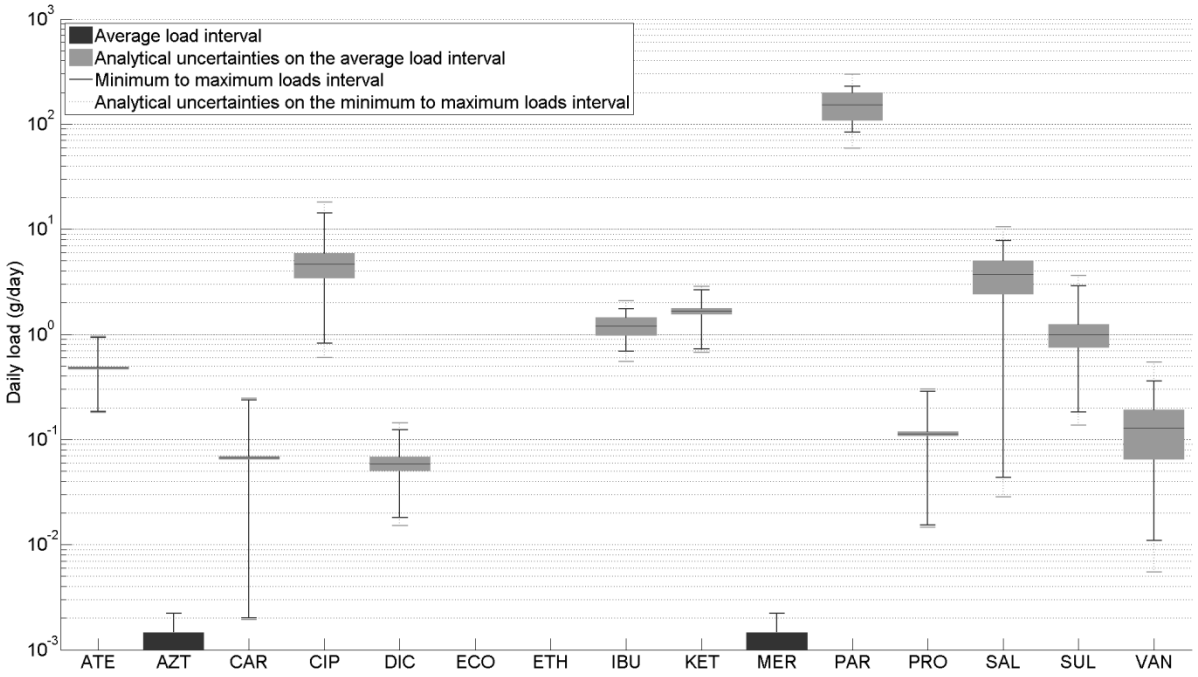


Figure 59: Dissolved daily pharmaceuticals loads in the CHAL hospital.

It is possible to group the different molecules according to their average daily load levels:

- **Less than 0.002 g/day: Aztreonam, Econazole, Ethinylestradiol and Meropenem.** Except for Econazole that is sometimes detected and once quantified, they are never detected.
- **Between 0.05 and 0.2 g/day: Carbamazepine, Diclofenac, Propranolol and Vancomycin.** They are always quantified.
- **Between 0.5 and 5 g/day: Atenolol, Ciprofloxacin, Ketoprofen, Ibuprofen, Salicylic acid and Sulfamethoxazole.** They are always quantified.
- **Higher than 150 g/day: Paracetamol.** It is always quantified.

Concerning the quantified molecules (> 0.05 g/day), it is important to note that the dispersions of the daily loads are quite high since their coefficients of variation ranges from 21 to 112 % of their average values (average of 59 %).

The twenty campaigns took places between August 2013 and October 2015. The dynamics of the molecules loads have not been analysed because there are too few samples on a too short period of time (appendix 13 for time series figures).

Regarding the concentrations of the molecules, some appear to be in range of the values reported by other studies, while others clearly are above them. However, comparing daily loads per hospital bed would be more meaningful.

Dissolved hourly loads

Three “24 x 1 h” campaigns were made. This is too less data to make any reliable analysis and all the following results are to be considered accordingly. It is also important to note that sometimes an hourly load is missing in a time series. This can be due to various reasons: a lost sample, a sample of not “correct” quality or an unreliable flow measurement… Many samples have a quality rated “uncertain” (13 in the 3 campaigns). Indeed the sampling strategy chosen required in real condition larger sampling bottles than provided. Thus the “uncertain” hourly samples does not represent the full hour. This could lead to either over or under estimate the hourly load. An analysis is proposed anyway.

First, it was verified that the pharmaceuticals loads of the “24 x 1 h” campaigns were summing up to be in the range of the “24 h” campaigns. The results are presented in figure 60. For each molecule, each time a “24 x 1 h” campaign has a reconstructed daily loads lower or greater than the minimum and maximum daily loads measured in the “24 h” campaigns, it is considered to be “out of range” and is discarded from the next analysis. Except for three molecules, all three campaigns are kept. Atenolol, Ciprofloxacin and Vancomycin have one campaign with a higher reconstructed daily load.

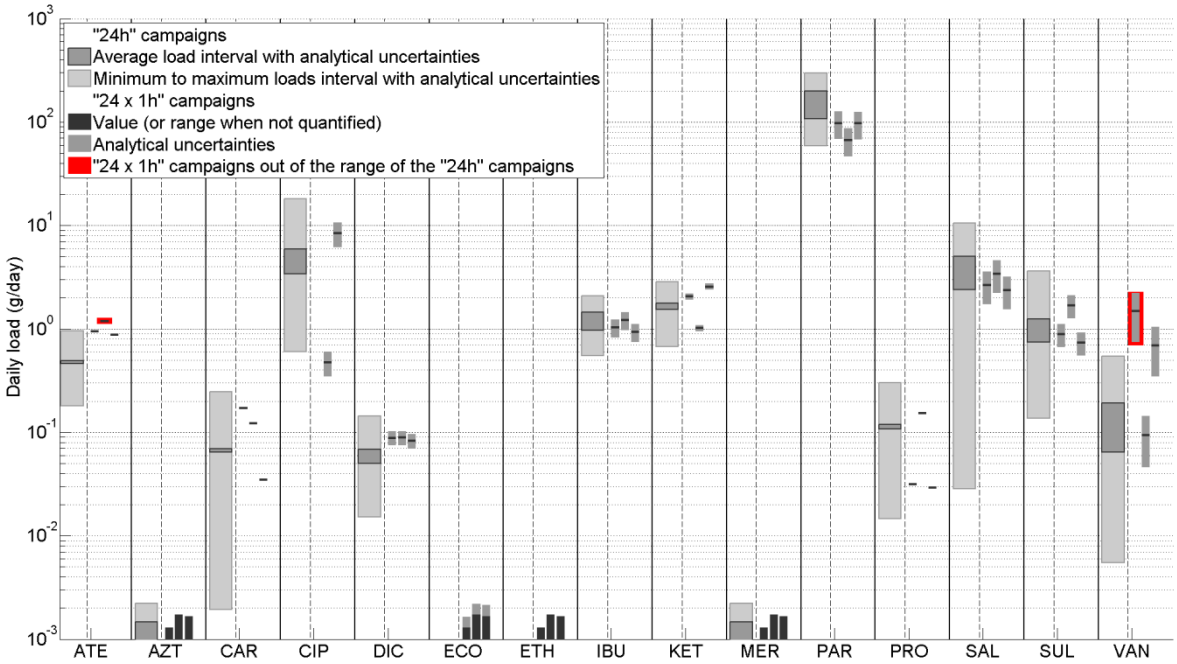


Figure 60: Comparison of the daily loads of the "24 x 1 h" campaigns with the ones of the "24 h" campaigns in the CHAL hospital.

The next step checks if the hourly loads time series of one pharmaceutical are alike from one campaign to another. Results are shown in table 33.

Table 33: Repeatability of the dynamics of the pharmaceuticals hourly loads in the CHAL hospital.

Molecule	Number of "in range" campaigns	For the "in range" campaigns			
		Average reconstructed daily load (standard deviation) (mg/day)	Total number of missing hourly loads	Median with, as reference,	
				The median normalized hourly loads	The normalized wastewater flow
Atenolol	2/3	913 (53)	3	0.59	- 1.18
Aztreonam	3/3	0 (0) to 2 (0)	3	-	-
Carbamazepine	3/3	110 (69)	3	0.71	- 0.58
Ciprofloxacin	2/3	4 459 (5 636)	3	0.06	-
Diclofenac	3/3	87 (3)	3	- 0.47	-
Econazole	3/3	0 (0) to 2 (0)	3	-	-
Ethinylestradiol	3/3	0 (0) to 2 (0)	3		
Ibuprofen	3/3	1 055 (141)	3	0.18	-
Ketoprofen	3/3	1 877 (790)	3	- 0.26	-
Meropenem	3/3	0 (0) to 2 (0)	3	-	-
Paracetamol	3/3	86 962 (17 611)	3	0.5	0.28
Propranolol	3/3	71 (70)	3	0.44	-
Salicylic acid	3/3	2 807 (530)	3	- 0.33	-
Sulfamethoxazole	3/3	1 104 (513)	3	0.03	-
Vancomycin	2/3	393 (426) to 395 (423)	3	- 0.54	-

According to the results, the molecules can be divided in three groups:

- **No observed dynamics: Aztreonam, Econazole, Ethinylestradiol and Meropenem** because as they are seldom detected or quantified, it is not possible to analyse their dynamics.
- **Repeatable dynamics: Atenolol, Carbamazepine and Paracetamol** with a median NSE score of at least 0.5. As an example, figure 61 illustrates the case of Carbamazepine. All the time series are shown in appendix 14.

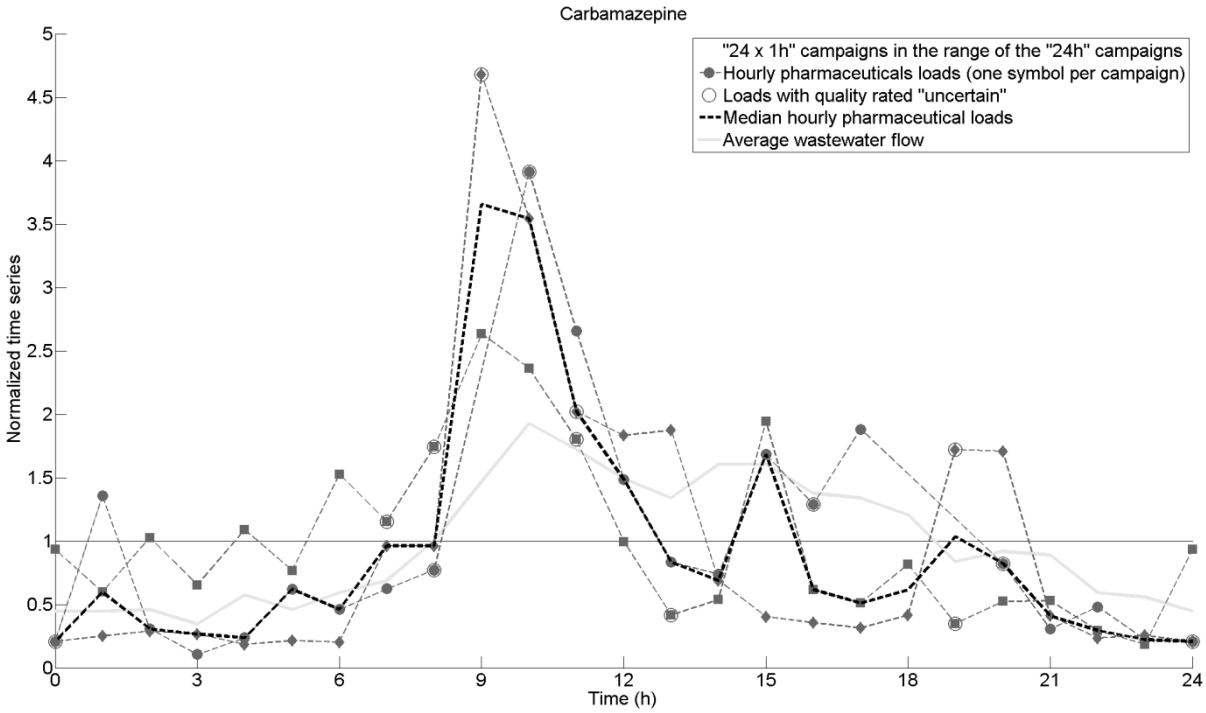


Figure 61: Hourly loads time series of Carbamazepine in the CHAL hospital (average reconstructed daily load equal to 110 mg/day).

- **Chaotic dynamic: Ciprofloxacin, Diclofenac, Ibuprofen, Ketoprofen, Propranolol, Salicylic acid, Sulfamethoxazole and Vancomycin.** Except for Propranolol with a median NSE equal to 0.44, their median NSE score is never higher than 0.18. Considering the rate of consumption of the molecules (DDD/day/beds) and the scale of the CHAL hospital (450 beds), it is not surprising to observe chaotic dynamics in three campaigns. The very presence and discharges of a few patients can change drastically the dynamics of the loads leading to isolated peak loads. Figure 62 illustrates this effect in the case of Diclofenac. All three “24 x 1 h” campaigns show isolated peak loads at different times.

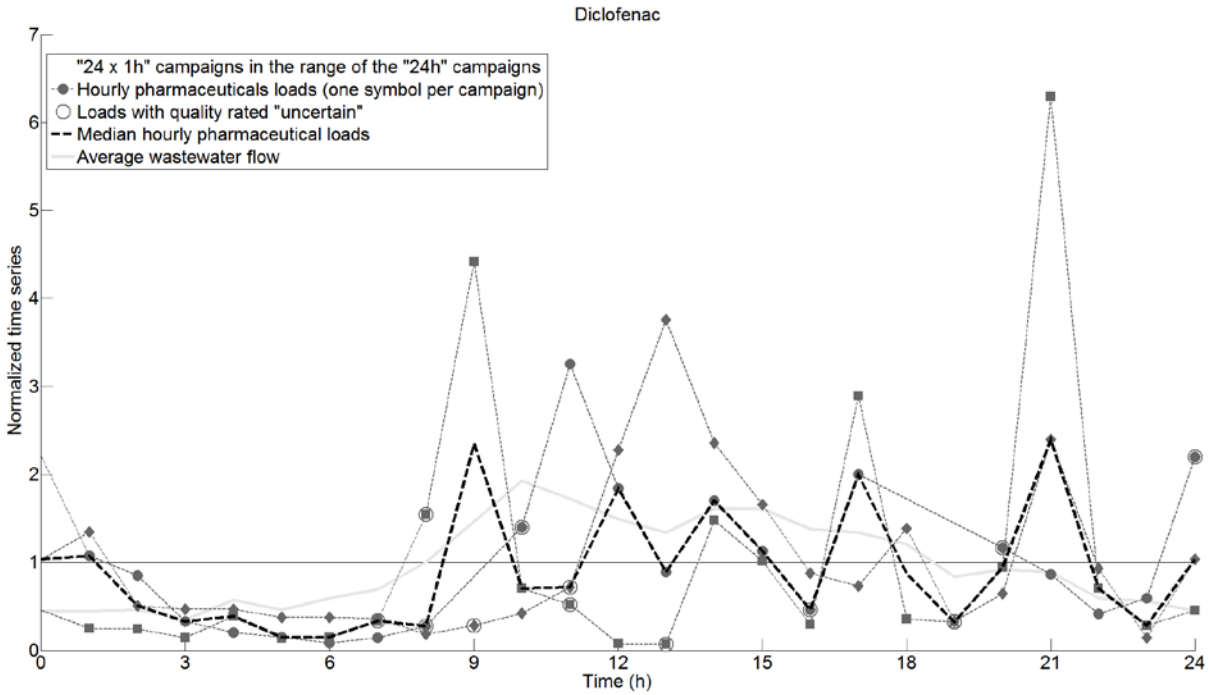


Figure 62: Hourly loads time series of Diclofenac in the CHAL hospital (average reconstructed daily load equal to 87 mg/day).

For the molecule with repeatable dynamics, the results shown in table 33 indicate that dynamics of wastewater flow and pharmaceuticals are not similar. The discharge of pharmaceuticals has its own dynamics that is not directly related to the discharge of wastewater.

The last analysis checks if the dynamics of the different molecules are alike (figure 63).

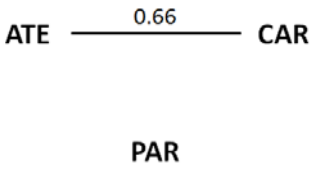


Figure 63: Map of molecules with similar hourly loads dynamics in the CHAL hospital. Only the smallest NSE score is indicated.

Only Atenolol and Carbamazepine seem to share the same dynamics. Paracetamol stands aside.

Dissolved daily loads through the week

Three “7 x 24 h” campaigns were made. However, the quality of the samples have mostly been rated “uncertain” (19/21 samples) due to the fact that the protocol to clean the sample containers has not been followed. Results are presented in table 34 and appendix 15.

Considering the analytical uncertainties and the variability of the pharmaceuticals loads measured in the “24 h” campaigns, no dynamics in the pharmaceuticals loads during the week was observed.

Table 34: Daily pharmaceutical loads of the CHAL hospital in the "7 x 24 h" campaigns.

Molecule	Median NSE with, as reference, the median normalized daily loads	Average daily load (standard deviation) (g/day) "7 x 24 h" campaigns							"24h" campaigns
		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	
Atenolol	0.63	0.4 (0.2)	0.5 (0.1)	0.2 (0.1)	0.3 (0.1)	0.7 (0.7)	0.3 (0.1)	0.2 (0.1)	0.5 (0.2)
Aztreonam									
Carbamazepine	-0.4	0.1 (0.1)	0.0 (0.0)	0.1 (0.0)	0.0 (0.0)	0.1 (0.1)	0.0 (0.0)	0.0 (0.0)	0.1 (0.1)
Ciprofloxacin	-0.27	6 (4.8)	8.5 (7.7)	6 (6.8)	6.9 (6.3)	5.8 (6.3)	3.4 (2.7)	4.2 (4.5)	4.6 (3.9)
Diclofenac	-1.68	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.1 (0.0)
Econazole	-0.07								
Ethinylestradiol									
Ibuprofen	0.28	1.3 (0.5)	1.5 (0.2)	0.6 (0)	1.1 (0.6)	1.5 (0.1)	0.8 (0.1)	0.9 (0.1)	1.2 (0.3)
Ketoprofen	0.47	1.6 (1)	1.9 (1.4)	1.1 (0)	2.3 (1.5)	1.7 (0.9)	1.6 (0.9)	0.9 (0.2)	1.7 (0.5)
Meropenem									
Paracetamol	0.37	92.4 (9.3)	117.1 (27.4)	91.1 (19.7)	99.3 (1)	84.7 (32.7)	85.1 (28.6)	63.2 (36.4)	153.9 (33.0)
Propranolol	0.01	0.1 (0)	0.2 (0.1)	0.6 (0.7)	0.2 (0.3)	0.3 (0.2)	0.0 (0.0)	0.0 (0.0)	0.1 (0.1)
Salicylic acid	-7.6	4.1 (3.4)	4.8 (5.3)	0.7 (0.3)	1.5 (1.9)	1.5 (1.6)	1.6 (2)	1.9 (1.5)	3 .7 (2.0)
Sulfamethoxazole	-2.79	0.9 (1)	0.5 (0.4)	0.8 (0.5)	0.8 (0.7)	0.6 (0.2)	1 (1.2)	0.6 (0.7)	1.0 (0.8)
Vancomycin	0.62	0.2 (0.2)	0.1 (0.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.1)	0.1 (0.1)	0.0 (0.0)	0.1 (0.1)

6.3.3 URBAN VERSUS HOSPITAL SITE

Comparing the two sites, the partitions of pharmaceuticals between dissolved and particulate phases are very similar. Most of the molecules are mainly in the dissolved fraction with a few exceptions: Econazole and Propranolol.

The main comparison point is about the daily pharmaceuticals concentrations and loads. To compare the two sites, it is important to consider the variability of the daily pharmaceuticals concentrations and loads and not only the average values (average values are compared in appendix 16).

Since Aztreonam, Ethinylestradiol and Meropenem are never detected in both sites, it is not possible to provide a comparison for these molecules. Even if Econazole is detected a few times and quantified once in the CHAL hospital, it is not possible to provide a sound comparison.

Concerning the daily pharmaceuticals concentrations, the molecules are split in two groups (figure 64):

- **Similar concentrations:** Atenolol, Carbamazepine, Diclofenac, Ibuprofen, Propranolol and Salicylic acid have ratios hospital over urban daily measured concentrations ranging from 0.41 to 1.34.
- **Greater concentrations in the CHAL hospital:** Ciprofloxacin, Ketoprofen, Paracetamol, Sulfamethoxazole and Vancomycin have ratios hospital over urban daily measured concentrations never less than 6.

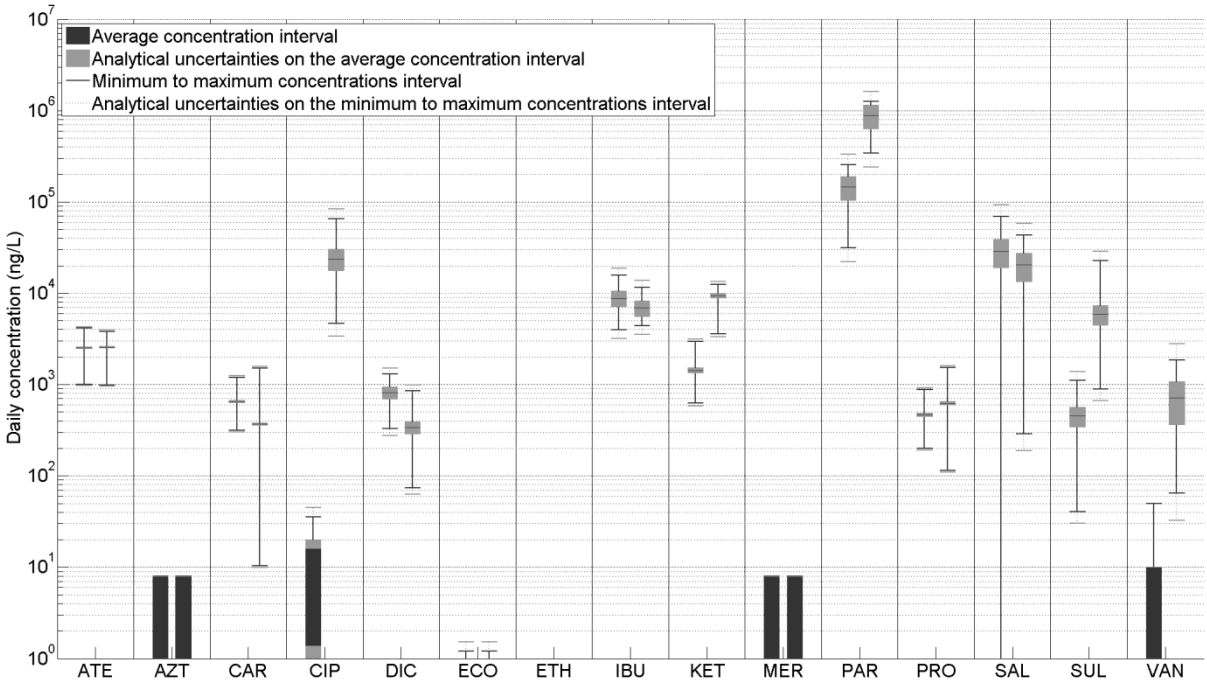


Figure 64: Comparison of the daily concentrations in the two sites. For each molecule, the urban and the hospital sites are respectively on the left and the right of the molecule abbreviation.

Results should be considered with care. Indeed, pharmaceuticals in the urban catchment can be diluted by the infiltration of parasitic water (section 6.2), which is not the case for the CHAL hospital.

Concerning the daily pharmaceuticals loads, the molecules are split in two groups (figure 65):

- **Greater loads in the urban catchment:** Atenolol, Carbamazepine, Diclofenac, Ibuprofen, Ketoprofen, Paracetamol, Propranolol, Salicylic acid and Sulfamethoxazole have ratios hospital over urban daily measured loads ranging from 0.02 to 0.58.
- **Greater loads in the CHAL hospital:** Ciprofloxacin and Vancomycin have ratios hospital over urban daily measured loads never less than 3.

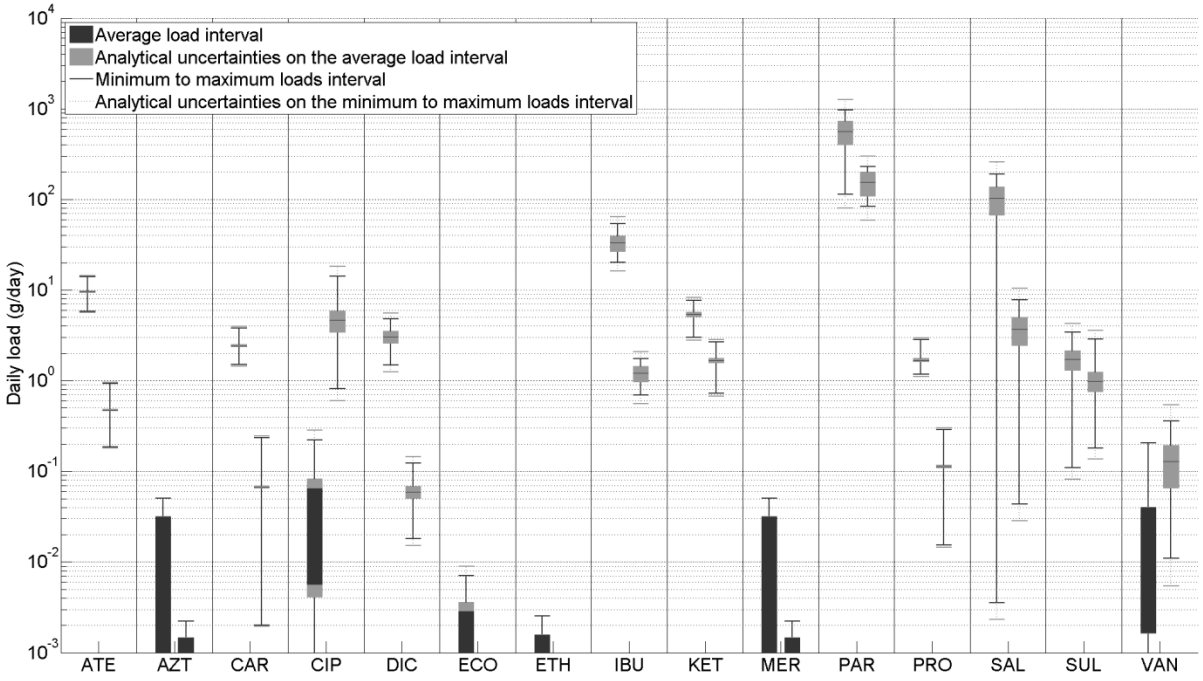


Figure 65: Comparison of the daily loads in the two sites. For each molecule, the urban and the hospital sites are respectively on the left and the right of the molecule abbreviation.

Even though the daily pharmaceuticals concentrations are most of the time comparable in both sites and sometimes greater in the hospital one, the difference of the daily wastewater volumes (section 6.2) makes all pharmaceuticals loads higher in the urban catchment, except for Ciprofloxacin and Vancomycin that appears to be almost exclusive to the CHAL hospital. This highlights the difference of scale between the two sites. A final comparison is proposed, in which daily pharmaceuticals loads are divided by the number of people generating the wastewater flow (≈16 000 inhabitants for the urban catchment and 450 beds for the CHAL hospital). This way, the molecules are split in two groups (figure 66):

- **Similar loads per capita in both sites:** Atenolol, Carbamazepine, Diclofenac, Ibuprofen, Propranolol and Salicylic acid have ratios hospital over urban daily measured loads per capita ranging from 0.68 to 2.34.
- **Greater loads per capita in the CHAL hospital:** Ciprofloxacin, Ketoprofen, Paracetamol, Sulfamethoxazole and Vancomycin have ratios hospital over urban daily measured loads per capita never less than 10.

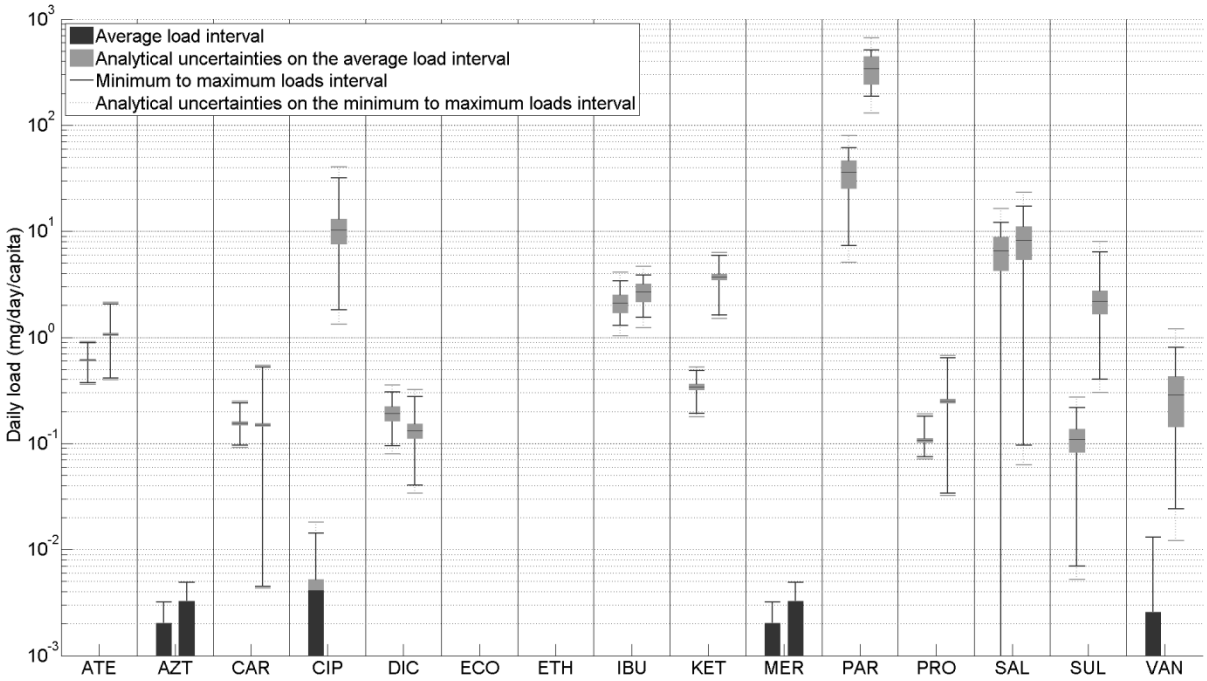


Figure 66: Comparison of the daily loads per capita in the two sites. For each molecule, the urban and the hospital sites are respectively on the left and the right of the molecule abbreviation.

Comparing the hourly pharmaceuticals loads dynamics is not useful since a simple look at the time series shows that they are very different (appendix 11 and 14). However, in both sites, there can be some isolated peak loads in the time series, revealing the random behaviour of some pharmaceuticals discharges. These events are difficult to measure and require a very high frequency sampling strategy.

6.4 CORRELATION BETWEEN PHARMACEUTICALS SALES OR DISTRIBUTIONS AND LOADS AT THE WWTP

As seen in chapter 3, it is assumed that the pharmaceuticals loads in wastewater are linearly proportional to their sales or distributions. The goal of this section is to test this hypothesis. For both sites, each measurement of pharmaceuticals daily loads is, when possible, linked to a sale or distribution data which period of time includes the date of the load measurement. Pharmaceuticals daily loads that are not linked to sales or distributions data are left out. Also, only molecules that are, most of the time, detected in wastewater are analyzed.

6.4.1 URBAN SITE

Out of the 15 studied molecules, six are not studied here. Aztreonam, Meropenem and Vancomycin are never sold nor quantified in wastewater. Ciprofloxacin, Econazole and Ethinylestradiol are sold but never quantified in wastewater.

For the nine remaining molecules, only six daily loads can be linked to sales data (only five for Paracetamol). Since the sales data represent the 30 015 inhabitants of the urban catchment but only approximately 16 000 are actually connected to the sewer network, the sales data are proportionally scaled to only represent the connected inhabitants.

Assuming that there is no pharmaceutical load if the molecule is not sold, the linear regression is done to fit the following relation:

$$\varphi_i = \alpha_i \times m_i$$

With:
i: index of the pharmaceutical
φ_i: daily load of pharmaceutical i
α_i: linear coefficient for molecule i
m_i: daily mass of pharmaceutical i sold or distributed

In order to determine the goodness of fit of these linear regressions, the coefficient of determination R^2 is used:

$$R^2 = \frac{\sum_{n=1}^{N}(\hat{y}_n - \bar{y})^2}{\sum_{n=1}^{N}(y_n - \bar{y})^2}$$

With:
N: number of correlation points
n: index of the correlation point
$\hat{y}_n$: nth predicted value (here pharmaceuticals sales multiplied by α_i)
$\bar{y}$: average of the measured values
y_n: nth measured value (here measured pharmaceuticals loads)

Also, considering the pair (daily mass measured and sold or distributed) individually, the range of individual linear coefficients is determined (figure 67):

$$\alpha_{i,min} = \min\left(\frac{\varphi_{i,j}}{m_{i,j}}\right) \text{ and } \alpha_{i,max} = \max\left(\frac{\varphi_{i,j}}{m_{i,j}}\right)$$

With:
i: index of the pharmaceutical
$\alpha_{i,min}$, $\alpha_{i,max}$: minimum and maximum linear coefficients for molecule i
$\min(d)$, $\max(d)$: returns the smallest or highest value of a list of values d
j: index of the pair (daily mass measured and sold or distributed) for pharmaceutical i
$\varphi_{i,j}$: daily load j of pharmaceutical i
$m_{i,j}$: mass j of pharmaceutical i sold or distributed

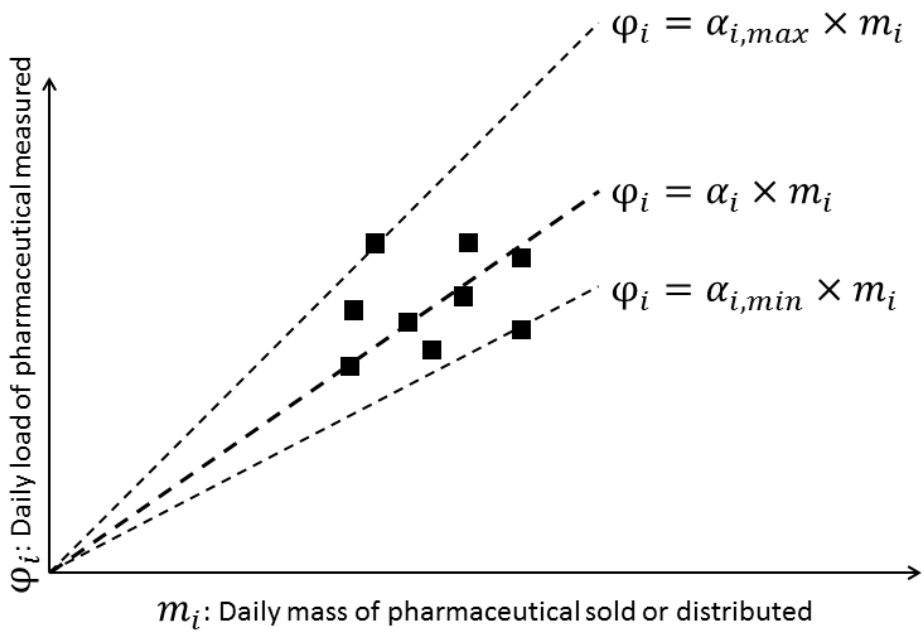


Figure 67: Illustration of the range of individual linear coefficients.

The results are shown in table 35. Also, individual figures for each of the nine molecules can be found in appendix 17.

Table 35: Correlation between pharmaceuticals sales and daily loads for the urban catchment.

Molecule name	Linear regression		Range of the individual linear coefficients	Coefficient of variation of sales	Coefficient of variation of loads	Ratios of the CV
	α_i (%)	R^2	$\alpha_{i,min} - \alpha_{i,max}$ (%)	$CV(sales)$ (%)	$CV(loads)$ (%)	$R = \frac{CV(sales)}{CV(loads)}$ (%)
Atenolol	64	0.21	43 – 94	11	24	46
Aztreonam						
Carbamazepine	11	0.84	9 – 15	18	19	92
Ciprofloxacin						
Diclofenac	13	0.24	10 – 19	8	16	49
Econazole						
Ethinylestradiol						
Ibuprofen	12	0.09	8 – 15	8	28	29
Ketoprofen	34	0.09	29 – 39	6	19	30
Meropenem						
Paracetamol	22	0.02	5 – 33	6	50	12
Propranolol	26	0.2	18 – 40	14	30	45
Salicylic acid	22	0.01	0 – 62	6	93	6
Sulfamethoxazole	21	0.26	4 – 40	3	57	52
Vancomycin						

Except for one molecule (CAR), all the linear regressions are poor. Indeed, their R^2 are never higher than 0.26. This poor "goodness of fit" can be partially explained by the lack of data (only 6 pairs). Carbamazepine stands apart with a R^2 equal to 0.84. This is probably because it is mostly used in very long term treatments. All the linear coefficients found are plausible ($0 < \alpha < 100$ %).

Concerning the variability of both pharmaceuticals sales and loads, data indicate that pharmaceuticals sales are always less variable than pharmaceuticals daily loads. Carbamazepine is an exception with a ratio of coefficients of variation close to 1 (0.92). The rest of the molecules are divided in two groups:

- **2 to 3 times more variability in loads:** Atenolol, Diclofenac, Ibuprofen, Ketoprofen, Propranolol and Sulfamethoxazole.
- **More than 8 times more variability in loads:** Paracetamol and Salicylic acid.

The overall conclusion is that a simple linear model would fail to reproduce the pharmaceuticals daily loads measured in wastewater in terms of both levels and variabilities.

However, identifying the part of the model that is failing is not that trivial. Both the theoretical global excretion rates and the use of monthly sales data to estimate daily consumptions (and then loads in wastewater) are suspected to be part of the problem. To overcome these difficulties, one should prefer a stochastic model using probability distributions for sales and loads rather than a date specific model associating one sale volume to one daily load. Also, proposing an infra-day model could allow more complex processes to be modelled.

6.4.2 CHAL HOSPITAL

Out of the 15 studied molecules, four are not studied here. Aztreonam and Ethinylestradiol are never distributed nor quantified in wastewater. Econazole and Meropenem are distributed but almost never quantified in wastewater (once for Econazole).

For the eleven remaining molecules, twelve to fourteen daily loads can be linked to daily distributions data. The results are shown in table 36. Also, individual figures for each of the eleven molecules can be found in appendix 18.

Table 36: Correlation between pharmaceuticals distributions and daily loads for the CHAL hospital.

Molecule name	Linear regression		Range of the individual linear coefficients	Coefficient of variation of distributions	Coefficient of variation of loads	Ratios of the CV
	α_i (%)	R^2	$\alpha_{i,min} - \alpha_{i,max}$ (%)	$CV(distributions)$ (%)	$CV(loads)$ (%)	$R = \frac{CV(distributions)}{CV(loads)}$ (%)
Atenolol	29	0.3	15 – 93	31	54	57
Aztreonam						
Carbamazepine	2	0.08	0 – 7	36	120	30
Ciprofloxacin	93	0.07	19 – 437	29	110	26
Diclofenac	3	0.12	1 – 7	17	49	35
Econazole						
Ethinylestradiol						
Ibuprofen	5	0.34	2 – 9	16	28	59
Ketoprofen	22	0.50	12 – 52	24	33	72
Meropenem						
Paracetamol	24	0.23	18 – 41	10	21	48
Propranolol	15	0.11	2 – 28	25	75	33
Salicylic acid	17	0.12	0 – 41	21	60	35
Sulfamethoxazole	11	0.24	3 – 48	40	77	52
Vancomycin	2	0.49	0 – 9	77	92	84

All the linear regressions are poor ($R^2 < 0.50$). This poor "goodness of fit" can be partially explained by the lack of data (only 12 pairs). All the linear coefficients found are plausible ($0 < \alpha < 100$ %).

Concerning the variability of both pharmaceuticals distributions and loads, data indicate that pharmaceuticals distributions are always less variable than pharmaceuticals daily loads. They are 1.19 to 3.85 times more variable in loads (average of 2.36).

The overall conclusion of these analyses is similar to the one for the urban catchment. A simple linear model will fail to reproduce the pharmaceuticals daily loads measured in wastewater in terms of both levels and variabilities.

CHAPTER 7: MODELLING RESULTS

The modelling results are analyzed first for the urban catchment and then for the CHAL hospital. For the urban catchment, the model is first calibrated and verified according to the wastewater flow and then verified with the pharmaceuticals loads (section 5.5). For the CHAL hospital, the wastewater flow is not modelled, so only the pharmaceuticals loads are analyzed. The pharmaceuticals loads analysis is focused on two points: quantities with daily loads and dynamics through hourly loads. Both are compared to measurements in terms of magnitude and variability.

7.1 URBAN CATCHMENT

7.1.1 WASTEWATER FLOW MODELLING

As explained in section 5.5, the wastewater flow model is calibrated with the following process:

a) 10 000 sets of parameters for the pipe fundamental elements are tested. Only the set that provides the best overall results for the 86 calibration dates is selected (appendix 7).
b) Using the first step results, 10 000 sets of parameters for the source fundamental elements are tested. Only the set that provides the best overall results for the 86 calibration dates is selected (appendix 7).
c) The non-parasitic non-domestic wastewater model (NPND model) is created by analyzing the results after the two firsts steps of the calibration process.
d) Using the parameters found for the pipe and source fundamental elements and the NPND model, the model is compared to the 43 verification dates.

Throughout the process, the performance of the model is evaluated with the Nash-Sutcliffe model efficiency coefficient (NSE) using smoothed time-series for both measured and modelled wastewater flows.

Figure 68 shows the evolution of the results for the wastewater flow modelling during the calibration and verification steps. For all steps the NSE is never lower than 0, meaning that the model is always more accurate than the mean of the measured flow. After the two calibration steps, the NSE is almost always greater than 0.5 (3 out of 86 calibration dates are under 0.5 but over 0.4). Adding the contribution of the non-parasitic non-domestic wastewater makes the model really efficient with an average NSE of 0.9 and a minimum of 0.58. As expected, the model performs less for verification but is still very efficient with an average NSE of 0.89 and a minimum of 0.60 (only 5 out of 43 verification dates are below 0.8). This means that the model successfully reproduces the wastewater daily volume and dynamics. Indeed, the average daily volume of wastewater measured at the WWTP is 2 022 m^3 (standard deviation of 172 m^3) and the modelled average daily volume is 1 822 m^3 (standard deviation of 13 m^3). The model averagely underestimates the daily volume by 200 m^3 (10 %).

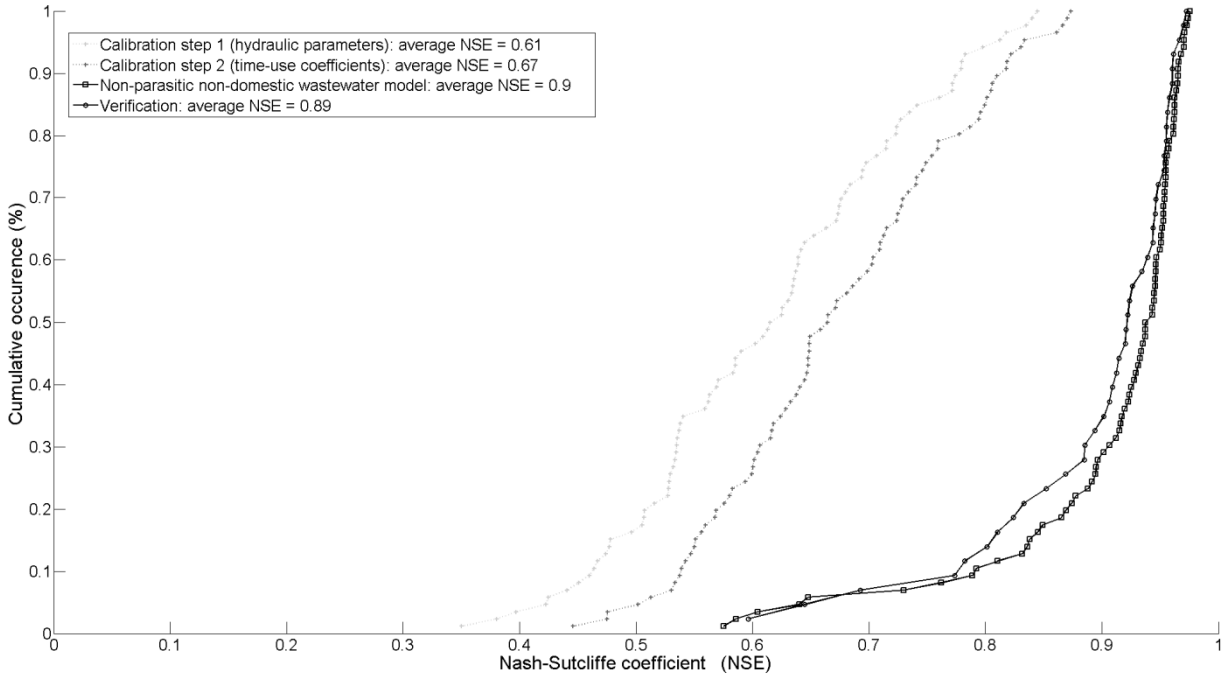


Figure 68: Evolution of the results for the wastewater flow modelling during calibration and verification steps.

An example of the evolution during the calibration steps is shown in figure 69. The two steps of the calibration behave as expected. Indeed, after the first calibration, the morning increase and evening decrease of the wastewater flow are correctly reproduced. However, the morning and evening peaks values show a lower accuracy in simulation. The second calibration corrects the peaks values and still correctly reproduces the morning increase and evening decrease. Finally, the NPND model adds wastewater during the business hours.

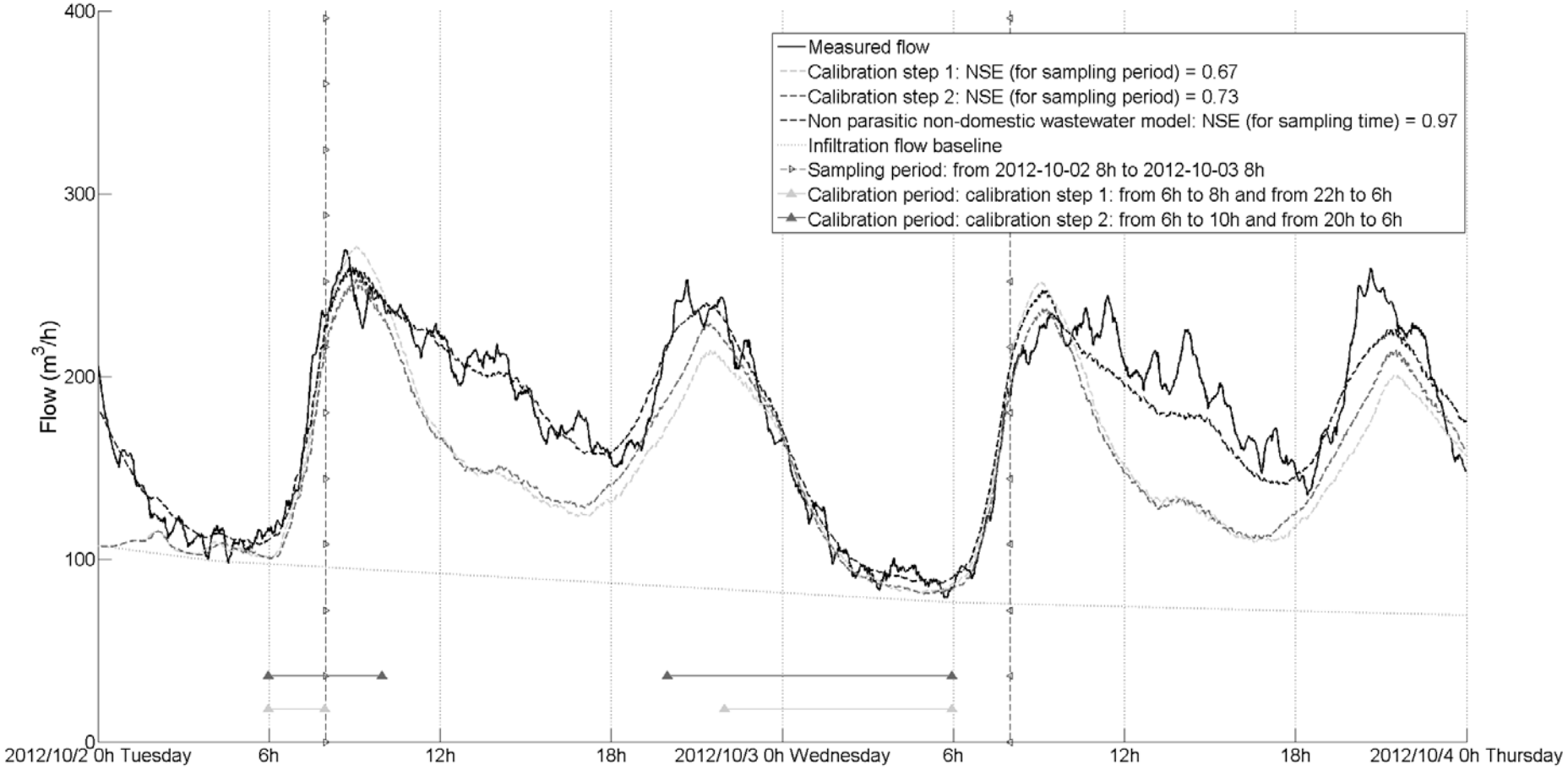


Figure 69: Example of the calibration process with one calibration date.

The NPND model results are shown in figure 70. The NPND model mostly adds wastewater during the business hours. The contributions peaks from 6h to 9h and 18h to 21h are likely to be a compensation for the not perfect calibration of the domestic wastewater model during those periods. The NPND model averagely adds 494 m^3/day (standard deviation of 7 m^3/day) and represents 21 % of the modelled wastewater volume. Compared to the 20.5 % of drinking water demand for non-domestic uses reported in section 4.2, **the results of the NPND model indicate that the model is relevant and realistic**.

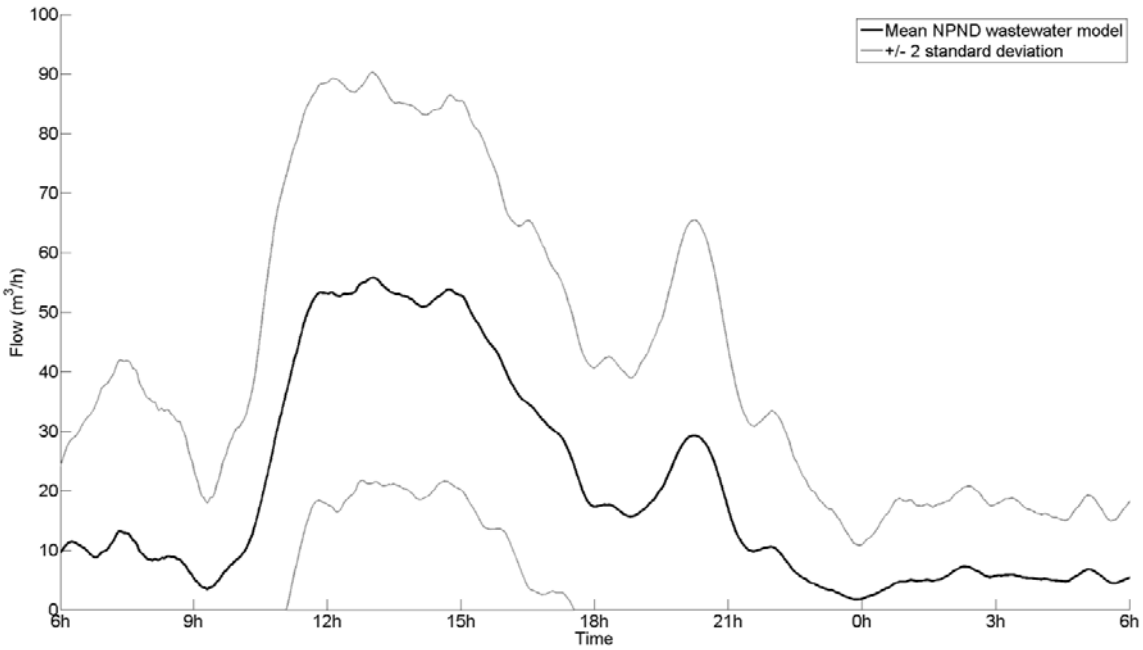


Figure 70: NPND model contribution for the urban catchment.

One shortcoming of the model concerns its variability. Indeed, the variability of the modelled wastewater flow only accounts, averagely, for 37 % of the variability of the measured wastewater flow (with the parasitic flow set aside). Figure 71 shows the comparison of the variabilities of the measured and modelled wastewater flows.

Two reasons may explain the underestimation of the wastewater flow variability by the model. Firstly, the human behaviours toward time-use and water uses are simplified by the model. Secondly, the modelling of the sewer network simplifies the actual network and tends to smooth the flow.

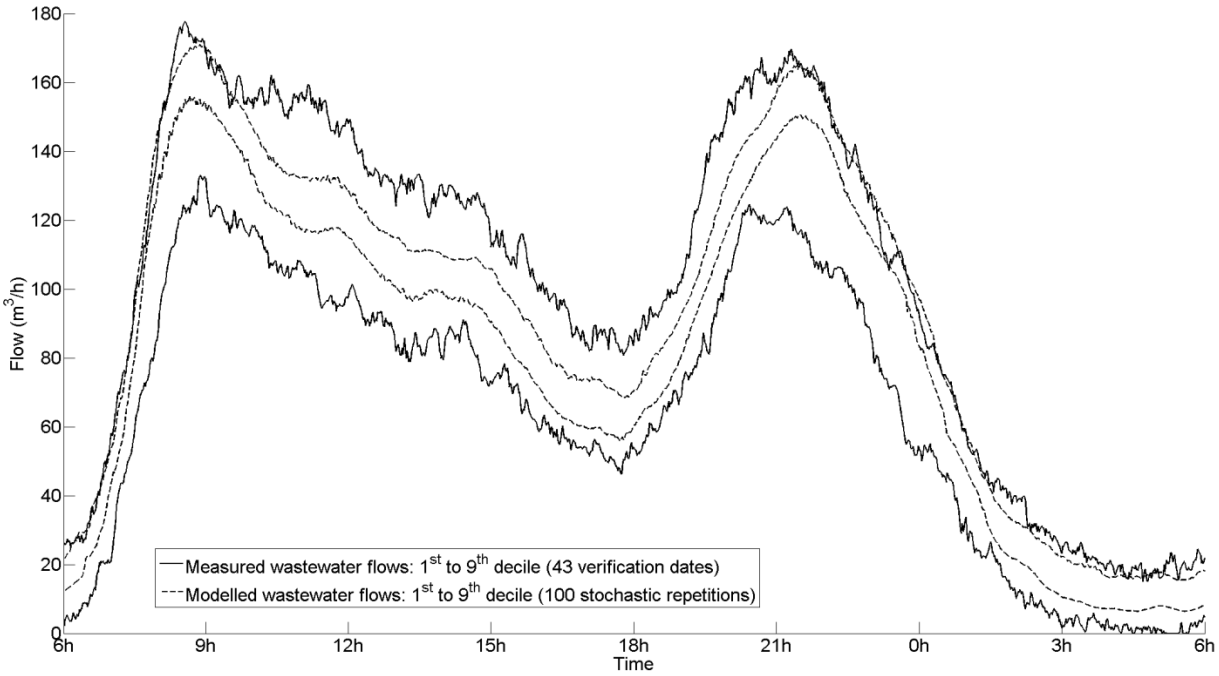


Figure 71: Comparison of the variabilities of the measured and modelled wastewater flows. The infiltration flow baseline of every verification dates has been removed.

Regarding the wastewater flow generated by domestic uses, it is interesting to look at the different dynamics of the water uses. It is shown in figure 72. Four types of uses are considered: personal care (shower, bathroom tap, bath), kitchen (kitchen tap, dishwasher), washing machine and toilet. According to the results of the model, personal care and toilet uses are the main sources of domestic wastewater with respectively 26 and 56 L/day/inhabitant. All together the model averagely generates 113 L/day/inhabitant. During the night, all uses seldom happen but during the day three dynamics can be identified. Toilet and washing machine uses are almost constant through the day with higher occurrence after waking up and in the evening. Kitchen uses are strongly correlated to meal periods. Personal care uses are mostly in the morning after waking up and also in the evening. Assuming that pharmaceuticals loads in wastewater are linked to toilet uses and only considering these results, one could expect that pharmaceuticals loads may reach the WWTP at any hour during business hours.

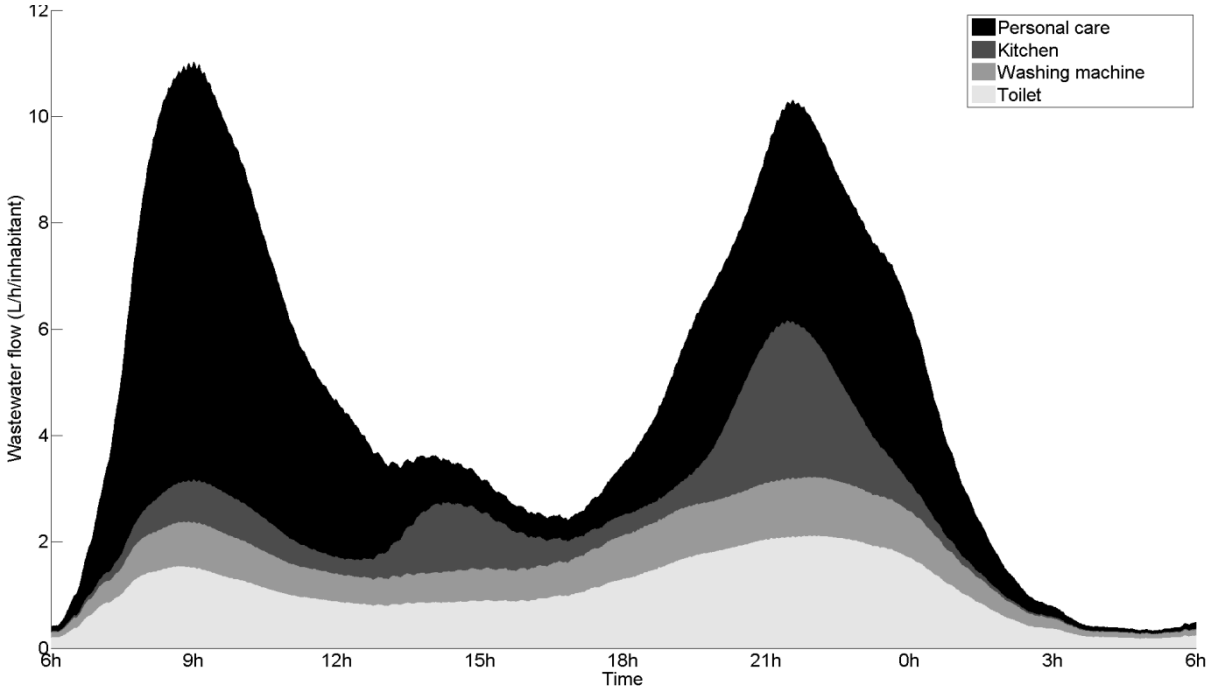


Figure 72: Dynamics of the domestic wastewater contributions at WWTP from the urban catchment.

Given the structure of the sewer network (section 4.2), the wastewater discharged in different locations does not reach the WWTP at the same time. It is possible to estimate a travel time for each "main source area" of the model by detecting the morning peak flow at the outlet of the "main source area" and its corresponding peak at the inlet of the WWTP. Results are presented in table 37. Travel times range from 6 min to 3.5 h. Taking into consideration that each "main source area" generates a different volume of wastewater, the weighted average travel time is 58 min. This sets the frame for the possible transformations or sorption of pharmaceuticals in the sewer network. An example of the effect of the sewer network on the wastewater flow is proposed in figure 73. The wastewater flow is delayed in time and smoothed.

Table 37: Travel times of the 18 "main source areas" of the model for the urban catchment.

Main source area	Average travel time (min)	Average daily wastewater volume (m^3)
Contamine-sur-Arve	6	105
Reignier-Esery (part 1)	19	314
Scientrier	21	90
Nangy (part 2)	33	91
Fillinges (part 3)	33	53
Marcellaz	44	71
Fillinges (part 1)	48	63
Nangy (part 1)	49	16
Arenthon	53	34
Fillinges (part 2)	58	150
Faucigny	60	26
Bonne	70	25
Arthaz-Pont-Notre-Dame	71	78
Pers-Jussy	76	116
Reignier-Esery (part 2)	78	63
Monnetier-Mornex	113	233
Arbusigny	193	26
La Muraz	207	35

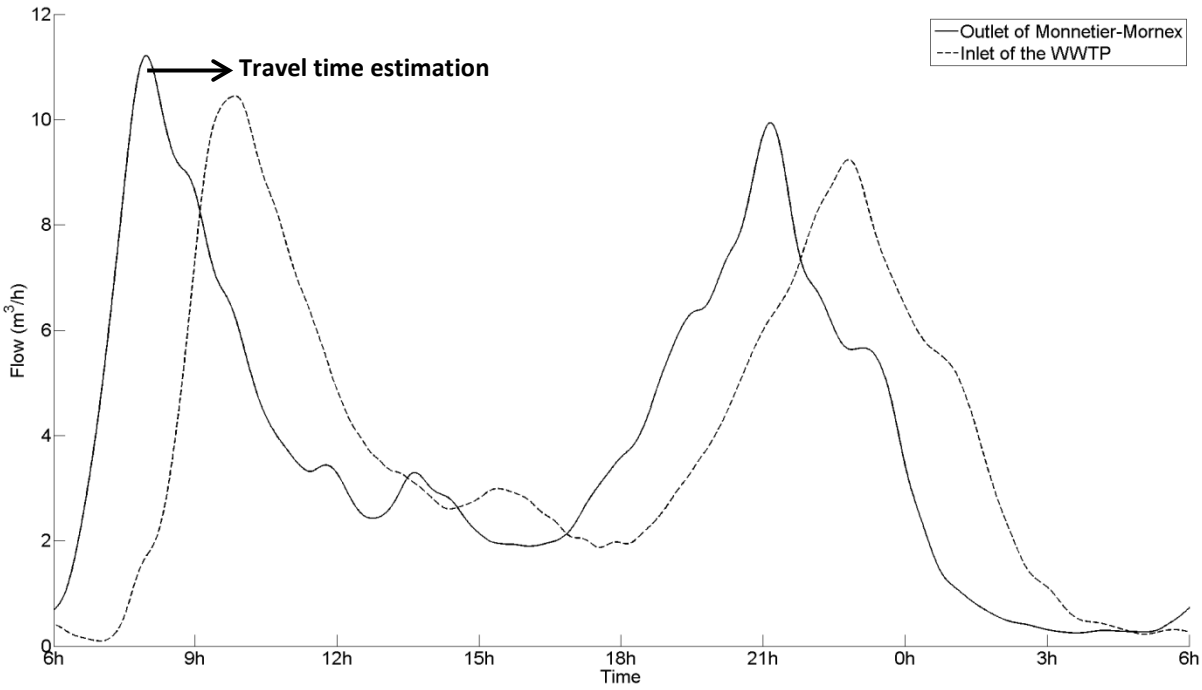


Figure 73: Wastewater flow at the outlet of the "main source area" Monnetier-Mornex and at the inlet of the WWTP. The two points are connected by approximately 2.8 km and three pumping stations.

7.1.2 PHARMACEUTICALS LOADS MODELLING

As seen in section 6.3.1, some molecules are never (or almost never) quantified in both daily and hourly loads. For this reason, they are left out of the analysis of the model results. Six molecules are concerned: Aztreonam, Ciprofloxacin, Econazole, Ethinylestradiol, Meropenem and Vancomycin. The loads of the nine other ones are simulated with the model (section 5.4.2).

7.1.2.1 DAILY LOADS

In order to compare the measured and modelled daily loads, the ratio modelled over measured daily loads is used. Given the data available and the analytical uncertainties of the 15 molecules, the results of the model for one molecule are considered satisfactory whenever the ratio modelled over measured daily loads is between 0.5 and 2 (*i.e.* whenever the model over or under estimates less than two times the measured daily loads). Also, the model is considered reliable if it has satisfactory results for every molecule. Results are shown in table 38 and figure 74.

Table 38: Comparison of the measured and modelled daily loads for the urban catchment. For clarity purposes, ratios considering glucuro and sulfo-conjugates are only shown when such metabolites are actually excreted.

Molecule	Average measured daily load (standard deviation) (mg/day)	Average modelled daily load of parent compound with glucuro-conjugates only (standard deviation) (mg/day)	Ratios of modelled over measured daily loads, parent compound				Ratios of the coefficients of variation
			only	with glucuro-conjugates	with sulfo-conjugates	with glucuro and sulfo-conjugates	
Atenolol	9 578 (2 319)	11 400 (520)	1.19	-	-	1.19	0.18
Aztreonam							
Carbamazepine	2 422 (639)	2 000 (220)	0.81	-	-	0.81	0.41
Ciprofloxacin							
Diclofenac	3 030 (780)	5 000 (310)	1.42	1.64	-	1.64	0.23
Econazole							
Ethinylestradiol							
Ibuprofen	33 043 (8 387)	57 000 (2 350)	1.73	-	-	1.73	0.16
Ketoprofen	5 376 (1 488)	11 800 (880)	0.57	2.19	-	2.19	0.26
Meropenem							
Paracetamol	564 429 (192 844)	1 104 600 (27 680)	0.19	1.96	1.31	3.07	0.07
Propranolol	1 683 (487)	1 200 (110)	0.19	0.73	-	0.73	0.31
Salicylic acid	≈ 102 396 (56 090)	50 700 (2 290)	0.38	0.50	-	0.50	0.08
Sulfamethoxazole	1 709 (917)	2 000 (930)	0.91	1.17	1.18	1.44	0.83
Vancomycin							

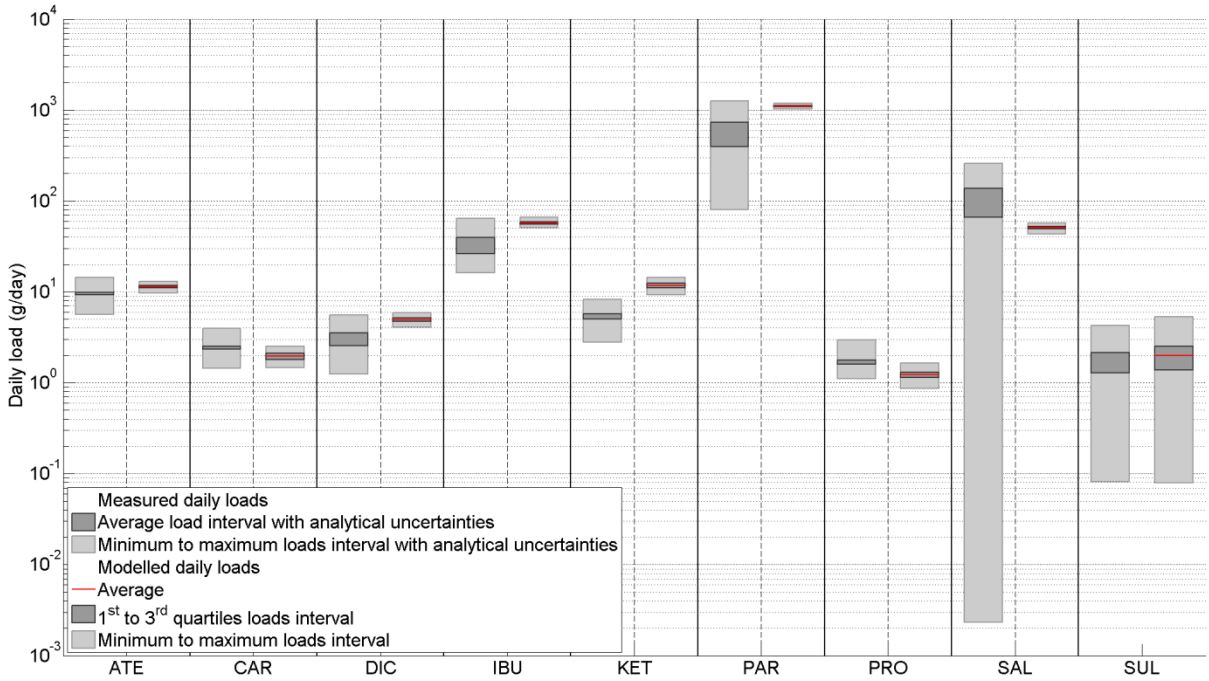


Figure 74: Comparison of the measured and modelled daily loads for the urban catchment. The modelled daily loads include the parent molecule and the glucuro-conjugates.

Looking at the ratios modelled over measured daily loads, only six out of the nine modelled molecules have ratios between 0.5 and 2 if only the parent molecules loads are taken into account for the modelled loads. Six molecules have glucuro-conjugates, if they are taken into account, then eight out of the nine molecules have satisfactory ratios. Two molecules have glucuro and sulfo-conjugates, if they are taken into account, then seven out of the nine molecules have satisfactory ratios. No molecule has sulfo-conjugates without glucuro-conjugates.

These results indicate that the model has better performance when metabolites are taken into account. Glucuro-conjugates are essential, the only molecule out of the 0.5 to 2 ratio interval is Ketoprofen (ratio of 2.19), but the range of the molecule excreted as glucuro-conjugates is wide (from 66 to 95 %, appendix 4). Also, with Diclofenac, they are the only two molecules that are not sold only as oral forms (Diclofenac: 53 % dermal forms; Ketoprofen: 17 % dermal forms). Their fractions directly discharged into the sewer are not well known and approximated by the model (from 25 to 75 %, appendix 4) which over-estimates their daily loads. Approximations for both the fraction directly discharged into the sewer and the fraction excreted as glucuro-conjugates could explain the small over-estimation of the Ketoprofen daily loads. However, sulfo-conjugates lead to overestimations. Ratios for Paracetamol and Sulfamethoxazole increase respectively from 1.96 and 1.17 without sulfo-conjugates to 3.07 and 1.44 with them.

Thus, with the current results, it seems reasonable and realistic to assume that glucuro-conjugates are rapidly and totally transformed back to their parent molecule when discharged into the sewer network while sulfo-conjugates are not.

As seen in section 6.3.1, the dispersion of the measured daily loads is quite important (coefficients of variation mostly between 24 and 34 %). The ratios between the coefficients of variation of the modelled over the measured daily loads indicate that the model is underestimating the dispersion of the daily loads (table 38). This seems to be mainly the result of the temporal scale used for the pharmaceutical sales. Indeed, daily sales derived from monthly data are understandably unable to represent daily sales and so daily consumption and loads in wastewater. This is, however, mitigated in the case of low consumption pharmaceuticals. The dispersion of Sulfamethoxazole that is the less sold pharmaceutical of the nine molecules (section 6.1.1) is even

overestimated (135 %). Conversely, the dispersion of the most consumed pharmaceutical, Paracetamol, is hugely underestimated.

It appears that the model, in its current state, is able to predict reliably the daily loads of pharmaceuticals at the WWTP with an acceptable accuracy considering the available data and the analytical uncertainties. Daily loads are either over or underestimated depending on the molecule. The variability of the daily loads is under-estimated. The difference between modelled and measured loads can be the result of many factors (non-exhaustive list):

- Uncertainties in estimating the number of people associated to a specific pharmaceutical sales record,
- Discrepancies between quantities of pharmaceuticals bought and consumed by a set of population (in both space and temporal scales),
- Un-exclusive and incomplete representation of the population discharging in the catchment by the population associated to the pharmaceutical sales records,
- Specificity of the population sample regarding pharmaceuticals consumption in comparison to consumption trends on a larger scale (only a few patients per day on the whole catchment for some molecules),
- Incomplete or badly defined human metabolism of pharmaceuticals,
- Rapid and daily evolution of the definition of the population discharging in the catchment (workers or visitors entering the catchment, inhabitants leaving momentarily the catchment),
- Unknown physico-chemical processes in the sewer systems (transformation of either parent molecule to transformation products or metabolites to parent molecule, absorption and transformation by biofilm, unknown transformation rates and influencing factors).

Weighting these different factors is not possible without further data. Each and every one of them should be considered for further studies.

A proportional model based on Heberer and Feldmann (2005) is used as a comparison. The details of the proportional model are given in appendix 21. The relative error (Re) of each model is calculated and then compared (table 39):

$$Re = \frac{|\varphi_{meas} - \varphi_{mod}|}{\varphi_{meas}}$$

With:
Re: relative error
φ_{meas} and φ_{mod}: respectively the measured and modelled daily loads (mg/day)

Table 39: Comparison between the classic proportional model and the new stochastic model for the urban catchment

Molecule	Average measured daily load (mg/day)	Classic proportional model		New stochastic model	
		Average modelled daily load (mg/day)	Relative error (%)	Average modelled daily load (mg/day)	Relative error (%)
Atenolol	9 578	13 600	42	11 400	19
Aztreonam					
Carbamazepine	2 422	2 300	6	2 000	19
Ciprofloxacin					
Diclofenac	3 030	2 300	24	5 000	64
Econazole					
Ethinylestradiol					
Ibuprofen	33 043	68 000	106	57 000	73
Ketoprofen	5 376	14 400	167	11 800	119
Meropenem					
Paracetamol	564 429	2 027 000	259	1 104 600	96
Propranolol	1 683	1 400	19	1 200	27
Salicylic acid	102 396	61 100	40	50 700	50
Sulfamethoxazole	1 709	3 400	99	2 000	17
Vancomycin					
		Average	**84**		**54**

Relative errors for the new stochastic model are smaller than for the classic proportional model for five of the nine modelled molecules. Also, the average, minimum and maximum relative errors of all the molecules of the new stochastic model are smaller compared to the classic proportional model. This indicates that the new stochastic model gives better results than the classic proportional one. Also, it provides data on the variability of the daily loads. Apart from the stochastic nature of the new model, the main difference impacting the daily loads between the two models is the consideration of the dynamics of population during the course of the day (people leaving or entering the catchment to go to work).

7.1.2.2 HOURLY LOADS

Comparing the dynamics of modelled and measured hourly loads is based on the NSE score of the average time series of the normalized modelled hourly loads with, as reference, the median time series of the normalized measured hourly loads. However, as seen in section 6.3.1, the median (or average) normalized hourly loads time series are not representatives of the dynamics (too few measurements: 3 or 4 times series; and sometimes chaotic dynamics).

As an alternative, it is proposed to calculate a modified NSE score for each measured time series that takes into account the distribution of all the modelled time series. This modified NSE score is named NSE_{fuzzy}. The average of the NSE_{fuzzy} is calculated and interpreted like a normal NSE score. NSE_{fuzzy} is calculated as follows:

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

$$\boldsymbol{if}\ Q_1(\tilde{L}_{modelled}(t)) \geq \tilde{L}_{measured}(t)\ \boldsymbol{then}\ \tilde{L}_{fuzzy}(t) = Q_1(\tilde{L}_{modelled}(t))$$
$$\boldsymbol{if}\ Q_3(\tilde{L}_{modelled}(t)) \leq \tilde{L}_{measured}(t)\ \boldsymbol{then}\ \tilde{L}_{fuzzy}(t) = Q_3(\tilde{L}_{modelled}(t))$$
$$\boldsymbol{else}\ \tilde{L}_{fuzzy}(t) = \tilde{L}_{measured}(t)$$

With:
t: time ($t \in P$)
P: time period on which the NSE is calculated
$\tilde{L}_{measured}(t)$: normalized measured pharmaceutical hourly load at time t
$\tilde{L}_{fuzzy}(t)$: normalized modelled hourly load at time t constructed for the NSE_{fuzzy} calculation
$\overline{\tilde{L}_{measured}}$: average normalized measured hourly load at time t
$Q_1(X)$, $Q_3(X)$: first and third quartile of a list of values X
$\tilde{L}_{modelled}(t)$: distribution of the normalized modelled hourly loads at time t

The results of the model for one molecule are considered satisfactory whenever the NSE_{fuzzy} is above 0.5. Also, the model is considered reliable if it has satisfactory results for every molecule. Results are presented in table 40. A graphic comparison of the measured and modelled hourly loads for each molecule is proposed in appendix 19.

Table 40: NSE, NSE_{fuzzy} and coefficients of variation of the modelled hourly loads time series for the urban catchment.

Molecule	NSE of the average time series of the normalized modelled hourly loads with, as reference, the median time series of the normalized measured hourly loads	Average of the NSE_{fuzzy} of the normalized modelled hourly loads with, as reference, the normalized measured hourly loads	Average coefficient of variation of the modelled hourly loads (standard deviation) (%)
Atenolol	0.14	0.18	29 (19)
Aztreonam			
Carbamazepine	-0.34	0.19	51 (28)
Ciprofloxacin			
Diclofenac	0.42	0.50	35 (16)
Econazole			
Ethinylestradiol			
Ibuprofen	0.54	0.71	20 (9)
Ketoprofen	0.45	0.72	26 (12)
Meropenem			
Paracetamol	0.63	0.53	31 (13)
Propranolol	0.28	0.65	19 (15)
Salicylic acid	0.31	0.45	39 (24)
Sulfamethoxazole	0.27	0.60	48 (23)
Vancomycin			

Seven out of the nine modelled molecules have a NSE_{fuzzy} above or close to 0.5. Atenolol and Carbamazepine have low NSE_{fuzzy}, respectively 0.18 and 0.19. However, Carbamazepine is the second lowest consumed pharmaceuticals in terms of number of theoretical patients (10.5 DDD per day) and the occurrence of isolated hourly peak measured loads (section 6.3.1) dramatically lowers the NSE_{fuzzy}. Moreover, the NSE_{fuzzy} of

Atenolol is also dramatically lowered due to an isolated hourly peak load measured in one of the campaigns. More "24 x 1 h" campaigns would help to determine the average dynamics of the hourly loads with more confidence and the comparison with the model would be undisturbed by random artifacts in measured hourly loads not representative of the average dynamics.

The average of the coefficients of variation of the modelled hourly loads calculated for each hour show that the dispersion of hourly loads is significant (19 to 51 %). This reinforces the fact that three or four "24 x 1h" campaigns are not enough to analyse hourly dynamics of pharmaceuticals loads.

It appears that the model, in its current state, is able to predict reliably the dynamics of the hourly loads of pharmaceuticals at the WWTP with an acceptable accuracy considering the available data and the analytical uncertainties. However, results are sensitive to isolated measured hourly peak loads. The variability of the modelled and measured hourly loads cannot be compared due to an insufficient number of measurements.

For all the molecules, the model underestimates the night time hourly loads. This indicates that the toilet uses modelling needs refining. And for Paracetamol and Salicylic acid, the model underestimates the afternoon loads (appendix 19). This could be the result of the posology descriptions. Indeed, both exclude consumption when people are outside the household (appendix 3). But they are easily bought (no prescription needed) and massively consumed in France. So it is not unrealistic to assume that some people take Paracetamol or Salicylic acid at any time.

The NSE_{fuzzy} score seems a good indicator of the predictive performance of such a model. This way, the stochastic nature of the studied processes is taken into account and does not penalize the score. Also the average of the NSE_{fuzzy} does not simply increase the NSE score of the average time series. Indeed, it decreases in the case of Paracetamol. Also, the increases for the other molecules show different magnitudes.

Finally, figure 75 shows five examples of the modelled Ibuprofen hourly loads dynamics. Each example corresponds to one stochastic simulation of the model (*i.e.* one different simulation). From one stochastic simulation to another, the dynamics of the pharmaceuticals hourly loads are different. Peaks reach different magnitude at different times. It is the results of both the stochastic nature of pharmaceuticals consumptions and excretions and the presence of several pumping stations in the sewer network. The five examples highlight the random nature of the model results. The model adequately reproduces the random dynamics measured in the "24 x 1 h" campaigns.

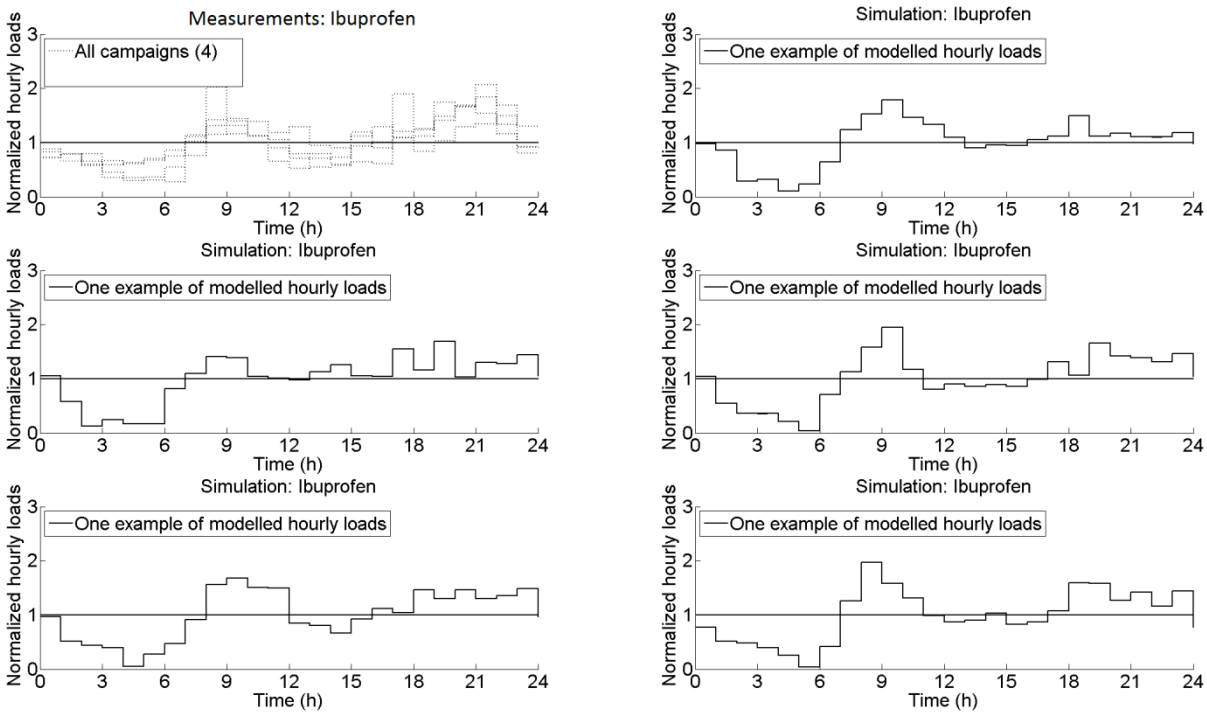


Figure 75: Examples of modelled Ibuprofen hourly loads dynamics. Each example corresponds to one stochastic simulation of the model (*i.e.* one different simulation).

As of today, it is not possible to compare the 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 objective criteria to assess the model performance. However, it seems to give results with rather similar accuracy and performance.

7.2 CHAL HOSPITAL

Similarly to the urban catchment, four molecules are excluded as they are not (or seldom) measured (section 6.3.2): Aztreonam, Econazole, Ethinylestradiol and Meropenem.

7.2.1 DAILY LOADS

Applying the same methodology as for the urban catchment, the modelled daily loads of the CHAL hospital are analyzed. Results are shown in table 41 and figure 76.

Table 41: Comparison of the measured and modelled daily loads for the CHAL hospital. For clarity purposes, ratios considering glucuro and sulfo-conjugates are only shown when such metabolites are actually excreted.

Molecule	Average measured daily load (standard deviation) (mg/day)	Average modelled daily load of parent compound with glucuro-conjugates only (standard deviation) (mg/day)	Ratios of modelled over measured daily loads, parent compound				Ratios of the coefficients of variation
			only	with glucuro-conjugates	with sulfo-conjugates	with glucuro and sulfo-conjugates	
Atenolol	477 (204)	910 (220)	1.91	-	-	1.91	0.56
Aztreonam							
Carbamazepine	67 (75)	210 (90)	3.06	-	-	3.06	0.37
Ciprofloxacin	4 635 (3 948)	2 230 (820)	0.48	-	0.50	0.50	0.43
Diclofenac	59 (31)	500 (130)	8.04	8.49	-	8.49	0.49
Econazole							
Ethinylestradiol							
Ibuprofen	1 204 (285)	3 110 (900)	2.59	-	-	2.59	1.22
Ketoprofen	1 665 (475)	4 240 (780)	0.41	2.55	-	2.55	0.64
Meropenem							
Paracetamol	153 881 (32 959)	251 700 (27 280)	0.15	1.64	1.09	2.57	0.51
Propranolol	113 (83)	110 (40)	0.26	1.00	-	1.00	0.42
Salicylic acid	3 704 (2 026)	3 350 (660)	0.70	0.90	-	0.90	0.36
Sulfamethoxazole	991 (835)	2 240 (970)	1.64	2.26	2.26	2.88	0.52
Vancomycin	128 (95)	3 740 (1 870)	29.1	-	-	29.1	0.67

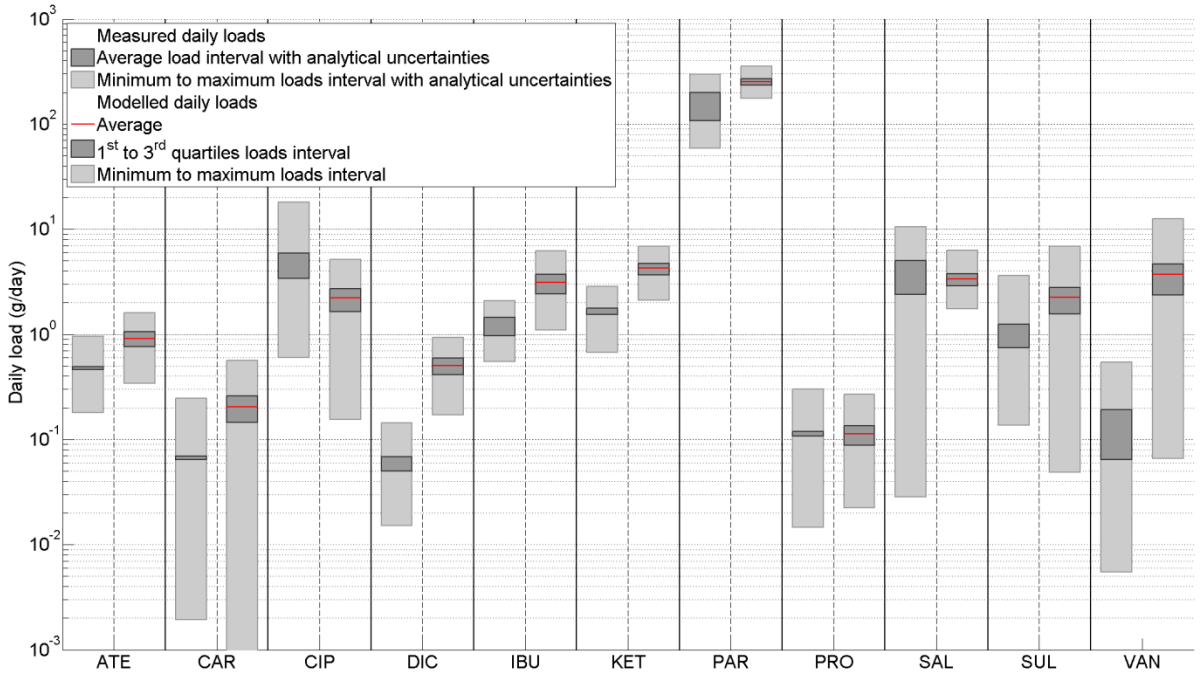


Figure 76: Comparison of the measured and modelled daily loads for the CHAL hospital. The modelled daily loads include the parent molecule and the glucuro-conjugates.

Looking at the ratios modelled over measured daily loads, only three out of the eleven modelled molecules have ratios between 0.5 and 2 if only the parent molecules loads are taken into account. When taking into account glucuro-conjugates only, sulfo-conjugates only or glucuro and sulfo-conjugates combined, only four out of the eleven modelled molecules have satisfactory ratios. Moreover, daily loads are often overestimated when the ratio is not satisfactory (4 out of 8 with no metabolites, 6 out of 7 with glucuro-conjugates only, 5 out of 7 with sulfo-conjugates only and 7 out of 7 with both glucuro and sulfo-conjugates). Considering loads with glucuro-conjugates only, the ratios ranges from 0.48 to 29.1 (median ratio of 2.26).

However, the variability of the modelled daily loads is close to the one of the measured daily loads. Indeed, the ratios modelled over measured coefficients of variations range from 0.36 to 1.22 (average of 0.56). As a result, the ranges of the modelled daily loads often intercept the ranges of the measured daily loads (10 out of 11 modelled molecules).

It appears that the model, in its current state, is not able to predict reliably the daily loads of pharmaceuticals at the WWTP with an acceptable accuracy. Most of the time, daily loads are greatly overestimated. In addition to the factors listed for the urban catchment, some factors specific to the hospital could explain the poor quality results of the model (non-exhaustive list):

- Distribution of pharmaceuticals from central pharmacy not necessarily exclusive to bedded patients,
- Pharmaceuticals stock management (return to the central pharmacy, distribution in batches…),
- Suppression of the negative values for the treatment of the distributions data (*i.e.* pharmaceuticals returned to the central pharmacy) leading to over-estimation of modelled daily loads,
- Patients leaving the hospital before complete excretion of the pharmaceuticals: the duration of hospitalization is a function of the diseases of the patients and so of the used pharmaceuticals,
- Other discharging populations (ambulatory patients, visitors and staff),
- Low and irregular consumption of some pharmaceuticals.

Weighting those different factors is not possible without further data. Each and every one of them should be considered for further studies. More specifically, modelling the hospital pharmaceuticals loads would probably

require to divide the hospital in sub-units, each one with its specific patterns for patients and pharmaceuticals practices.

The same proportional model as for the urban catchment is used as a comparison (appendix 21). The relative errors (Re) are given in table 42.

Table 42: Comparison between the classic proportional model and the new stochastic model for the CHAL hospital.

Molecule	Average measured daily load (mg/day)	Classic proportional model		New stochastic model	
		Average modelled daily load (mg/day)	Relative error (%)	Average modelled daily load (mg/day)	Relative error (%)
Atenolol	477	1 200	157	910	91
Aztreonam					
Carbamazepine	67	300	343	210	206
Ciprofloxacin	4 635	2 800	39	2 230	52
Diclofenac	59	200	239	500	753
Econazole					
Ethinylestradiol					
Ibuprofen	1 204	4 200	248	3 110	159
Ketoprofen	1 665	5 900	254	4 240	155
Meropenem					
Paracetamol	153 881	523 800	240	251 700	64
Propranolol	113	200	47	110	0
Salicylic acid	3 704	4 800	30	3 350	10
Sulfamethoxazole	991	4 800	386	2 240	126
Vancomycin	128	5 500	4 184	3 740	2 820
		Average	**560**		**400**

Relative errors for the new stochastic model are smaller than for the classic proportional model for nine of the eleven modelled molecules. Also, the average, minimum and maximum relative errors of all the molecules of the new stochastic model are smaller compared to the classic proportional model. This indicates that the new stochastic model gives better results than the classic proportional one.

7.2.2 HOURLY LOADS

As for the urban catchment, the NSE_{fuzzy} is used to compare the dynamics of modelled and measured hourly loads. Results are presented in table 43. A graphic comparison of the measured and modelled hourly loads for each molecule is given in appendix 20.

Table 43: NSE, NSE_{fuzzy} and coefficient of variations of the modelled hourly loads time series for the CHAL hospital.

Molecule name	NSE of the average time series of the normalized modelled hourly loads with, as reference, the median time series of the normalized measured hourly loads	Average of the NSE_{fuzzy} of the normalized modelled hourly loads with, as reference, the normalized measured hourly loads	Average coefficient of variation of the modelled hourly loads (standard deviation) (%)
Atenolol	0.24	0.62	28 (22)
Aztreonam			
Carbamazepine	0.38	0.55	45 (23)
Ciprofloxacin	0.17	0.59	38 (32)
Diclofenac	-0.34	0.42	52 (25)
Econazole			
Ethinylestradiol			
Ibuprofen	-0.17	0.54	45 (19)
Ketoprofen	-0.91	0.40	39 (18)
Meropenem			
Paracetamol	-0.39	0.06	27 (17)
Propranolol	0.23	0.52	44 (23)
Salicylic acid	-0.32	0.34	50 (27)
Sulfamethoxazole	-0.65	0.18	73 (34)
Vancomycin	-0.22	0.18	59 (35)

Five out of the eleven modelled molecules have NSE_{fuzzy} scores higher than 0.5, the minimum score is 0.06 and the average is 0.4. The insufficient number of measurements (only 3 “24 x 1h” campaigns) and the small number of theoretical patients in the hospital (less than 17 DDD/day for 9 of the 11 molecules) are dramatically lowering the NSE_{fuzzy} scores. However, in spite of these perturbations, Paracetamol and Salicylic acid hourly loads in the evening (18 h to 22 h) are over-estimated by the model. This indicates that time-use behaviour of the patients and posology at the hospital can be different from an urban catchment.

Also the average of the coefficients of variation of the modelled hourly loads calculated for each hour show that the dispersion of hourly loads is important (27 to 73 %). This reinforces the fact that three “24 x 1 h” campaigns are not enough to analyse the hourly dynamics of pharmaceuticals loads.

In this context (insufficient number of measurements and low consumptions), it is not really possible to conclude on the reliability of the model. However, results are encouraging and most of the unsatisfactory results are expected to improve with additional measurements.

As for the urban catchment, no comparison with models found in literature is possible.

CONCLUSIONS AND PERSPECTIVES

This thesis has three main objectives which are reviewed hereafter:

- **Monitoring, in both sites, the pharmaceuticals loads entering the WWTP, compare them and assess their variability at different time scales (seasonal, day to day and hourly).**

  Four types of campaigns have been made on both sites. Materials and methods have been defined with care to avoid any misrepresentations. All campaigns were made over a few years, always on the same weekday (Tuesday to Wednesday) and during normal periods (no vacations). Some molecules were never or seldom quantified, thus making their analysis difficult. For the urban catchment, they are six: Aztreonam, Ciprofloxacin, Econazole, Ethinylestradiol, Meropenem and Vancomycin. For the CHAL hospital, they are four: Aztreonam, Econazole, Ethinylestradiol and Meropenem.

  The "24 h particulate" campaigns compared the distribution of pharmaceuticals loads between the dissolved and particulate phases. Seven were made for both sites. They show that the quantified molecules are mainly found in the dissolved fraction (at least 90 % of the load). However this cannot be generalized to other pharmaceutical molecules as they do not represent an uniform class of chemicals.

  The "24 h" campaigns allowed measuring the daily dissolved loads. Respectively, 20 and 24 campaigns were done for the urban catchment and the CHAL hospital during a period of 2 years. The range of the measured loads is significant for both sites. The average daily load ranges from 1.7 to 564 g/day for the urban catchment and from 0.06 to 154 g/day for the hospital. The variability of the daily loads for each molecule is also high. Indeed, the coefficients of variation are rarely less than 25 %. No seasonal or annual dynamic patterns are identified, because the data are not sufficient for such an analysis. Concentrations are either similar in both sites or greater in the hospital. But loads are always greater in the urban catchment due to the high wastewater volume, except for two molecules that are exclusively used in the hospital. However, it is arguably not relevant to compare the two sites this way. It would be interesting to propose a weighted ratio taking into account the number of people concerned, *i.e.* dividing the urban loads by the number of people connected to the sewer network and dividing the hospital loads by the population susceptible to be treated in it (data are not available for such an analysis).

  The "24 x 1 h" campaigns measured the dynamics of the loads through a day. Respectively four and three campaigns were made for the urban catchment and the CHAL hospital. The key element to interpret the results of the "24 x 1 h" campaigns is taking into account the theoretical number of patients per day for each molecule (DDD/day). If there are many patients in the catchment, the randomness of their excretions is averaged and thus the hourly loads at the WWTP represent an average time series. Conversely, if there are only a few patients in the catchment, the measured time series is extremely impacted by the randomness of their excretions and it is thus hard to estimate any average time series with a limited number of campaigns. This is the case for some molecules in the urban catchment (number of DDD per day: Carbamazepine, 7; Sulfamethoxazole, 1) and for most molecules in the hospital (number of DDD per day: Ciprofloxacin, 4; Diclofenac, 17; Ibuprofen, 14; Propranolol, 5; Salicylic acid, 6; Sulfamethoxazole, 4; Vancomycin, 3). As a result, the measured times series are not very similar for those molecules. However, except for some more complicated cases, the measured time series of the molecules that are consumed by many patients every day are similar from one campaign to another. The measured average dynamics are not necessarily similar from one molecule to another, but some showed comparable behaviours. However, none is similar to the wastewater flow dynamics.

The “7 x 24 h” campaigns aim is to detect weekly dynamic pattern. Three campaigns were made for both sites. No clear dynamic pattern is observed.

- **Acquiring and analysing detailed pharmaceuticals sales or distributions data for both sites.**

  For the urban catchment, sales data have been bought by a pharmaceutical census company. Monthly sales over a 2.5 years period for two areas have been analysed. The first area corresponds to the six pharmacies on the Bellecombe catchment that supposedly provides pharmaceuticals for the 30 000 inhabitants. The second area corresponds to a much larger territory (Haute-Savoie) of 793 000 inhabitants. Data from the six pharmacies present more variability than the data from Haute-Savoie. However, data give different levels of pharmaceutical sales (mass sold per day per capita) depending of the area. As the number of inhabitants provided by the six pharmacies is much more uncertain than the one for Haute-Savoie, it was decided: *i*) to keep the Bellecombe data for modelling purposes due to its variability; but *ii*) to adjust its level with an empirical coefficient in order to fit the level of sales in the Haute-Savoie area.

  For the CHAL hospital, distributions data have been directly provided by the central pharmacy of the hospital. Three time scales have been analysed: days, weeks and months. Analyses reveal that distribution data are affected by stock management and thus do not necessarily represent the actual consumption of the patients. For examples, some data indicate pharmaceuticals re-entering the central pharmacy, or some pharmaceuticals are only distributed by batch (*i.e.* a fixed number at a time or a multiple of this number), or there is no distributions on weekends. The daily distributions are the most impacted, but they are potentially the closest to the true variability of the consumption. As a compromise, the weekly distributions are used and processed to estimate probable daily distributions (*i.e.* removal of suspicious values and smoothing process by mean of a mobile mean over three weeks).

  The 15 monitored molecules in the SIPIBEL project are sold as 188 different specialities in the urban catchment, and as 56 specialities in the hospital. For each molecule, the first five (respectively three) specialities account for more than 90 % of the mass sold in the urban catchment (respectively in the hospital). Most specialities consist of oral forms (tablets or pills), but for specific molecules an important proportion consist of dermal forms (creams). Intravenous forms are only present in the hospital and are for some molecules the only available form. The range of sales or distributions is significant. The average mass of pharmaceuticals sold or distributed in one day ranges from 0.04 to 4 346 g/day for the urban catchment and from 0.7 to 590 g/day for the hospital. Taking into account the DDD of each molecule, the theoretical average number of patients per day ranges from 6 to 1 620 in the urban catchment and from 0.4 to 200 in the hospital.

  In order to explore the link between sales or distributions and loads at the WWTP, sales and distributions data have been associated to measured daily loads. The available data did not show a linear correlation and the variability of the measured daily loads is always greater than the variability of the sales or distributions.

  Sales data have proven to be difficult to obtain, to analyse and their ability to accurately represent the consumption and thus occurrence in wastewater is questionable.

- **Modelling, in both sites, the pharmaceuticals daily and hourly loads entering the WWTP by accounting for the stochastic nature of the processes.**

  A minute time step model has been proposed and applied to both sites. Most of the processes are represented with a stochastic approach. Not all 15 molecules are modelled because some molecules are never (or almost never) quantified in both daily and hourly loads at both sites.

  For the urban catchment, only nine molecules are modelled.

  Daily loads

  Results indicate that the glucuro-conjugates loads should be added to the parent molecule loads. Without them, the model has worse performances. Also, the addition of sulfo-conjugates leads to over-estimations. **Thus, with the current results, it seems reasonable and realistic to assume that glucuro-conjugates are rapidly and totally transformed back to their parent molecule when discharged into the sewer network while sulfo-conjugates are not.**

  Considering only the parent molecule and the glucuro-conjugates loads, the ratios modelled over measured average daily loads ranges from 0.5 to 2 for eight of the nine modelled molecules (average ratio equal to 1.32). One molecule is over-estimated: Ketoprofen with a ratio equal to 2.19. However, its metabolic parameters are not precisely known. The ratios modelled over measured coefficients of variation range from 0.07 to 0.83 (average equal to 0.28), indicating that the variability of the daily loads is under-estimated by the model.

  Compared to the classic population proportional models found in the literature, the proposed stochastic model has better results for five out of nine molecules. The average relative error decreases from 84 % for the proportional model to 54 % for the stochastic model.

  In conclusion, the proposed stochastic model is able to reliably reproduce the daily loads in the range 0.5 to 2 times the measured values for the urban catchment, but under-estimates their variability. It improves the average performance of the classic population proportional model by a third.

  Hourly loads

  The average NSE_{fuzzy} indicators (variation of the NSE score) for each molecule range from 0.18 to 0.72 (average equal to 0.50). They are greater or close to 0.5 for seven of the nine modelled molecules. The limited performances for the two molecules with NSE_{fuzzy} less than 0.5 can be partially explained by the sensibility of the dynamics to low consumption pharmaceuticals and odd peak values in measurements.

  The model shows a high variability between stochastic repetitions: average coefficients of variation range from 19 to 51 % depending on the molecule. However, the comparison of the measured and modelled hourly loads variability is not possible due to the limited number of measurements.

  In conclusion, the proposed stochastic model is able to reliably reproduce the hourly loads with reasonable accuracy for an urban catchment.

For the CHAL hospital, eleven molecules are modelled.

Daily loads

Only four out of the eleven molecules have ratios modelled over measured average daily loads ranging from 0.5 to 2. Six of the seven other molecules have ratios higher than 2. This indicates that the proposed stochastic model globally over-estimates the daily loads (median ratio equal to 2.26). Also, the variability of the modelled daily loads is averagely half the one of the measured daily loads. The ranges of the modelled daily loads intercept the ranges of the measured daily loads of ten molecules. These results can be due to several factors, mainly the central pharmacy data inability to accurately represent the consumptions of the bedded patients. This confirms the specificity of the hospital compared to the urban catchment.

Compared to the classic proportional model found in literature, the stochastic model has better results for nine out of eleven molecules. The average relative error decreases from 560 % for the classic proportional model to 400 % for the stochastic model.

In conclusion, the model is not able to reliably reproduce the daily loads with accuracy for the hospital but still provides better results than the classic population proportional model.

Hourly loads

The average NSE_{fuzzy} indicators for each molecule range from 0.06 to 0.62 (average equal to 0.40). They are greater than 0.5 for five of the eleven modelled molecules. As for the urban catchment, the limited performance of the model can be partially explained by the sensitivity of the dynamics to low consumption pharmaceuticals (9 molecules with less than 17 DDD/day).

The model shows a high variability between stochastic repetitions (average coefficients of variation range from 27 to 73 % depending on the molecule). However, the comparison of the measured and modelled hourly loads variability is not possible due to the limited number of measurements.

The limited number of measurements combined with the low consumptions of pharmaceuticals in the hospital prohibits making any strong conclusion on the performance of the stochastic model for the hospital. However, results are encouraging and most of the unsatisfactory results should improve with additional measurements.

The performance of the proposed stochastic model is globally satisfactory. It produces reliable results for both daily and hourly loads. However, it still under-estimates the variability of the daily loads. Its results are better than those of the classic population proportional model. In its current state, the stochastic model can be used with confidence for urban catchments large enough to show repeatable consumed pharmaceuticals loads. The use of the model for hospitals is much less reliable because of their inherent variability and their low consumptions of pharmaceuticals. The stochastic model provides additional data on the modelled catchment (loads variability and dynamics) compared to the classic population proportional model. However, it requires much more data and expertise.

In addition, the model is able to predict the domestic wastewater flow of an urban catchment with great accuracy for both daily volumes and dynamics. After calibration, the model was verified for 43 one day periods at a minute time step. The average NSE score is equal to 0.89 with a minimum of 0.60.

In this context, further works should focus on:

- **Pharmaceutical hourly loads measurements:** 3 or 4 “24 x 1 h” campaigns were done on each site. As results showed important variability and sensitivity to low consumed pharmaceuticals, additional “24 x 1 h” campaigns for both sites are necessary to refine the dynamics of the pharmaceuticals in the model.
- **Domestic pharmaceuticals consumption:** as presented in this work, the link between pharmaceutical consumption and sales is not obvious (no linear correlation). Also, sales on a large territory and during a long period of time are more reliable in terms of magnitude than sales on a small territory and during a short period of time. However, the variability of the latter is closer to the variability of the loads measurements. New insight could be gain by surveying the population consumption directly. It shall provide inter-dependant probabilities of the different pharmaceuticals consumptions depending on age or sex: number of treatments per year, duration of the treatment, daily dosage, and posology (paired with the time-use behaviour). These data could be used to accurately simulate the pharmaceuticals consumption for both daily and hourly loads modelling.
- **Human pharmaceuticals metabolism:** data on the metabolism of the pharmaceuticals are difficult to access. The available ones have sometimes very small population samples. As a result, the required metabolic parameters to model the excretion of pharmaceuticals loads are not well determined or unknown.
- **Dynamics of toilet uses:** integrating the dynamics of toilet uses in time-use surveys to refine the modelling of pharmaceuticals excretions, especially for night hours and working hours.
- **Pharmaceuticals and their metabolites fate in sewers conditions:** information on transformation or sorption of pharmaceuticals or their metabolites during transfer in sewers is necessary to model pharmaceuticals loads accurately.
- **Refined urban model:** data gathered in the above points should be used to improve the results of the model for the urban catchment for both daily and hourly loads.
- **Detailed hospital model:** dividing the hospital in sub-entities with specific patients behaviour (number of bedded patients, number of ambulatory patients, length of stay, probability of pharmaceutical consumption, posology and time-use behaviour) and integrating the staff and visitors pharmaceuticals contributions should improve the results of the model for the hospital for both daily and hourly loads. Surveys should be conducted to gather all the necessary data.
- **Expansion of the model:** both the urban and hospital models should be integrated in a wider model that describes the sewers network and its overflow structures during rainfall events, the WWTP, the receiving environment and the contributions of veterinary products.
- **Extensive uncertainty analysis:** uncertainties of the whole measurements process should be evaluated. Results of the model concerning the dynamics of the pharmaceuticals loads could be used to estimate uncertainties of the sampling strategy.
- **Extension of the list of pharmaceuticals, metabolites and transformation products:** testing the model with additional pertinent molecules is paramount to assess its reliability.
- **Simplification of the model:** results of the model could be used to implement a new population proportional model that would be simple and fast to use while integrating more phenomena.

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APPENDIXES

APPENDIX 1: UNITED STATES OF AMERICA, PHARMACEUTICALS AND THE IMPORTANCE OF DEFINITION

1.1 PHARMACEUTICAL REGULATION IN THE UNITED STATES OF AMERICA (USA)

Pharmaceuticals in the USA are regulated by the Food and Drug Administration (FDA). Definitions relative to pharmaceutical are (U.S. FOOD AND DRUG ADMINISTRATION (a)):

> *"**Drug***
>
> *A drug is defined as:*
>
> - *A substance recognized by an official pharmacopoeia or formulary.*
> - *A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.*
> - *A substance (other than food) intended to affect the structure or any function of the body.*
> - *A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.*
>
> *Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)"*
>
> *"**Dosage Form***
>
> *A dosage form is the physical form in which a drug is produced and dispensed, such as a tablet, a capsule, or an injectable."*
>
> *"**Drug Product***
>
> *The finished dosage form that contains a drug substance, generally, but not necessarily in association with other active or inactive ingredients."*
>
> *"**Active Ingredient***
>
> *An active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals."*

The essence of the definition is not far from the one laid by European regulations as described in chapter 1, and so it has the same flaws.

1.2 ABOUT THE IMPORTANCE OF THE DEFINITION OF PHARMACEUTICAL

To offer perspectives on the importance of defining the notion of pharmaceutical and the economic strategies it can hide, the following example is proposed.

Once upon a time, in the USA, there was a happy firm called Diamond Food incorporation. It was a food company. One of their products was walnut, and to encourage sales they told everybody that:

"[Walnuts contains] *OMEGA-3s ... Every time you munch a few walnuts, you're doing your body a big favor."* (U.S. FOOD AND DRUG ADMINISTRATION (b))

And they lived happily ever after… or not!

In 2010, the company received a letter from the FDA (U.S. FOOD AND DRUG ADMINISTRATION (b)) stating that selling walnuts and saying that it is beneficial to human health define walnuts as a drug which has not been authorized and thus it was illegal:

"Because of these intended uses, your walnut products are drugs within the meaning of section […]*. Your walnut products are also new drugs under section* […] *because they are not generally recognized as safe and effective for the above referenced conditions. Therefore,* […]*, they may not be legally marketed with the above claims in the United States without an approved new drug application."* (U.S. FOOD AND DRUG ADMINISTRATION (b))

Sounds like a bad joke? One can maybe discuss the health benefits of walnuts, but stating that walnuts *"are not generally recognized as safe"* is a bit far-fetched if one would want to remain polite… In the same spirit, a few press articles were published (THE WALL STREET JOURNAL) (DAILY MAIL).

"They [walnuts] *may just be the hardest drugs on the market, if the FDA are to be believed."* (DAILY MAIL)

However the story continued. So the company removed any mention of health benefice associated to walnuts and after a class action procedure paid 2.6 million to consumers (LEXOLOGY).

If this example seems funny from a European point of view, one should know that similar battles with huge economic impact revolving around the notion of pharmaceuticals happen also in Europe. The example of the Danone Company in France is particularly interesting. They claimed that their product labelled as *"alicament"* (French mixed word from food and pharmaceutical) where beneficial to human health without any form of scientific proof and they never were disturbed by regulations (LE MONDE) (LIBERATION) (USINE NOUVELLE).

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APPENDIX 2: MATERIALS WASHING PROCEDURE

Translated and adapted from Lecomte, 2016.

The procedure is applied between every campaign.

A. Materials and products

Products

- GIGAPUR 13 (alkaline detergent) 5L bottle: to dilute at 2.5% with demineralized water
- GIGAPUR 14 (diluted acetic acid) 5L bottle
- Acetone
- Demineralized water

Materials

- Squeeze bottles, one for each product
- Brush for tubes exterior
- Bottle brush for tubes interior
- Drying rack
- Gloves
- Aluminium paper / plastic film (for clean glass storage)
- Adhesive tape
- Scissors

Infrastructure

- fume hood

B. Sampling bottle and other glass materials washing

Concerns:

- 25 L glass bottle used for primary sample
- 5 L glass bottle used for sampler washing
- […; *other glass materials for measuring points other than the WWTP inlet*]

For all the rinsing steps (except the first one), the product needs to be poured directly in the recipient, then agitated and put in contact with all the recipient surfaces by turning it slowly onto itself.

1. Washing with tap water to remove any particles (minimum 2 times)
2. Rinsing with GIGAPUR 13 diluted at 2.5 %
3. Rinsing with GIGAPUR 14
4. Abundant rinsing with demineralized water, a few litters for a 25 L bottle (2 times)
5. Rinsing with acetone (small quantities and discard in dedicated recipient, avoid contact with plastic elements)
6. Abundant rinsing with demineralized water (3 times, the first time without plastic cap). Important, otherwise COD (chemical oxygen demand) and BOD (biochemical oxygen demand) values can be hugely overestimated.
7. Let dry under fume hood.

C. Homogenization and distribution system washing

For homogenization system parts and distribution system pipes:

1. Washing with tap water (use brush and bottle brush when necessary)
2. Rinsing with GIGAPUR 13 diluted at 2.5 % using the squeeze bottle (2 min)
3. Rinsing with GIGAPUR 14 using the squeeze bottle (2 min)
4. Abundant rinsing with demineralized water using the squeeze bottle (a few times)
5. Let dry under fume hood.

For distribution pump:

1. Pump 2 L of demineralized water

D. Sampler washing

1. Materials and product preparation
2. Retrieve the sampling pipe, wash its exterior:
    - With tap water and a brush
    - Rinse with GIGAPUR 13 in a squeeze bottle
    - Rinse with GIGAPUR 14 in a squeeze bottle
    - Rinse abundantly with demineralized water in a squeeze bottle
    - If necessary, rinse the interior of the pipe with a bottle brush
3. Rinse the sample, first with tap water, then GIGAPUR 14 and finally demineralized water:
    - Insert sampling pipe in a dedicated 5L glass bottle filled with the rinsing product
    - Start the rinsing program: 10 successive samplings of 100 mL
4. Re-install the sampling pipe
5. In the sampler, retrieve the glass metering chamber and wash it according to procedure C

Re-install the glass metering chamber

APPENDIX 3: POSOLOGY DESCRIPTIONS

Table 44: Posology description for pharmaceutical specialities from urban pharmacies. Red text indicates that the speciality is either consumed at low levels (> 0.1 % of mass sold for the molecule) or not measured in wastewater form the urban catchment. In such cases, it is not necessary to model the speciality. PI: pain increase option.

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
7	Aztreonam, Other (intern use) 1 X 1000mg	1	1	-	0				
8	Aztreonam, Other 84 X 75mg	6.3	0.075	-	0				
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	Carbamazepine, Oral 1 X 20mg	0.02	0.02	Oral	0				
12	Carbamazepine, Oral 50 X 200mg	10	0.2	Oral	5.9	2 - 3	1 - 2	4 - 6	DB45 - DL10 - DS45
13	Ciprofloxacin, Other (intern use) 1 X 200mg	0.2	0.2	-	0				
14	Ciprofloxacin, Other 1 X 10.5mg	0.0105	0.0105	-	0				
15	Ciprofloxacin, Other 1 X 15mg	0.015	0.015	-	0				
16	Ciprofloxacin, Other 1 X 30mg	0.03	0.03	-	0				
17	Ciprofloxacin, Oral 1 X 500mg	0.5	0.5	Oral	0.1				
18	Ciprofloxacin, Oral 12 X 250mg	3	0.25	Oral	7.7				
19	Ciprofloxacin, Oral 12 X 500mg	6	0.5	Oral	92.2				
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	Diclofenac, Other 1 X 140mg	0.14	0.14	-	0				
37	Diclofenac, Oral 30 X 25mg	0.75	0.025	Oral	0				
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	Diclofenac, Other (intern use) 2 X 75mg	0.15	0.075	-	0				
40	Diclofenac, Other (intern use) 10 X 250mg	2.5	0.25	-	0				
41	Diclofenac, Other 20 X 100mg	2	0.1	-	0				
42	Diclofenac, Other 100 X 100mg	10	0.1	-	0				
43	Diclofenac, External use 10 X 140mg	1.4	0.14	Dermal	0				
44	Econazole, Other 1 X 150mg	0.15	0.15	Vaginal	21.4				
45	Econazole, Other 3 X 150mg	0.45	0.15	Vaginal	5.2				
46	Econazole, External use 1 X 300mg	0.3	0.3	Dermal	61.2				
47	Econazole, External use 1 X 1000mg	1	1	Dermal	8.9				
48	Econazole, Other 2 X 150mg	0.3	0.15	Vaginal	3.2				
49	Ethinylestradiol, Other (intern use) 3 X 0.02mg	0.00006	0.00002	-	0				
50	Ethinylestradiol, Other (intern use) 9 X 0.02mg	0.00018	0.00002	-	0.1				
51	Ethinylestradiol, Oral 63 X 0.015mg	0.000945	0.000015	Oral	4.3				
52	Ethinylestradiol, Oral 84 X 0.015mg	0.00126	0.000015	Oral	3.3				
53	Ethinylestradiol, Oral 63 X 0.02mg	0.00126	0.00002	Oral	22.8				
54	Ethinylestradiol, Oral 21 X 0.03mg	0.00063	0.00003	Oral	1.5				
55	Ethinylestradiol, Oral 28 X 0.03mg	0.00084	0.00003	Oral	0.1				
56	Ethinylestradiol, Oral 63 X 0.03mg	0.00189	0.00003	Oral	42				

57	Ethinylestradiol, Oral 84 X 0.03mg	0.00252	0.00003	Oral	5.1				
58	Ethinylestradiol, Oral 63 X 0.035mg	0.002205	0.000035	Oral	5.9				
59	Ethinylestradiol, Other 1 X 2.7mg	0.0027	0.0027	-	1.5				
60	Ethinylestradiol, Other 3 X 2.7mg	0.0081	0.0027	-	12				
61	Ethinylestradiol, Oral 21 X 0.015mg	0.000315	0.000015	Oral	0.2				
62	Ethinylestradiol, Oral 28 X 0.015mg	0.00042	0.000015	Oral	0.1				
63	Ethinylestradiol, Oral 21 X 0.02mg	0.00042	0.00002	Oral	0.4				
64	Ethinylestradiol, Oral 21 X 0.035mg	0.000735	0.000035	Oral	0.1				
65	Ethinylestradiol, Oral 21 X 0.05mg	0.00105	0.00005	Oral	0.1				
66	Ethinylestradiol, Oral 63 X 0.05mg	0.00315	0.00005	Oral	0.1				
67	Ethinylestradiol, Oral 15 X 0.05mg	0.00075	0.00005	Oral	0.1				
68	Ethinylestradiol, Oral 84 X 0.02mg	0.00168	0.00002	Oral	0				
69	Ethinylestradiol, Oral 28 X 0.02mg	0.00056	0.00002	Oral	0				
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	Ibuprofen, Oral 1 X 3000mg	3	3	Oral	0				
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	Ibuprofen, External use 1 X 100mg	0.1	0.1	Dermal	0				
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	Ibuprofen, Oral 10 X 200mg	2	0.2	Oral	0				
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	Ketoprofen, Oral 20 X 50mg	1	0.05	Oral	0				
104	Meropenem, Other (intern use) 10 X 1000mg	10	1	-	0				
105	Paracetamol, Oral 20 X 240mg	4.8	0.24	Oral	0				
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	Paracetamol, Oral 30 X 267mg	8.01	0.267	Oral	0				
108	Paracetamol, Oral 8 X 280mg	2.24	0.28	Oral	0				
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	Paracetamol, Other (intern use) 10 X 100mg	1	0.1	-	0				
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	Paracetamol, Oral 1 X 60mg	0.06	0.06	Oral	0				
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	Paracetamol, Other (intern use) 10 X 80mg	0.8	0.08	-	0				

129	Paracetamol, Other (intern use) 8 X 60mg	0.48	0.06	-	0				
130	Paracetamol, Other (intern use) 10 X 250mg	2.5	0.25	-	0				
131	Paracetamol, Other (intern use) 8 X 300mg	2.4	0.3	-	0				
132	Paracetamol, Other (intern use) 8 X 450mg	3.6	0.45	-	0				
133	Paracetamol, Oral 20 X 267mg	5.34	0.267	Oral	0				
134	Paracetamol, Oral 12 X 400mg	4.8	0.4	Oral	0				
135	Paracetamol, Oral 1 X 405mg	0.405	0.405	Oral	0				
136	Paracetamol, Other (intern use) 10 X 600mg	6	0.6	-	0				
137	Paracetamol, Oral 12 X 150mg	1.8	0.15	Oral	0				
138	Paracetamol, Oral 10 X 250mg	2.5	0.25	Oral	0				
139	Paracetamol, Oral 12 X 250mg	3	0.25	Oral	0				
140	Paracetamol, Other (intern use) 10 X 500mg	5	0.5	-	0				
141	Paracetamol, Oral 1 X 2700mg	2.7	2.7	Oral	0				
142	Paracetamol, Oral 12 X 100mg	1.2	0.1	Oral	0				
143	Paracetamol, Oral 12 X 80mg	0.96	0.08	Oral	0				
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	Paracetamol, Oral 1 X 6000mg	6	6	Oral	0				
146	Paracetamol, Oral 1 X 3000mg	3	3	Oral	0				
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	Propranolol, Other (intern use) 5 X 5mg	0.025	0.005	-	0				
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	Salicylic acid, Oral 20 X 267mg	5.34	0.267	Oral	0				
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	Salicylic acid, Oral 20 X 320mg	6.4	0.32	Oral	0				
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 4000mg	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

Table 45: Posology description for pharmaceutical specialities from the hospital central pharmacy. Red text indicates that the speciality is either consumed at low levels (> 0.1 % of mass sold for the molecule) or not measured in wastewater from the hospital catchment. In such cases, it is not necessary to model the speciality. Specialities names have been formatted to exclude brand names and to fit the "urban" data format.

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 100mg	0.1	0.1	Oral	46.1	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
2	Atenolol, Oral 50mg	0.05	0.05	Oral	53.7	1 - 1	1 - 2	1 - 1	DB45 - DL10 - DS45
3	Atenolol, Intravenous 5mg/10mL	0.005	0.005	Intravenous	0.2	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
4	Carbamazepine, Oral 200mg	0.2	0.2	Oral	34.2	2 - 3	1 - 2	4 - 6	DB45 - DL10 - DS45
5	Carbamazepine, Oral 400mg	0.4	0.4	Oral	24.2	2 - 3	1 - 1	4 - 6	DB45 - DL10 - DS45
6	Carbamazepine, Oral 200mg	0.2	0.2	Oral	41.6	2 - 3	1 - 2	4 - 6	DB45 - DL10 - DS45
7	Ciprofloxacin, Intravenous 200mg/100mL	0.2	0.2	Intravenous	5.6	2 - 3	1 - 1	4 - 6	DB45 - DL10 - DS45
8	Ciprofloxacin, Intravenous 400mg/200mL	0.4	0.4	Intravenous	3.2	2 - 3	1 - 1	4 - 6	DB45 - DL10 - DS45
9	Ciprofloxacin, Oral 500mg	0.5	0.5	Oral	91.2	2 - 2	1 - 1	4 - 6	DB45 - DL10 - DS45
10	Ciprofloxacin, Eyedrop 0.3% 5mL	0.01	0.01	-	0				
11	Diclofenac, Oral 100mg	0.1	0.1	Oral	9.6	1 - 2	1 - 1	4 - 6	Awake not out meal high +PI
12	Diclofenac, Oral 50mg	0.05	0.05	Oral	13.4	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
13	Diclofenac, Dermal 1% 50g	0.5	0.04	Dermal	77	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
14	Econazole, Dermal 1% 30g	0.3	0.04	Dermal	25.5				
15	Econazole, Dermal 1% 30g	0.3	0.04	Dermal	13.7				
16	Econazole, Dermal 1% 30g	0.3	0.04	Dermal	52.7				
17	Econazole, Dermal 1% 30g	0.3	0.04	Dermal	0.7				
18	Econazole, Vaginal 15mg	0.15	0.15	Vaginal	7.3				
19	Ibuprofen, Oral 200mg	0.2	0.2	Oral	100	1 - 3	1 - 2	5 - 6	Awake not out meal high +PI

20	Ketoprofen, Oral 100mg	0.1	0.1	Oral	35.1	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
21	Ketoprofen, Oral 100mg	0.1	0.1	Oral	30	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
22	Ketoprofen, Intravenous 100mg	0.1	0.1	Intravenous	33.8	1 - 3	1 - 1	4 - 6	Awake not out meal high +PI
23	Ketoprofen, Rectal 100mg	0.1	0.1	Rectal	1.1	1 - 3	1 - 1	4 - 6	Awake not out not meal +PI
24	Ketoprofen, Intravenous 100mg/2mL	0.1	0.1	Intravenous	0				
25	Meropenem, Intravenous 1g	1	1	Intravenous	100				
26	Paracetamol, Oral 500mg	0.5	0.5	Oral	2	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
27	Paracetamol, Oral 500mg	0.5	0.5	Oral	2	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
28	Paracetamol, Oral 3% 90mL	0.01	0.01	Oral	0				
29	Paracetamol, Oral 500mg	0.5	0.5	Oral	58.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
30	Paracetamol, Rectal 1 000mg	1	1	Rectal	0.2	1 - 3	1 - 1	4 - 5	Awake not out not meal +PI
31	Paracetamol, Oral 1 000mg	1	1	Oral	13.5	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
32	Paracetamol, Oral 100mg	0.1	0.1	Oral	0				
33	Paracetamol, Rectal 100mg	0.1	0.1	Rectal	0				
34	Paracetamol, Rectal 150mg	0.15	0.15	Rectal	0				
35	Paracetamol, Oral 200mg	0.2	0.2	Oral	0.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
36	Paracetamol, Rectal 200mg	0.2	0.2	Rectal	0				
37	Paracetamol, Oral 300mg	0.3	0.3	Oral	0.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
38	Paracetamol, Rectal 300mg	0.3	0.3	Rectal	0				
39	Paracetamol, Oral 500mg	0.5	0.5	Oral	9.6	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
40	Paracetamol, Oral 500mg	0.5	0.5	Oral	3.1	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
41	Paracetamol, Intravenous 1g/100mL	1	1	Intravenous	10.8	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
42	Paracetamol, Intravenous 500mg/50mL	0.5	0.5	Intravenous	0.3	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
43	Propranolol, Oral 160mg	0.16	0.16	Oral	26.7	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
44	Propranolol, Intravenous 5mg/5mL	0.005	0.005	Intravenous	0.2	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
45	Propranolol, Oral 40mg	0.04	0.04	Oral	73.2	1 - 2	1 - 2	4 - 6	DB45 - DL10 - DS45
46	Salicylic acid, Oral 160mg	0.16	0.16	Oral	26.6	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
47	Salicylic acid, Oral 300mg	0.3	0.3	Oral	2.4	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
48	Salicylic acid, Oral 75mg	0.075	0.075	Oral	38.8	1 - 1	1 - 1	1 - 1	DB45 - DL10 - DS45
49	Salicylic acid, Oral 1 000mg	1	1	Oral	19.2	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
50	Salicylic acid, Oral 250mg	0.25	0.25	Oral	1.6	1 - 3	1 - 1	4 - 5	Awake not out meal high +PI
51	Salicylic acid, Oral 500mg	0.5	0.5	Oral	4.9	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI

52	Salicylic acid, Intravenous 500mg	0.5	0.5	Intravenous	6.5	1 - 6	1 - 1	4 - 5	Awake not out meal high +PI
53	Sulfamethoxazole, Oral 800mg	0.8	0.8	Oral	66	1 - 1	1 - 1	1 - 1	Awake not out not meal
54	Sulfamethoxazole, Oral 200mg	0.2	0.2	Oral	0.1	1 - 1	1 - 1	1 - 1	Awake not out not meal
55	Sulfamethoxazole, Intravenous 800mg	0.8	0.8	Intravenous	33.9	1 - 1	1 - 1	1 - 1	Awake not out not meal
56	Vancomycin, Intravenous 500mg	0.5	0.5	Intravenous	100	1 - 4	1 - 2	6 - 6	Awake not out meal high

APPENDIX 4: METABOLIC PARAMETERS

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	$k_{absoprtion}$ (h^{-1})	$k_{elimination}$ (h^{-1})	F_{InBody} (%)	$F_{InSewerDirect}$ (%)	$F_{Absorption}$ (%)	$F_{GutUnchanged}$ (%)	$F_{Elimination\ PrentCompound}$ (%)	$F_{Elimination\ Gluco}$ (%)	$F_{Eliminatio\ Sulfo}$ (%)	$F_{Global\ Excretion}$ (%)
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
	IV	-		-	-	-	-				85 - 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
Ciprofloxacin	**oral**	1.44 - 3.1	0.1 - 0.17	100 - 100	0 - 0	70 - 80	100 - 100	75 - 80	0 - 0	2 - 5	5 - 17
	IV	-		-	-	-	-				80 - 85
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						20 - 74
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						21 - 77
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
	IV	-		-	-	-	-				73 - 100
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
	IV	-		-	-	-	-				81 - 98
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
	IV	-		-	-	-	-				11 - 26
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
	IV	-		-	-	-	-				12 - 20
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
	IV	-		-	-	-	-				27 - 49
Vancomycin	**IV**	-	0.09 - 0.35	-	-	-	-	85 - 95	0 - 0	0 - 0	85 - 95

APPENDIX 5: ELEMENTS OF THE URBAN CATCHMENT MODEL

The different elements used in the urban catchment model are detailed in table 46, table 47 and table 48.

Table 46: List of the main source areas used in the urban catchment model

Index	Name	Number of			Lengths of sewer between the discharge points and the outlet of the area	
		households N_{house}	workers N_{worker}	hospital beds N_{H-bed}	Average $\bar{L}$ (m)	Standard deviation $\sigma(L)$ (m)
1	La Muraz	140	81	0	420	42
2	Monnetier-Mornex	928	474	0	2 500	250
3	Reignier-Esery (1/2)	251	283	0	2 500	250
4	Arthaz-Pont-Notre-Dame	309	135	0	1 700	170
5	Bonne	100	703	0	500	50
6	Nangy (1/2)	362	200	0	600	60
7	Arbusigny	100	152	0	350	35
8	Pers-Jussy	462	440	0	1 500	150
9	Reignier-Esery (2/2)	1 249	1 411	0	3 000	300
10	Arenthon	137	218	0	250	25
11	Scientrier	358	359	0	890	89
12	Nangy (2/2)	66	36	0	110	11
13	Fillinges (1/3)	250	226	0	1 300	130
14	Fillinges (2/3)	596	539	0	1 800	180
15	Marcellaz	283	70	0	600	60
16	Fillinges (3/3)	209	189	0	350	35
17	Faucigny	103	78	0	350	35
18	Contamine-sur-Arve	416	1 421	0	2 000	200

Table 47: List of the pipe elements used in the urban catchment model

Pipe index	Pipe length L (m)
1	7 042
2	89
3	1 603
4	698
5	710
6	825
7	3 033
8	8 933
9	4 353
10	939
11	2 087
12	677
13	1 287
14	450
15	1 334
16	547
17	1 604
18	47
19	528
20	606
21	2 656
22	354
23	1 586
24	1 171
25	2 158
26	4 132
27	172

Table 48: List of the pumping station elements used in the urban catchment model

Index	Number of pumps	Pump index	maximum capacity of the pumps C_i (m^3/h)	Volume thresholds (m^3)	
				Start $V_{on,i}$	Stop $V_{off,i}$
1	2	1	50.8	2.212	0.402
		2	65.2	2.614	0.402
2	2	1	50.9	5.322	1.521
		2	64.8	6.082	1.521
3	2	1	50	4.856	0.809
		2	50	8.094	0.809
4	2	1	84.17	5.104	1.914
		2	91.87	6.379	1.914
5	2	1	30.6	1.571	0.314
		2	30.6	2.827	0.628
6	2	1	50	2.722	1.555
		2	50	3.499	1.555
7	2	1	39.7	2.614	0.804
		2	39.7	3.016	0.804
8	2	1	189	4.021	0.704
		2	189	4.423	0.704

APPENDIX 6: ELEMENTS OF THE CHAL HOSPITAL MODEL

The different elements used in the CHAL hospital model are detailed in table 49 and table 50.

Table 49: List of the main source areas used in the CHAL hospital model

Index	Name	Number of			Lengths of sewer between the discharge points and the outlet of the area	
		households N_{house}	workers N_{worker}	hospital beds N_{H-bed}	Average $\bar{L}$ (m)	Standard deviation $\sigma(L)$ (m)
1	CHAL	0	0	450	200	50

Table 50: List of the pipe elements used in the CHAL hospital model

Pipe index	Pipe length L (m)
1	500

APPENDIX 7: BEST PARAMETERS SET DETERMINATION METHOD

Given N_{Set}: the number of sets of parameters tested;

Given $N_{stochastic}$: the number of stochastic repetition run for each N_{Set};

Given $Q_{Modelled,i,j}$: the modelled wastewater flow time series ($1 \leq i \leq N_{Set}$ and $1 \leq i \leq N_{Stochastic}$) ($m^3/s$);

Given N_{Dates}: the number of measured wastewater flow time series picked for calibration;

Given $Q_{Measured,k}$: the measured wastewater flow time series ($1 \leq k \leq N_{Dates}$) (m^3/s);

And given $P_{Calibration}$: the time period selected for calibration;

The best parameter set is determined as follow:

- Each of the N_{Dates} measured wastewater flow time series is smoothed with a 30 minutes mobile mean.
- A parasitic water baseline is calculated for each measured wastewater flow time series (chapter 6).
- Each modelled wastewater flow time series is smoothed with a 30 minutes mobile mean.
- For each parameter set, an average smoothed modelled time series is calculated:

$$\overline{Q_{Smoothed\ Modelled,i}} = \frac{\sum_{j=1}^{N_{Stochastic}} Q_{Smoothed\ Modelled,i,j}}{N_{Stochastic}}$$

  With:
  i: parameter set index ($1 \leq i \leq N_{Set}$)
  $\overline{Q_{Smoothed\ Modelled,i}}$: average smoothed modelled time series of the parameter set i (m^3/s)
  j: index of the stochastic repetition ($1 \leq i \leq N_{Stochastic}$)
  $Q_{Smoothed\ Modelled,i,j}$: smoothed modelled time series of the parameter set i and stochastic repetition j (m^3/s)

- For each measured time series, N_{Set} NSE scores are calculated, taking into account the parasitic water baseline:

$$NSE_{k,i} = f_{NSE}(Q_{Smoothed\ Measured,k}; \overline{Q_{Smoothed\ Modelled,i}} + PWB_k; P_{Calibration})$$

  With:
  k: index of the measured time series ($1 \leq k \leq N_{Dates}$)
  i: parameter set index ($1 \leq i \leq N_{Set}$)
  $NSE_{k,i}$: NSE score of date k and parameter set i
  $f_{NSE}(x; y; P)$: return the NSE score of the measured time series x and modelled time series y for the time period P (chapter 5)
  $Q_{Smoothed\ Measured,k}$: smoothed measured time series of date k (m^3/s)
  $\overline{Q_{Smoothed\ Modelled,i}}$: average smoothed modelled time series of the parameter set i (m^3/s)
  PWB_k: parasitic water baseline of date k (m^3/s)

  This provides $N_{Dates} \times N_{Set}$ NSE scores.

- For each parameter set, an average NSE score is calculated:

$$\overline{NSE_i} = \frac{\sum_{k=1}^{N_{Dates}} NSE_{k,i}}{N_{Dates}}$$

  With:
  i: parameter set index ($1 \leq i \leq N_{Set}$)
  $\overline{NSE_i}$: average NSE score of parameter set i
  k: index of the measured time series ($1 \leq k \leq N_{Dates}$)

$NSE_{k,i}$: NSE score of date k and parameter set i

- The best parameter set is the one with the higher average NSE score $\overline{NSE_i}$

APPENDIX 8: SALES EVOLUTION FOR THE CORRECTED URBAN PHARMACEUTICALS SALES TIME SERIES

Sales evolution of all the molecules for the corrected urban pharmaceuticals sales time series are presented on the next four figures (figure 77, figure 78, figure 79 and figure 80). Only full and consecutive years of data are kept. In order to compare their monthly variations, they are normalized by the annual average. Analysis reveals that only 3 molecules (Ibuprofen, Paracetamol and Salicylic acid) present a clear seasonal effect in their sales. However, those results are to be considered with caution since they were obtained with only 2 years.

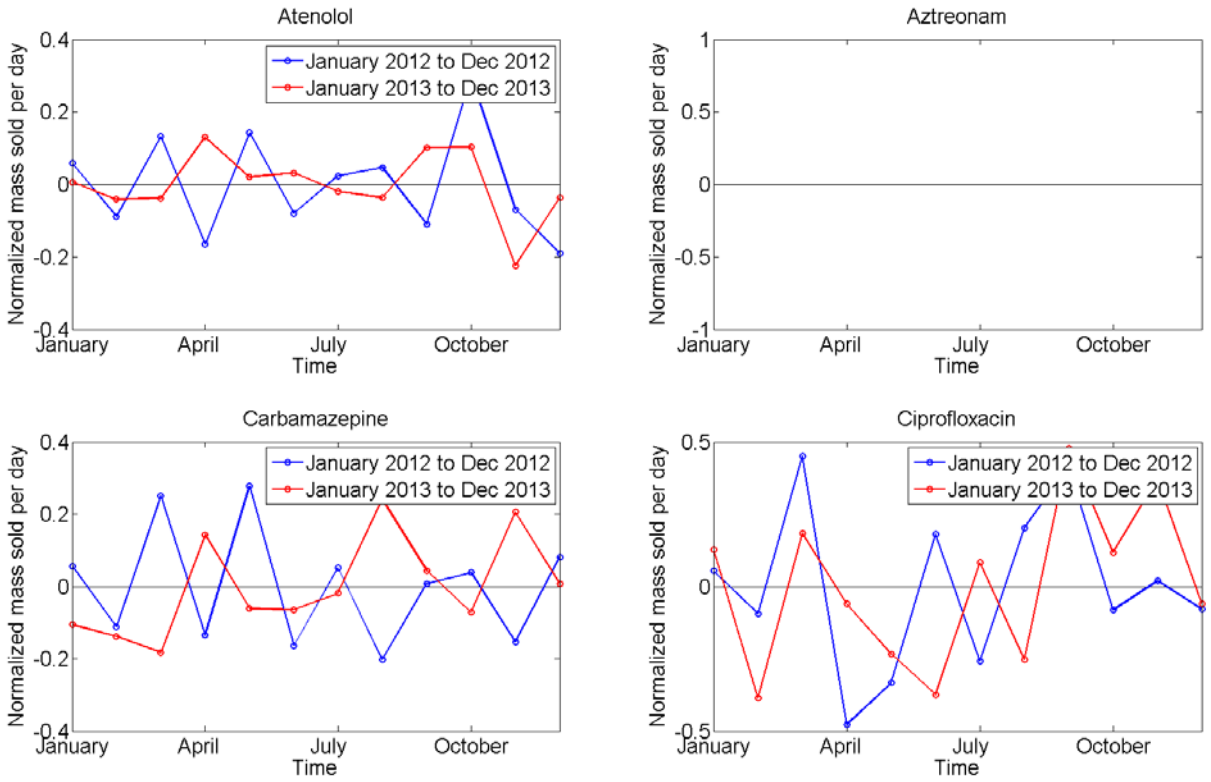

Figure 77: Sales evolution for Atenolol, Aztreonam, Carbamazepine and Ciprofloxacin for the corrected urban pharmaceuticals sales time series.

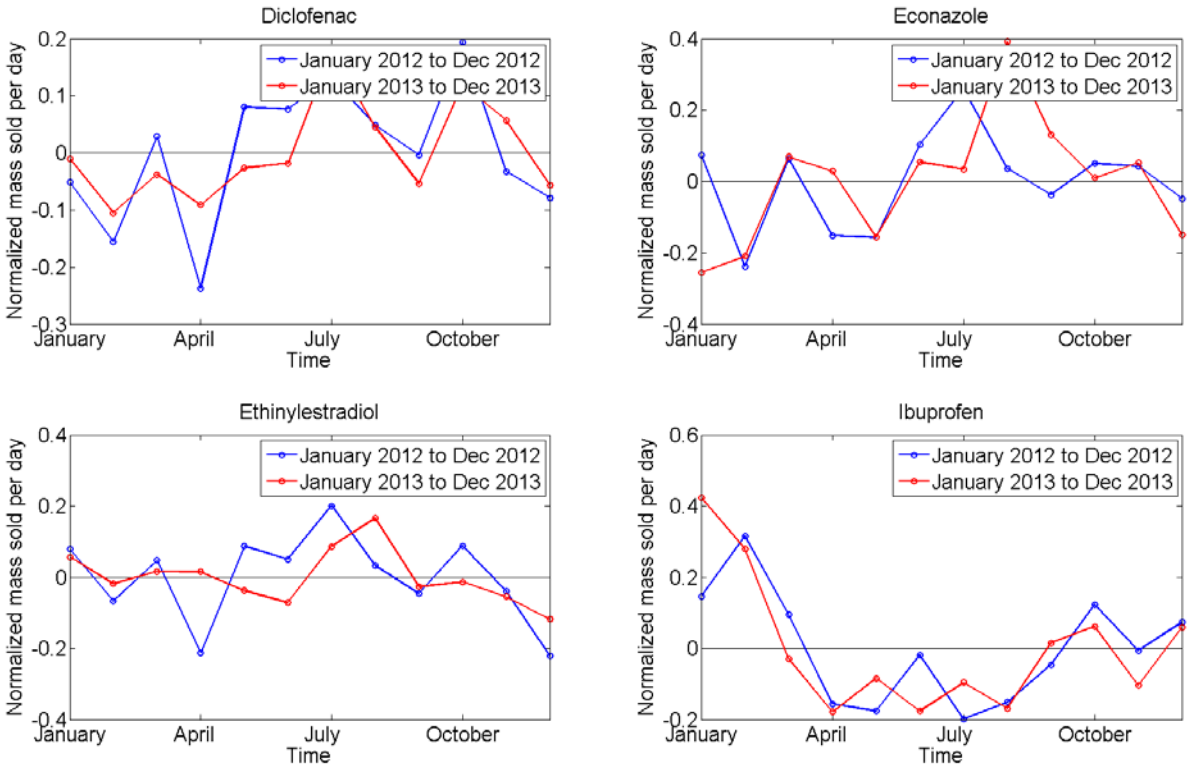

Figure 78: Sales evolution for Diclofenac, Econazole, Ethinylestradiol and Ibuprofen for the corrected urban pharmaceuticals sales time series.

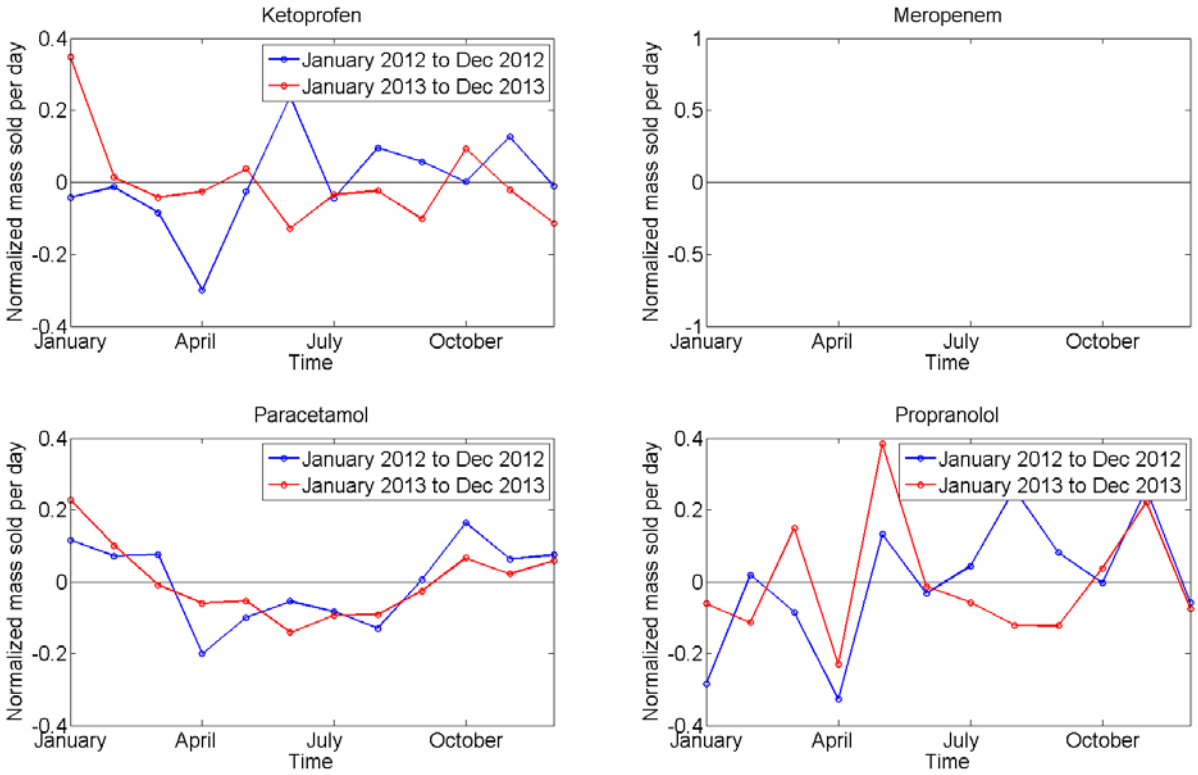

Figure 79: Sales evolution for Ketoprofen, Meropenem, Paracetamol and Propranolol for the corrected urban pharmaceuticals sales time series.

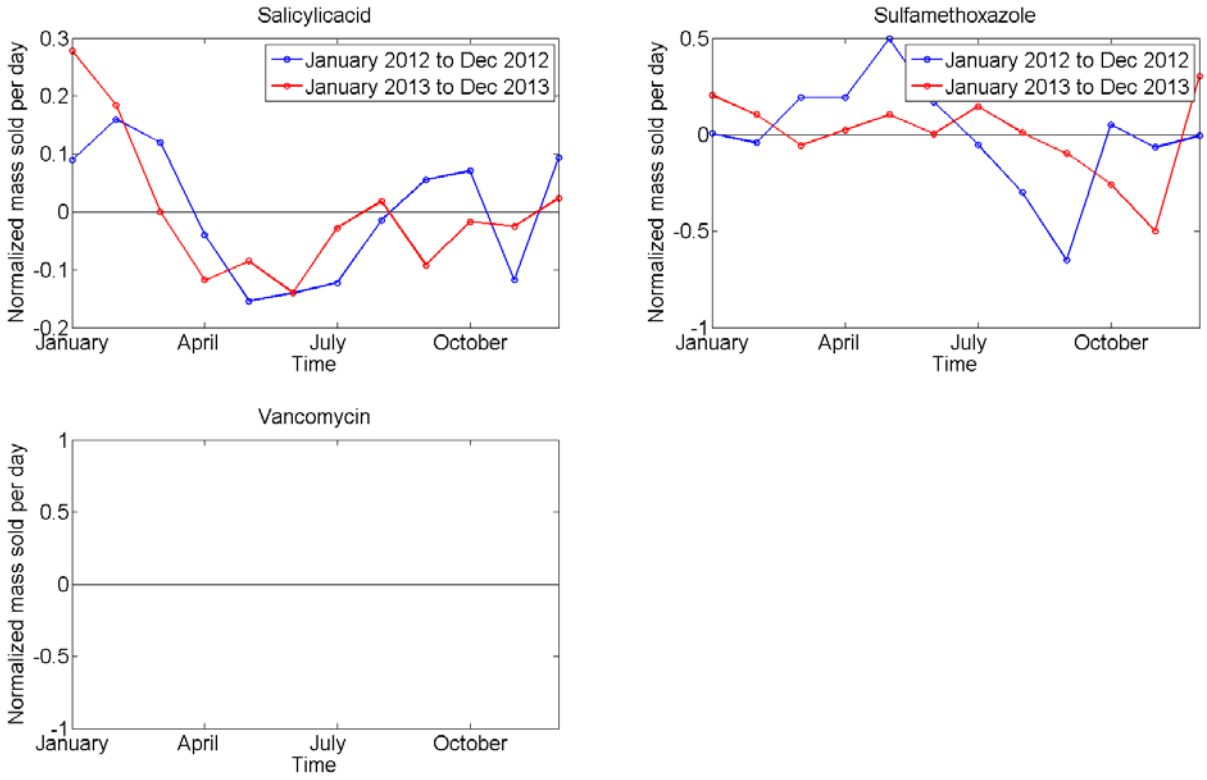

Figure 80: Sales evolution for Salicylic acid, Sulfamethoxazole and Vancomycin for the corrected urban pharmaceuticals sales time series.

APPENDIX 9: SALES EVOLUTION FOR THE CORRECTED CHAL PHARMACEUTICALS DISTRIBUTIONS TIME SERIES

Distributions evolution of all the molecules for the corrected CHAL pharmaceuticals distributions time series are presented on the next four figures (figure 81, figure 82, figure 83 and figure 84). Only full and consecutive years of data are kept. Weekly distributions were rearranged in monthly distributions. In order to compare their monthly variations, they are normalized by the annual average. Analysis reveals that only 2 molecules (Ibuprofen and Paracetamol) present a clear seasonal effect in their sales. However, those results are to be considered with caution since they were obtained with only 2 years.

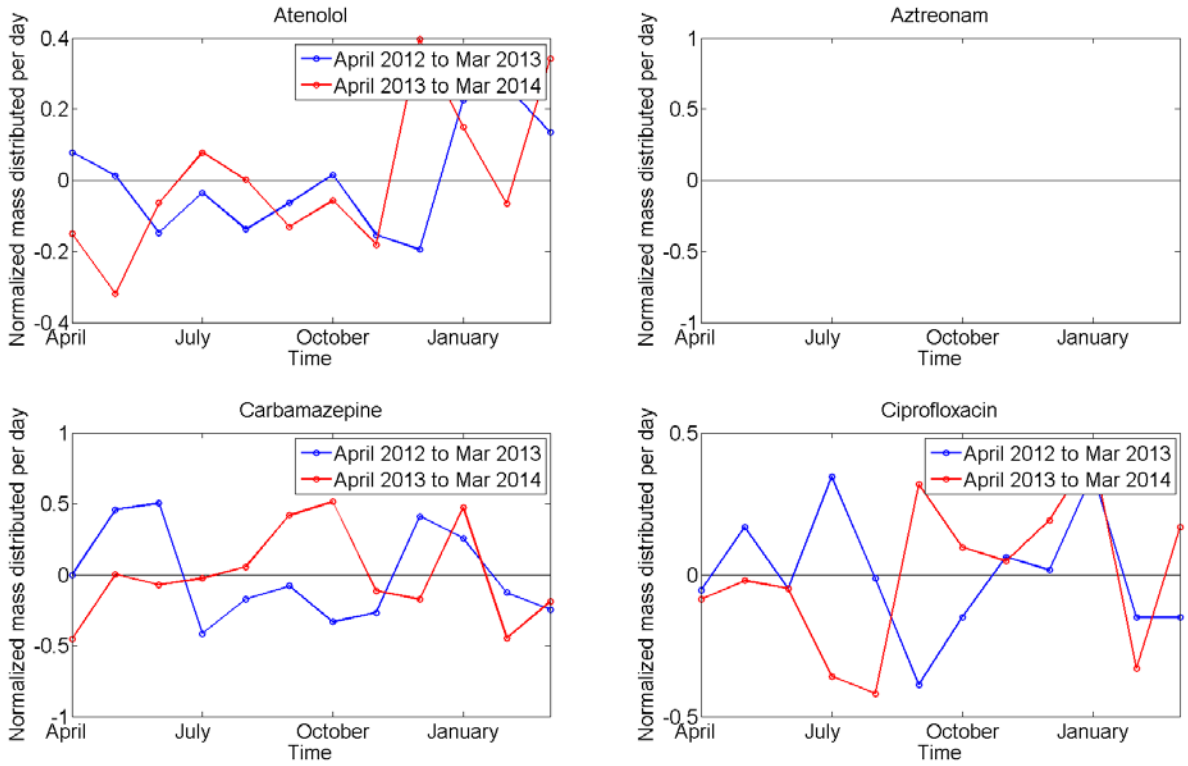

Figure 81: Sales evolution for Atenolol, Aztreonam, Carbamazepine and Ciprofloxacin for the corrected CHAL pharmaceuticals distributions time series.

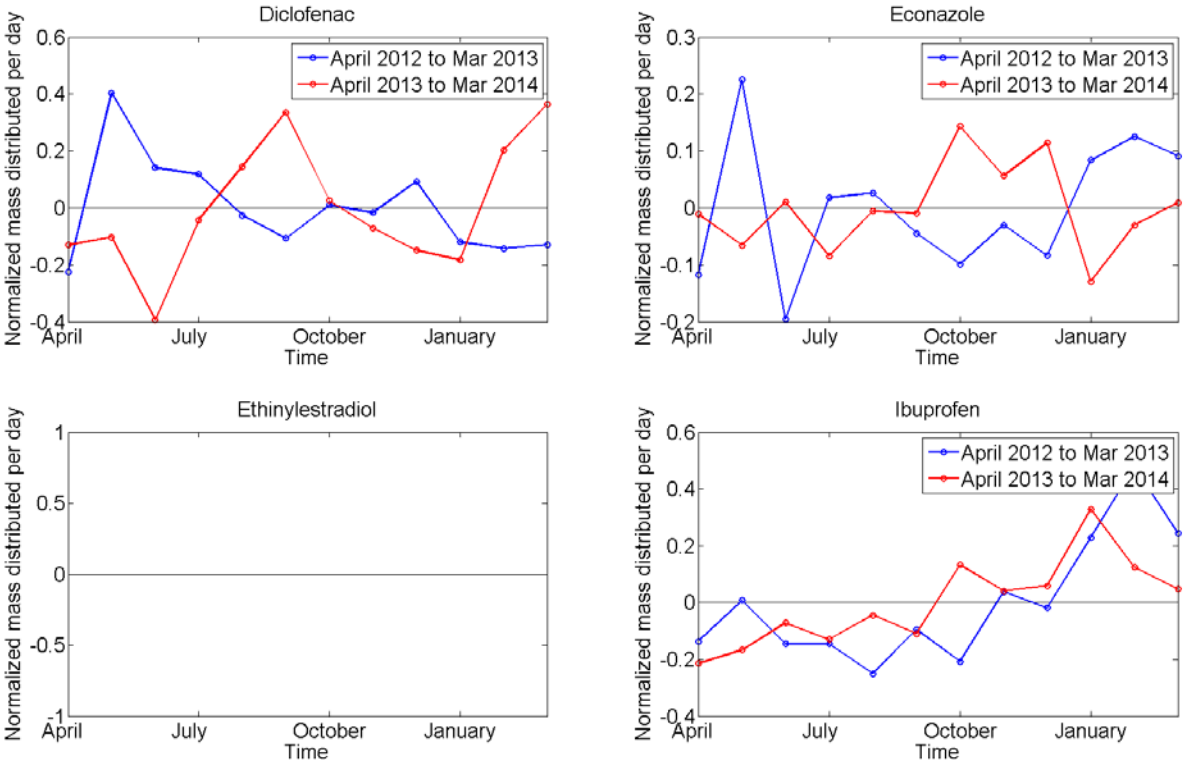

Figure 82: Sales evolution for Diclofenac, Econazole, Ethinylestradiol and Ibuprofen for the corrected CHAL pharmaceuticals distributions time series.

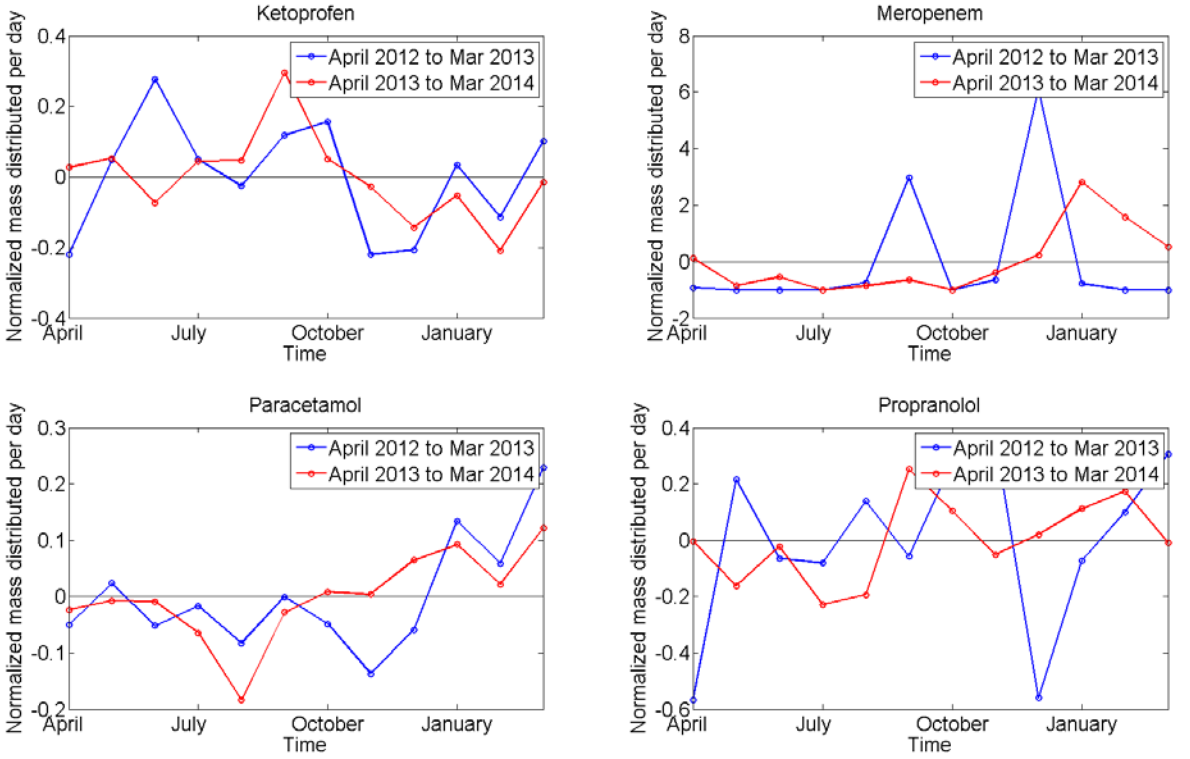

Figure 83: Sales evolution for Ketoprofen, Meropenem, Paracetamol and Propranolol for the corrected CHAL pharmaceuticals distributions time series.

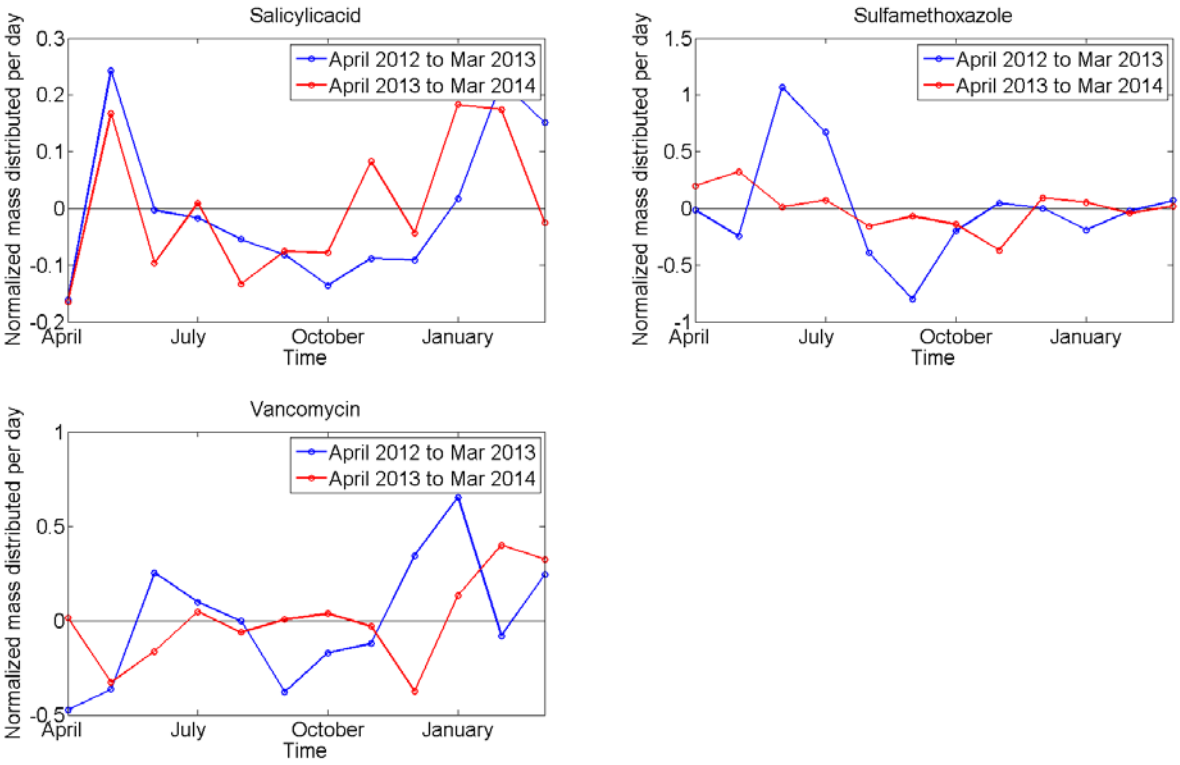

Figure 84: Sales evolution for Salicylic acid, Sulfamethoxazole and Vancomycin for the corrected CHAL pharmaceuticals distributions time series.

APPENDIX 10: DAILY PHARMACEUTICALS CONCENTRATIONS AND LOADS OF THE URBAN CATCHMENT

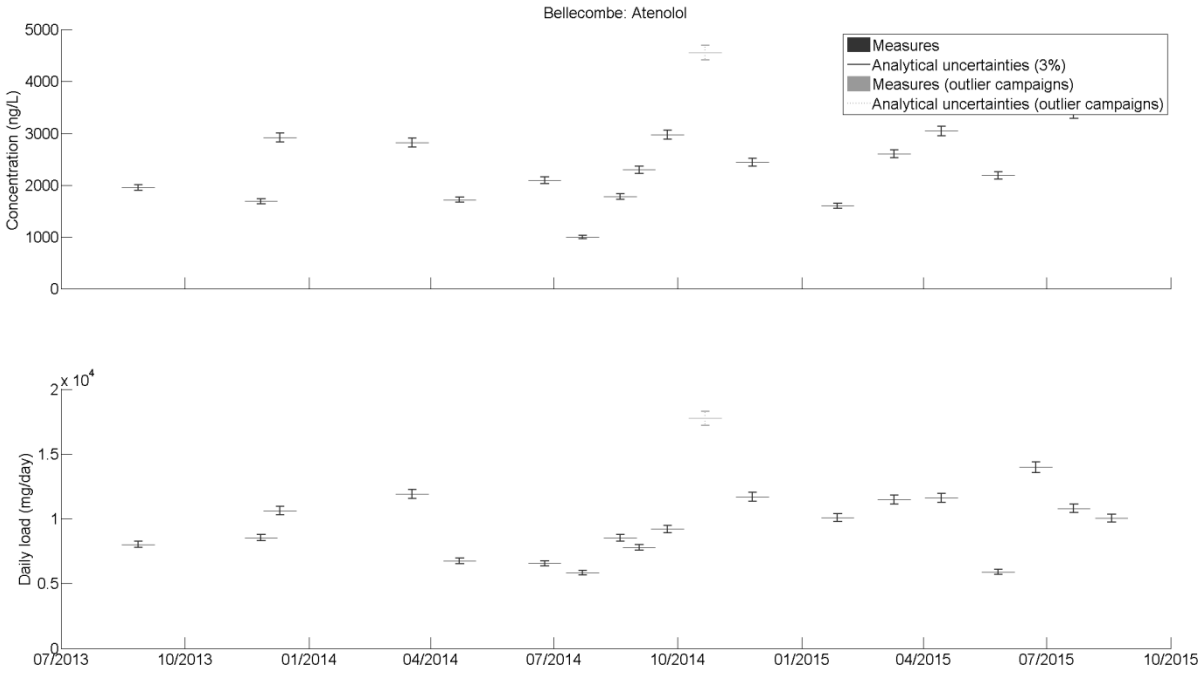

Figure 85: Time series of the daily concentrations and loads of the urban catchment for Atenolol.

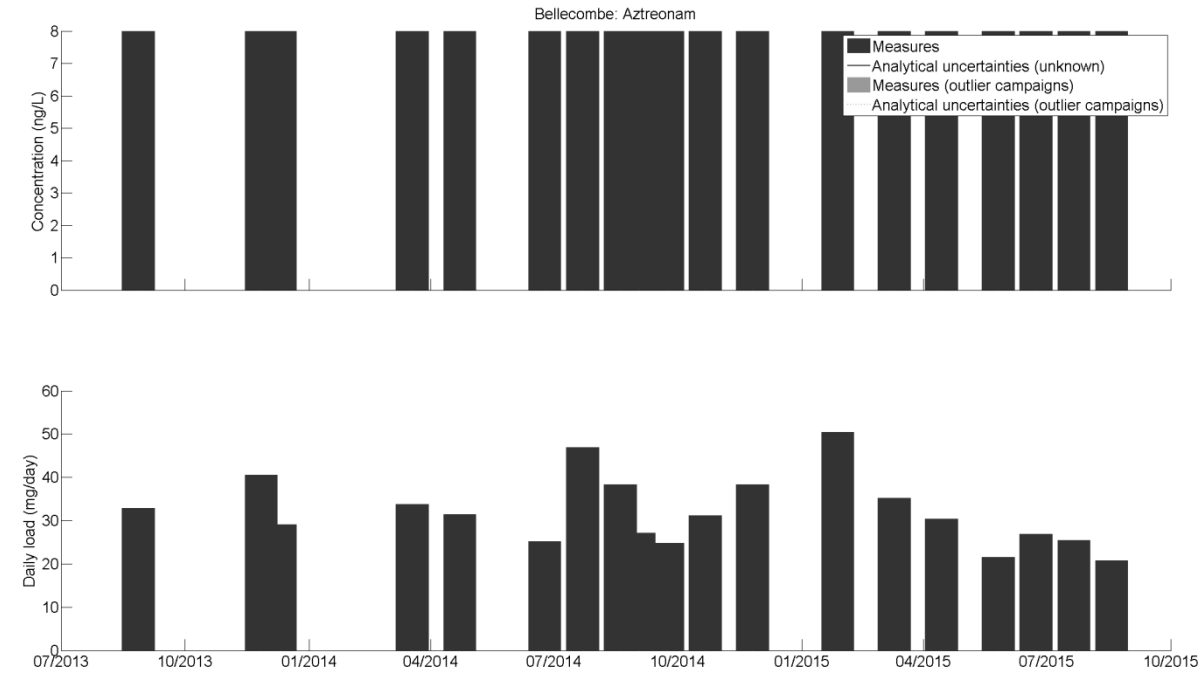

Figure 86: Time series of the daily concentrations and loads of the urban catchment for Aztreonam.

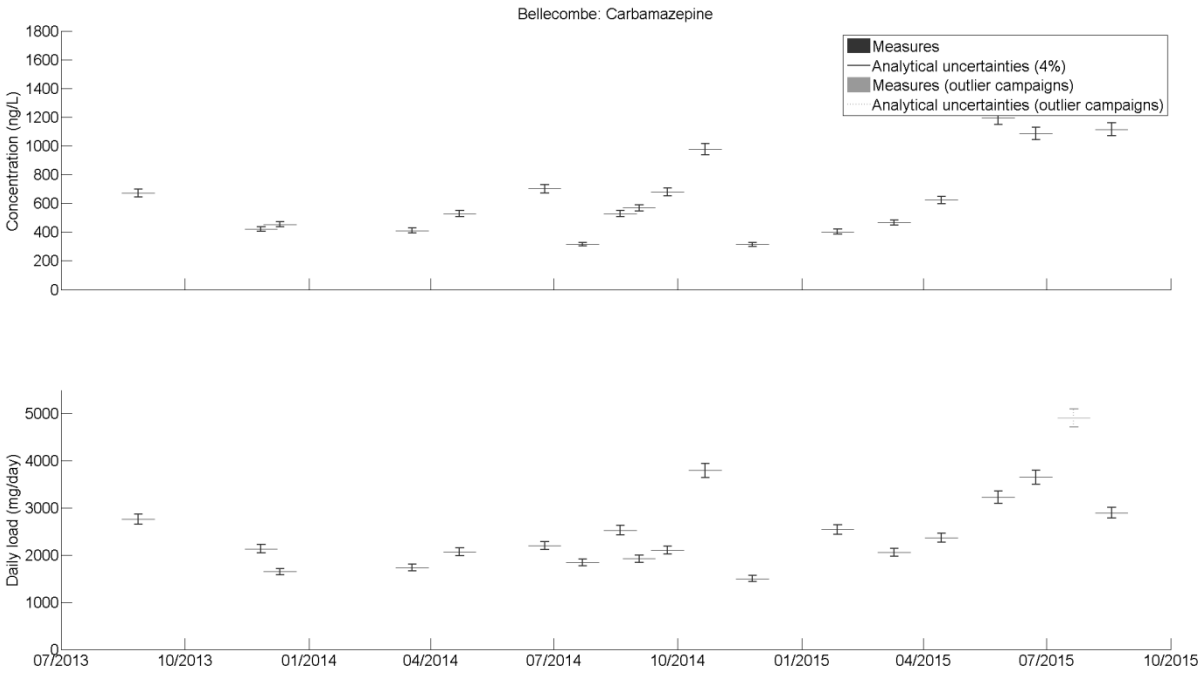

Figure 87: Time series of the daily concentrations and loads of the urban catchment for Carbamazepine.

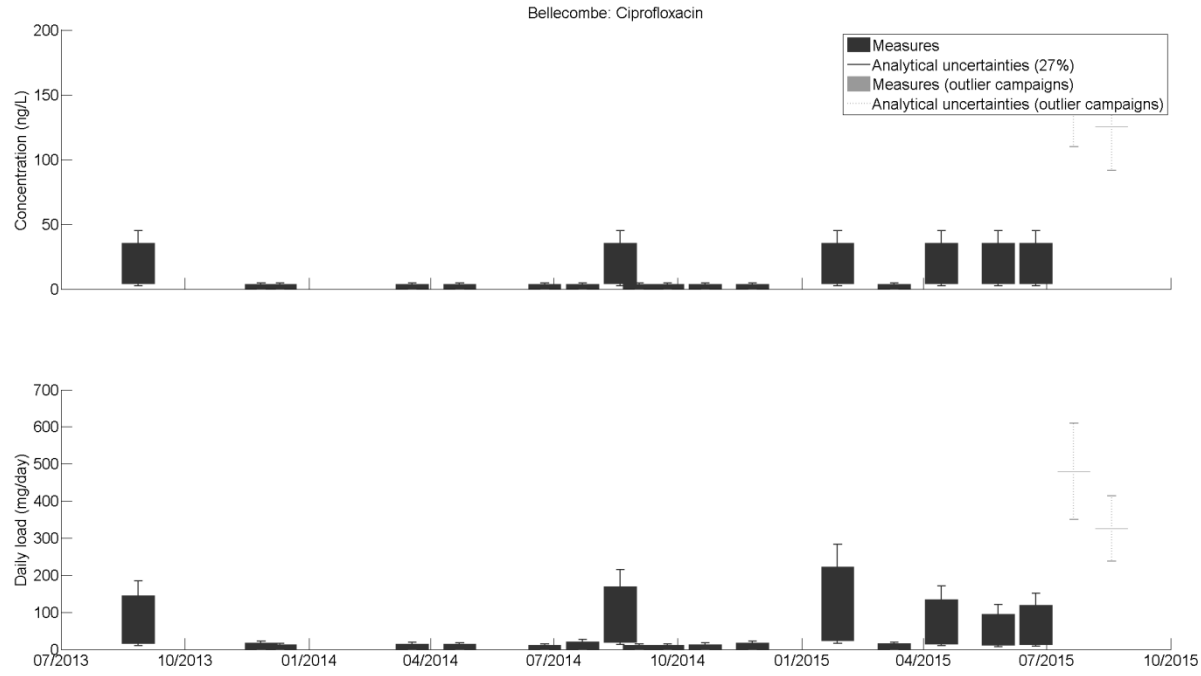

Figure 88: Time series of the daily concentrations and loads of the urban catchment for Ciprofloxacin.

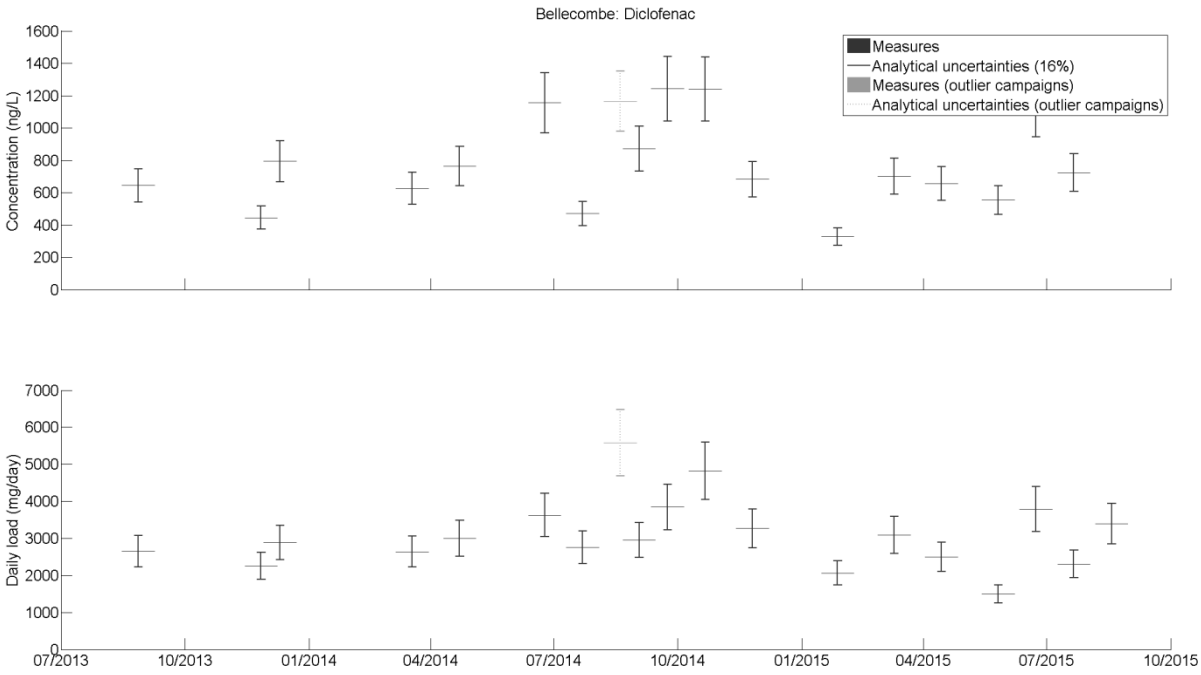

Figure 89: Time series of the daily concentrations and loads of the urban catchment for Diclofenac.

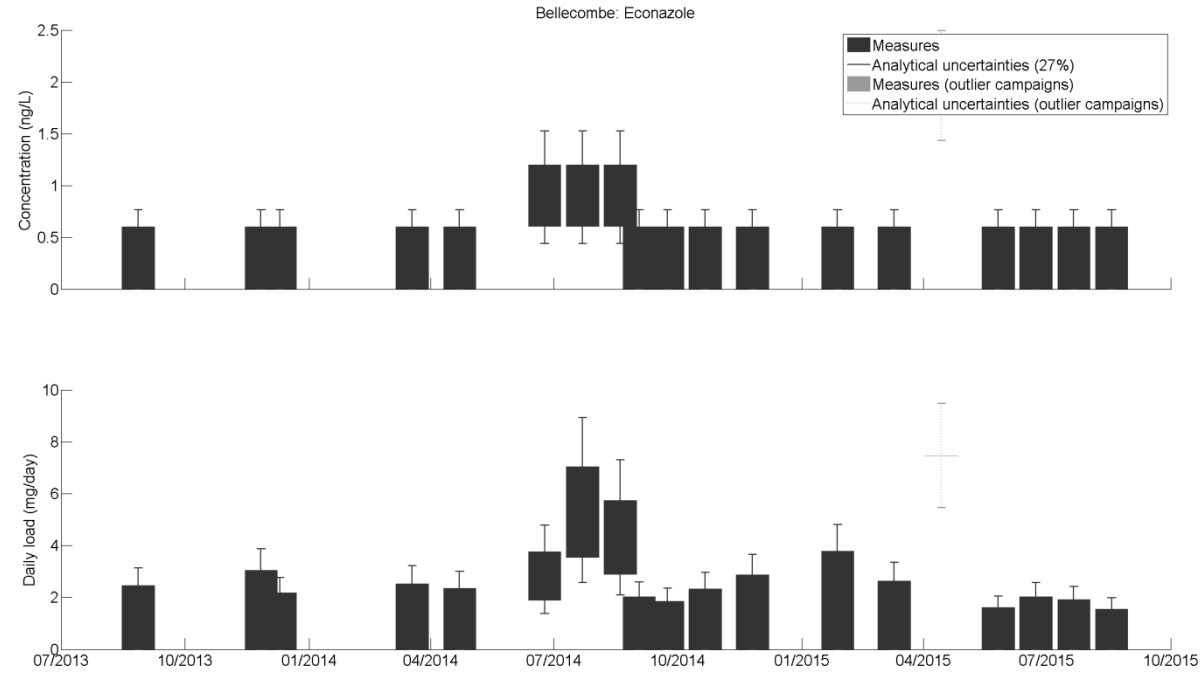

Figure 90: Time series of the daily concentrations and loads of the urban catchment for Econazole.

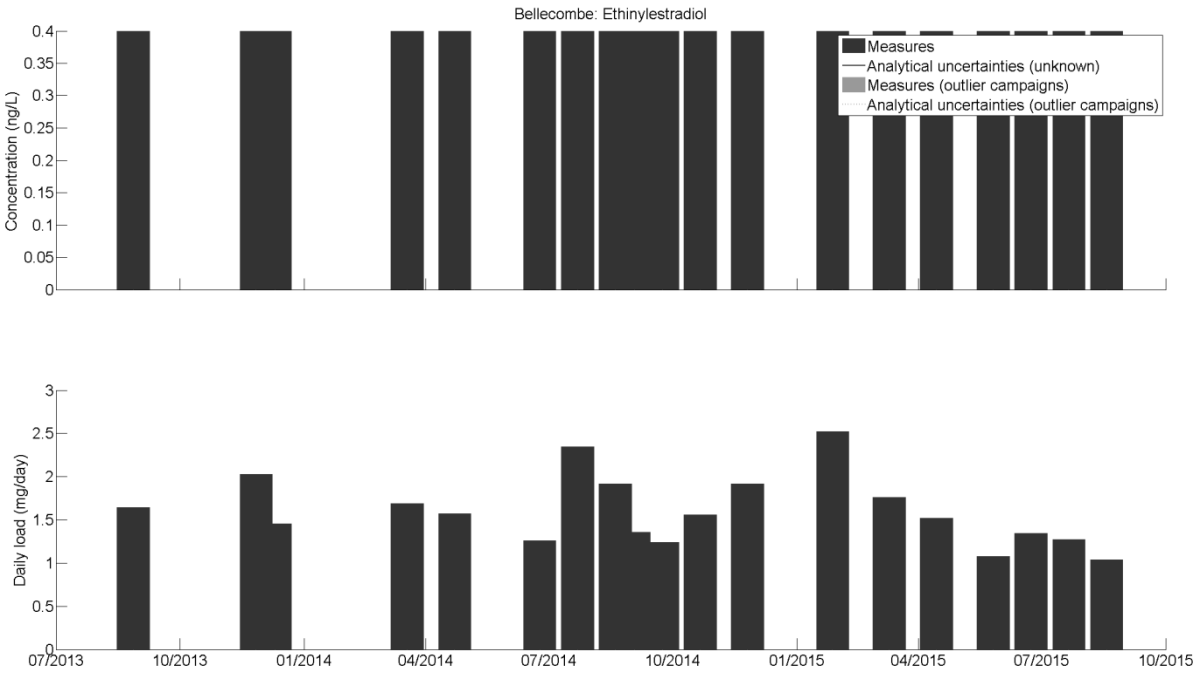

Figure 91: Time series of the daily concentrations and loads of the urban catchment for Ethinylestradiol.

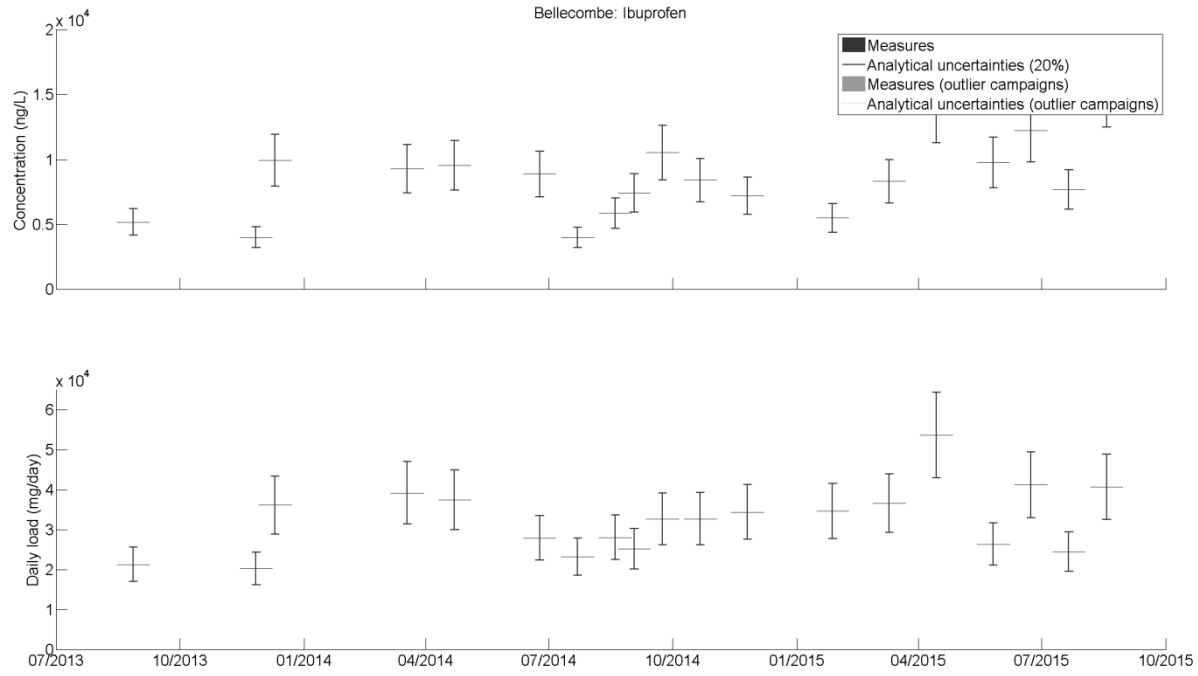

Figure 92: Time series of the daily concentrations and loads of the urban catchment for Ibuprofen.

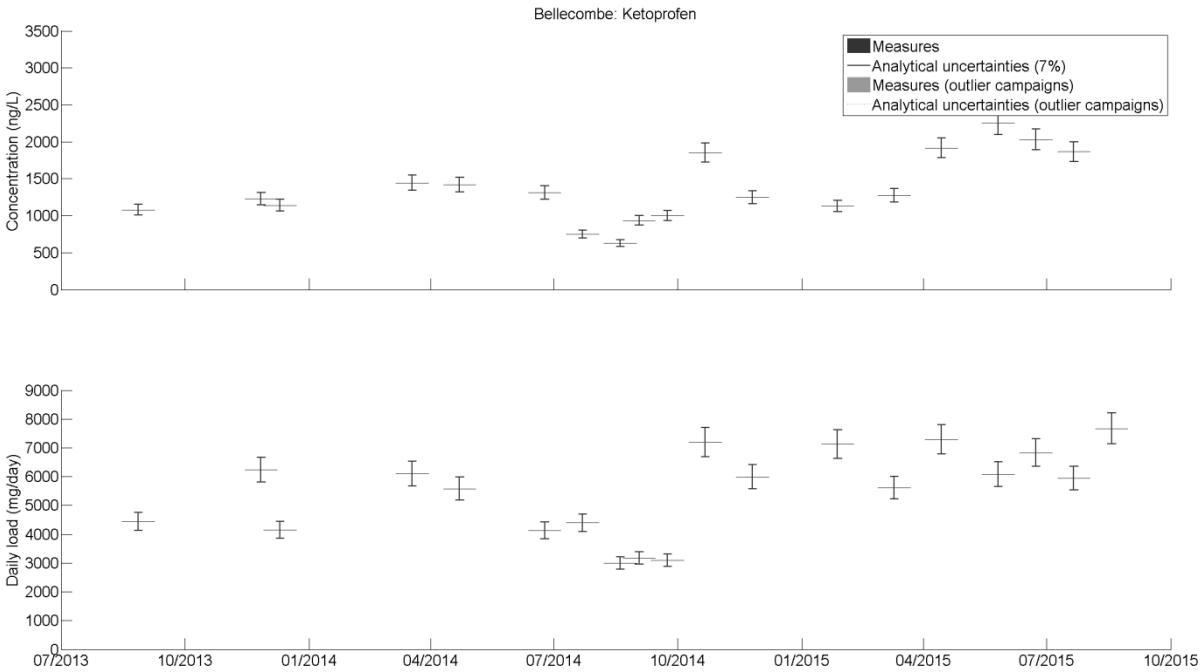

Figure 93: Time series of the daily concentrations and loads of the urban catchment for Ketoprofen.

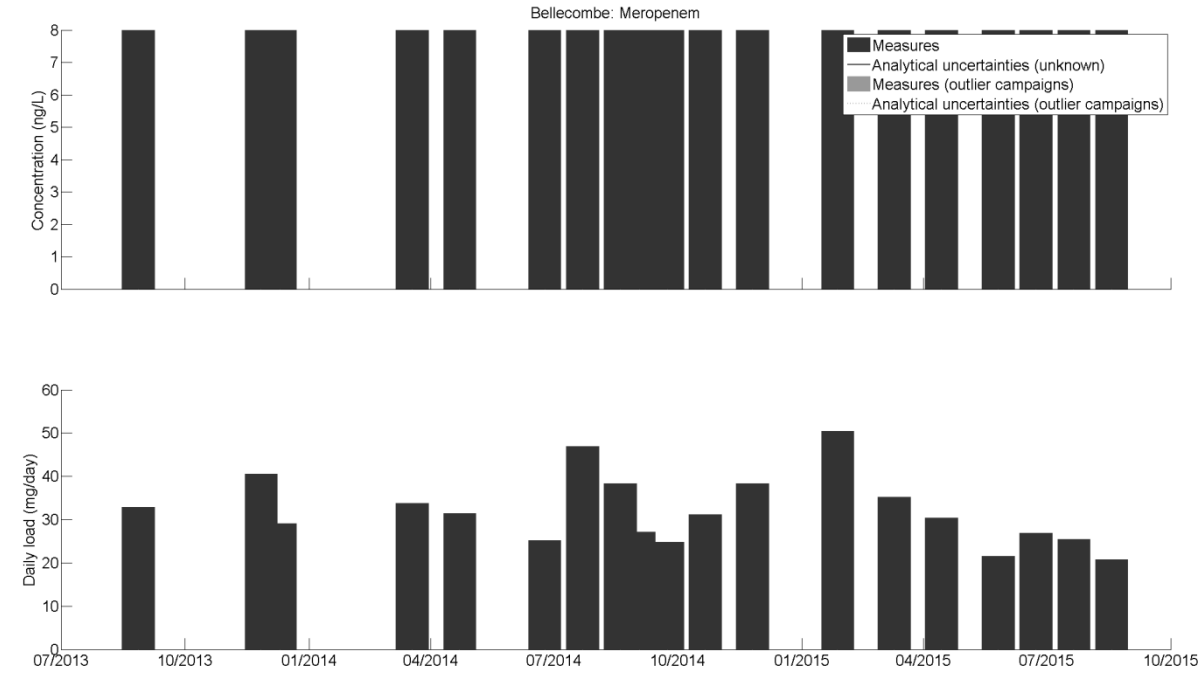

Figure 94: Time series of the daily concentrations and loads of the urban catchment for Meropenem.

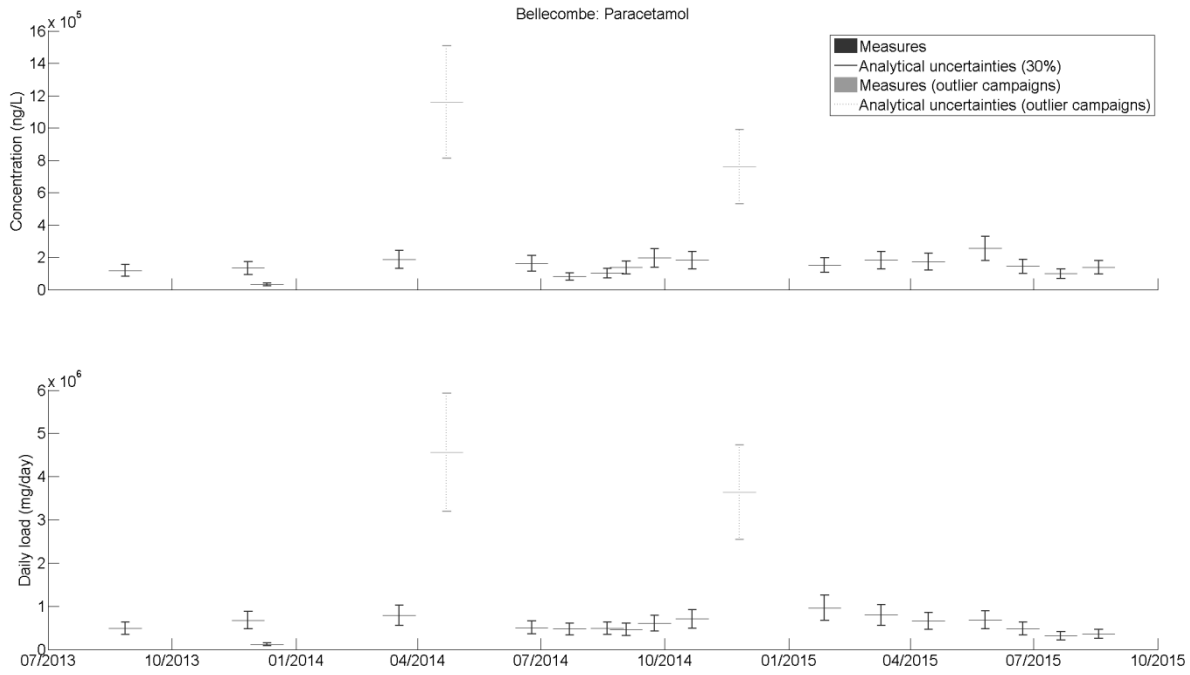

Figure 95: Time series of the daily concentrations and loads of the urban catchment for Paracetamol.

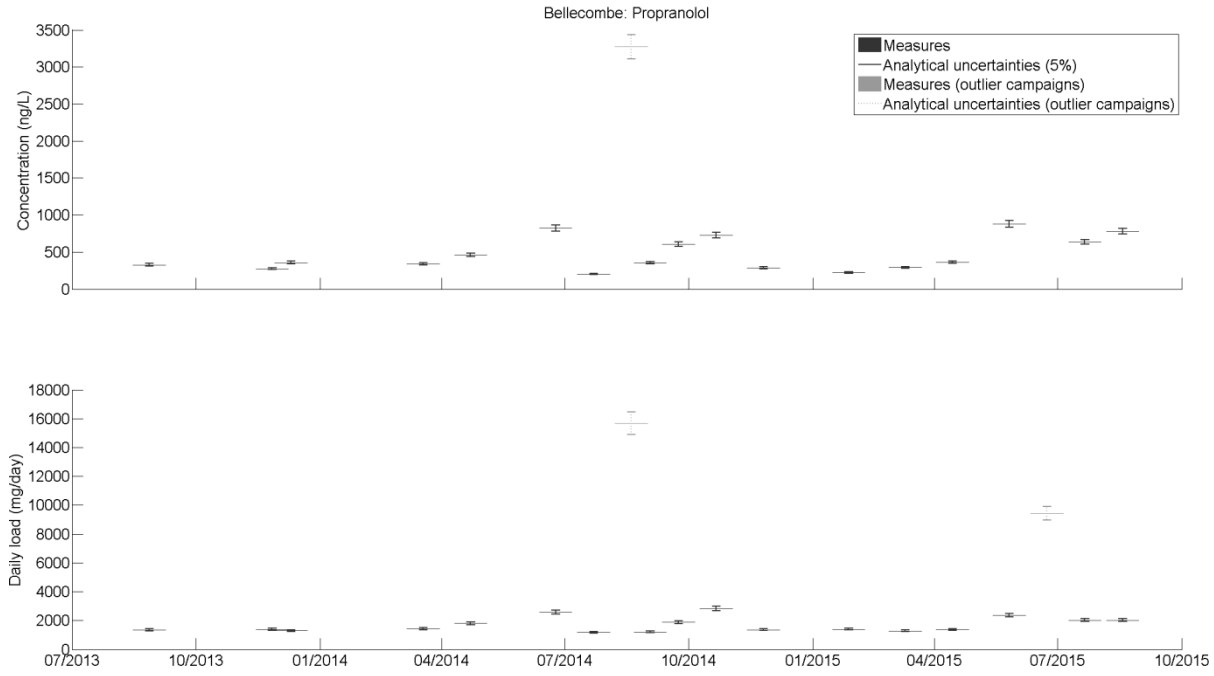

Figure 96: Time series of the daily concentrations and loads of the urban catchment for Propranolol.

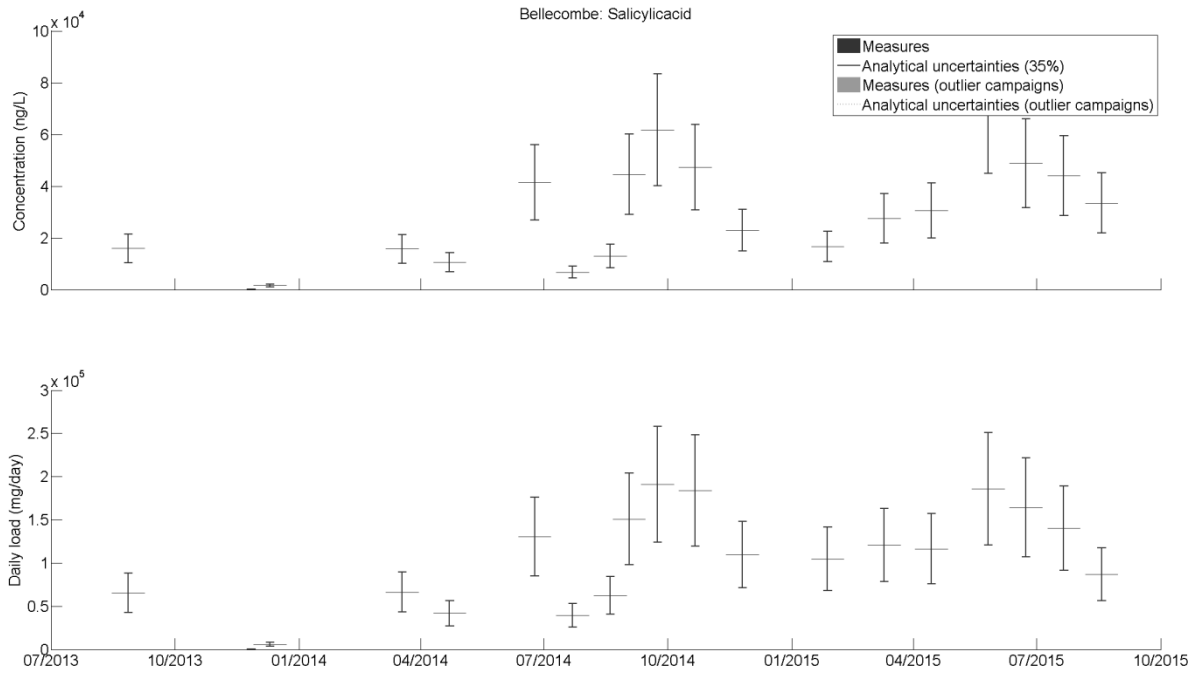

Figure 97: Time series of the daily concentrations and loads of the urban catchment for Salicylic acid.

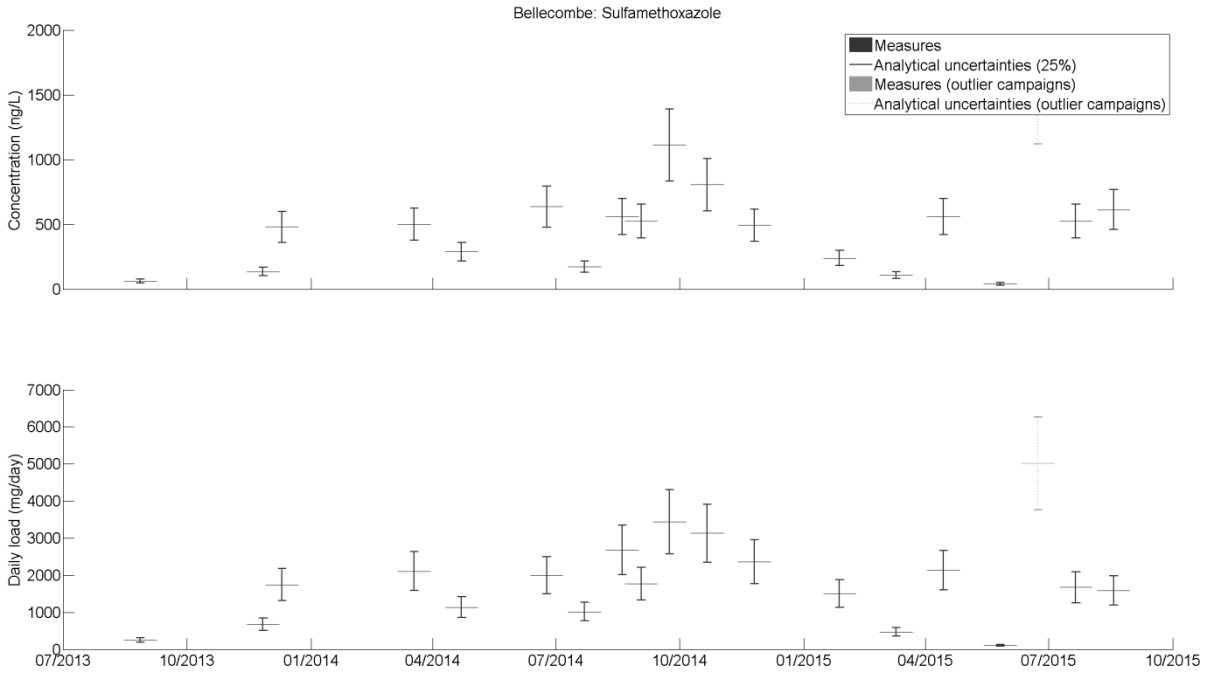

Figure 98: Time series of the daily concentrations and loads of the urban catchment for Sulfamethoxazole.

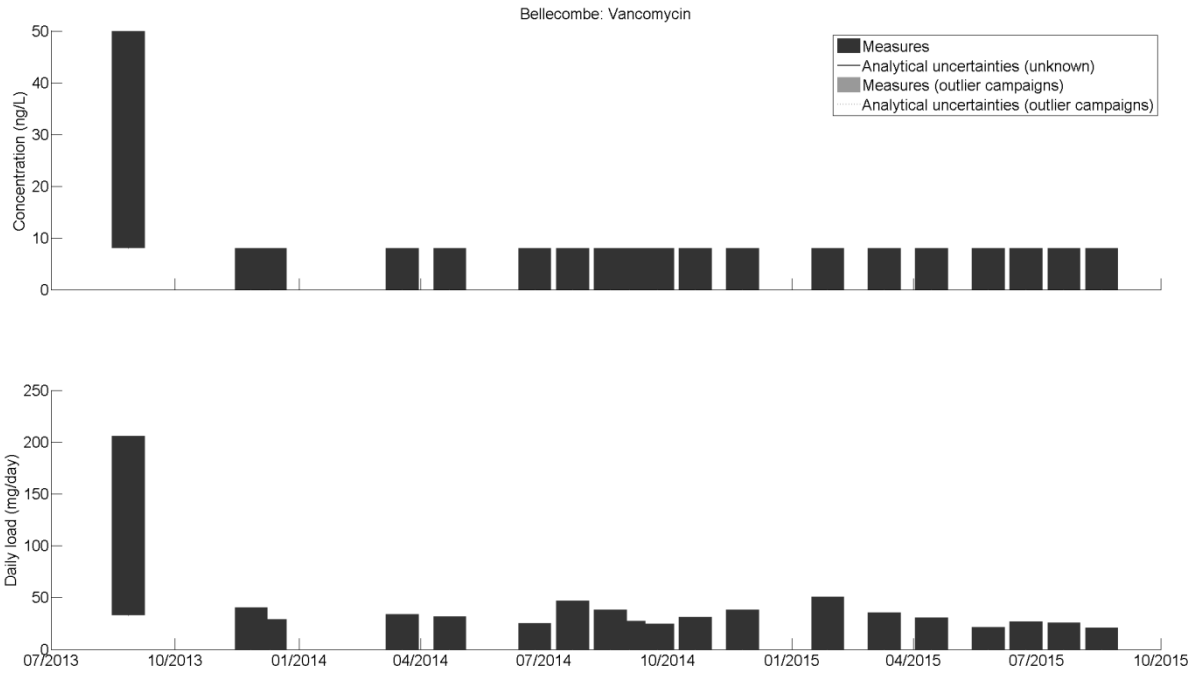

Figure 99: Time series of the daily concentrations and loads of the urban catchment for Vancomycin.

APPENDIX 11: HOURLY PHARMACEUTICALS LOADS OF THE URBAN CATCHMENT

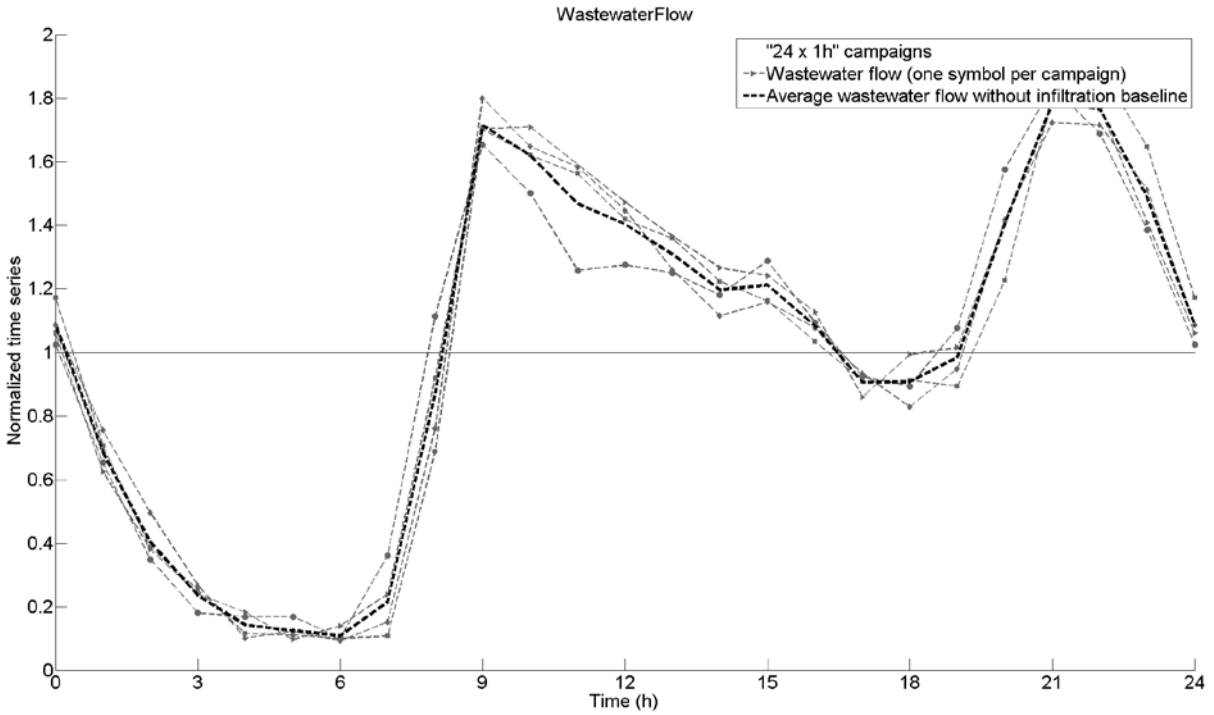

Figure 100: Time series of the hourly flow of the urban catchment for the wastewater without the infiltration baseline.

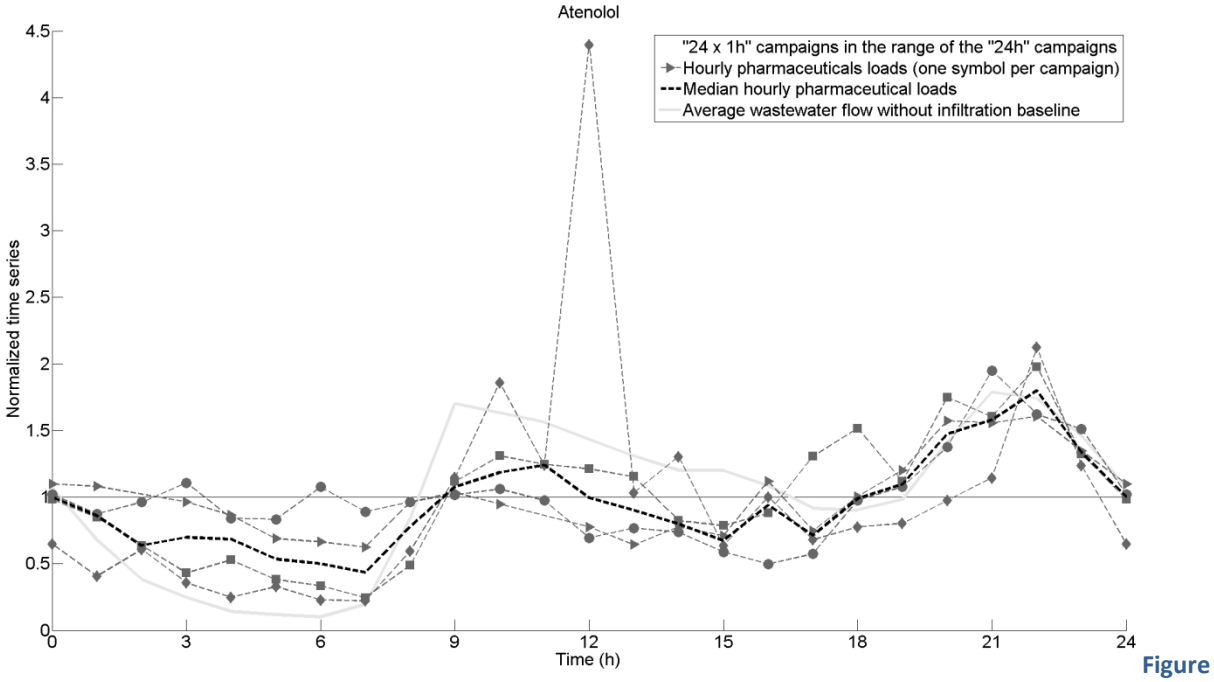

Figure 101: Time series of the hourly loads of the urban catchment for Atenolol.

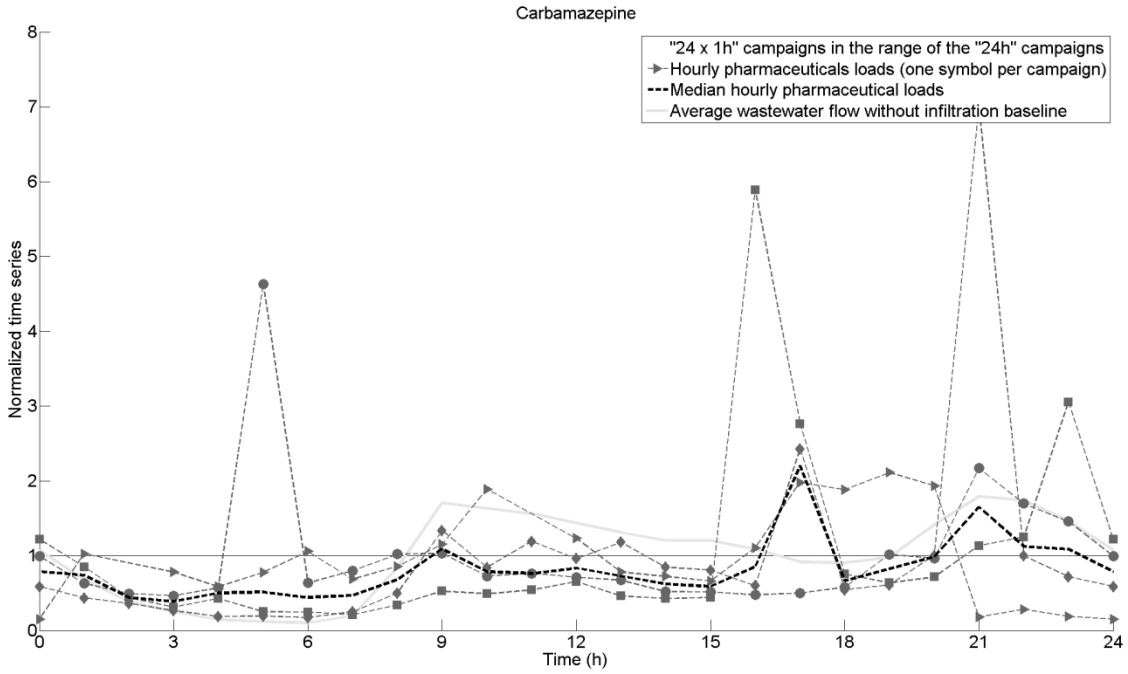

Figure 102: Time series of the hourly loads of the urban catchment for Carbamazepine.

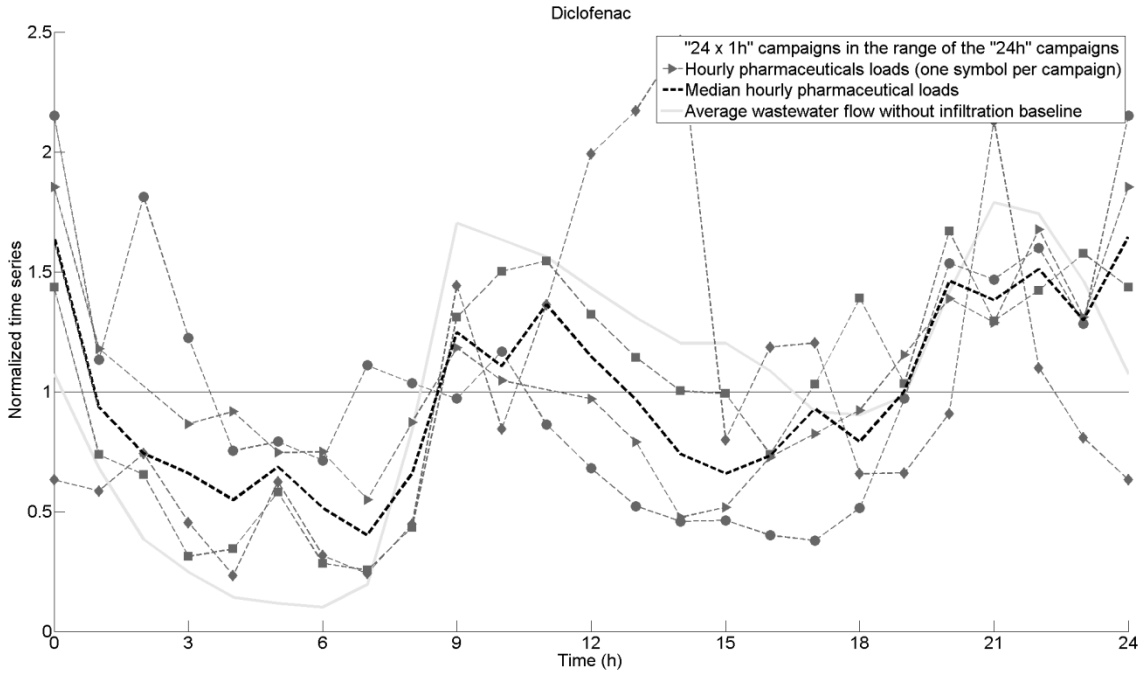

Figure 103: Time series of the hourly loads of the urban catchment for Diclofenac.

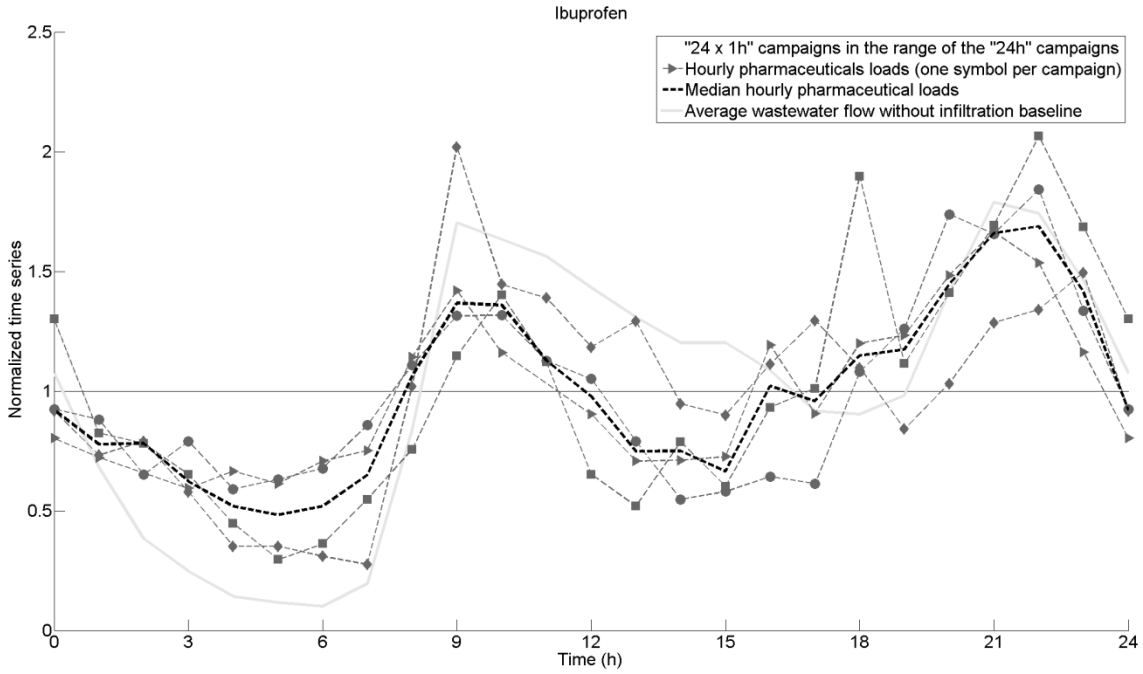

Figure 104: Time series of the hourly loads of the urban catchment for Ibuprofen.

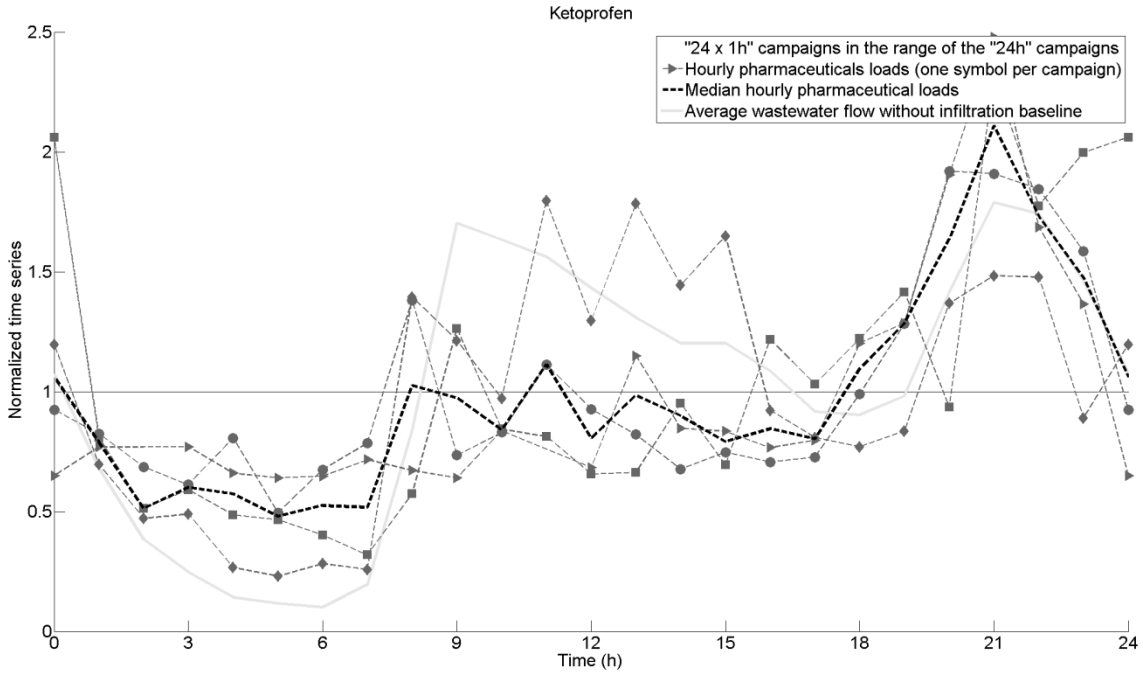

Figure 105: Time series of the hourly loads of the urban catchment for Ketoprofen.

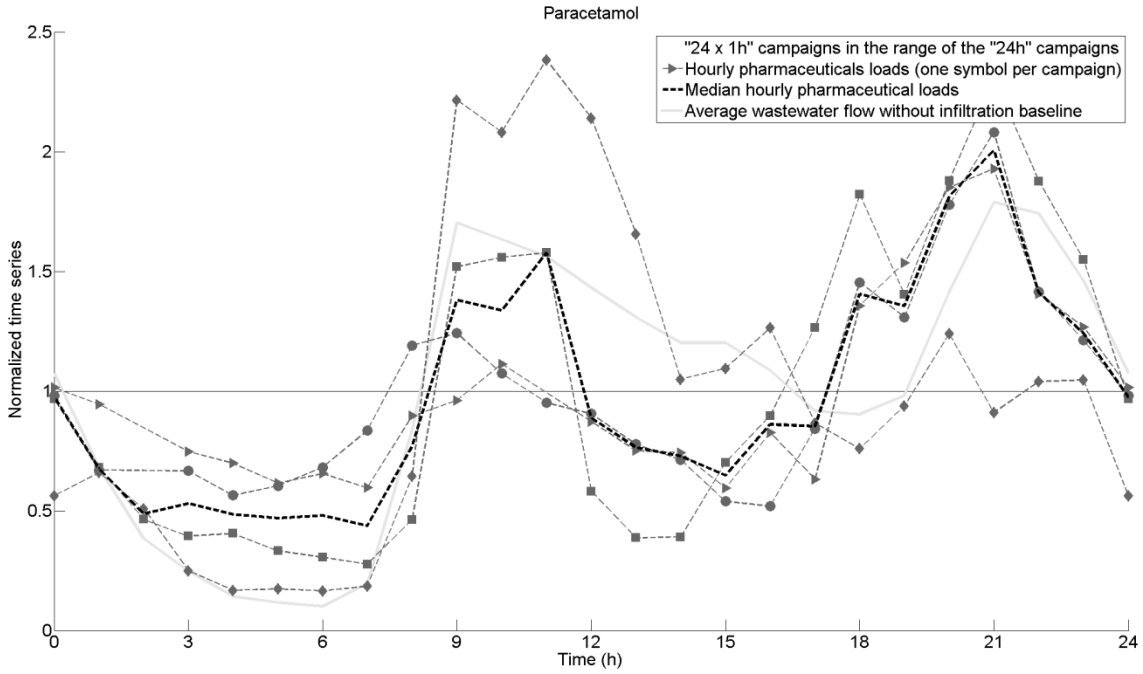

Figure 106: Time series of the hourly loads of the urban catchment for Paracetamol.

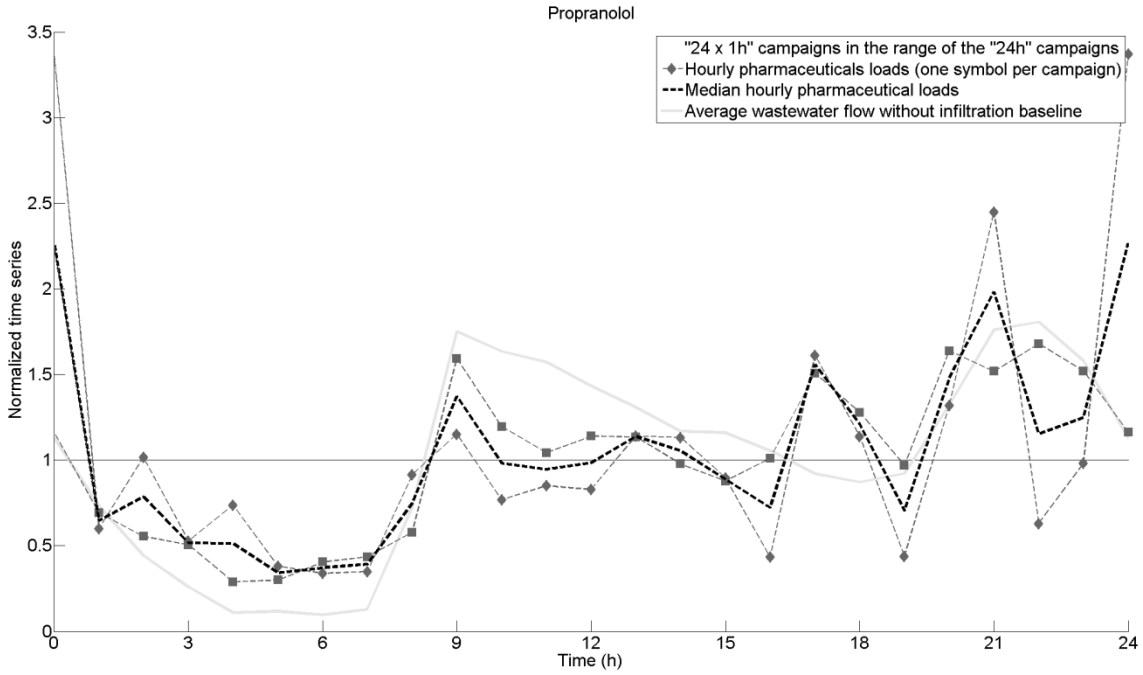

Figure 107: Time series of the hourly loads of the urban catchment for Propranolol.

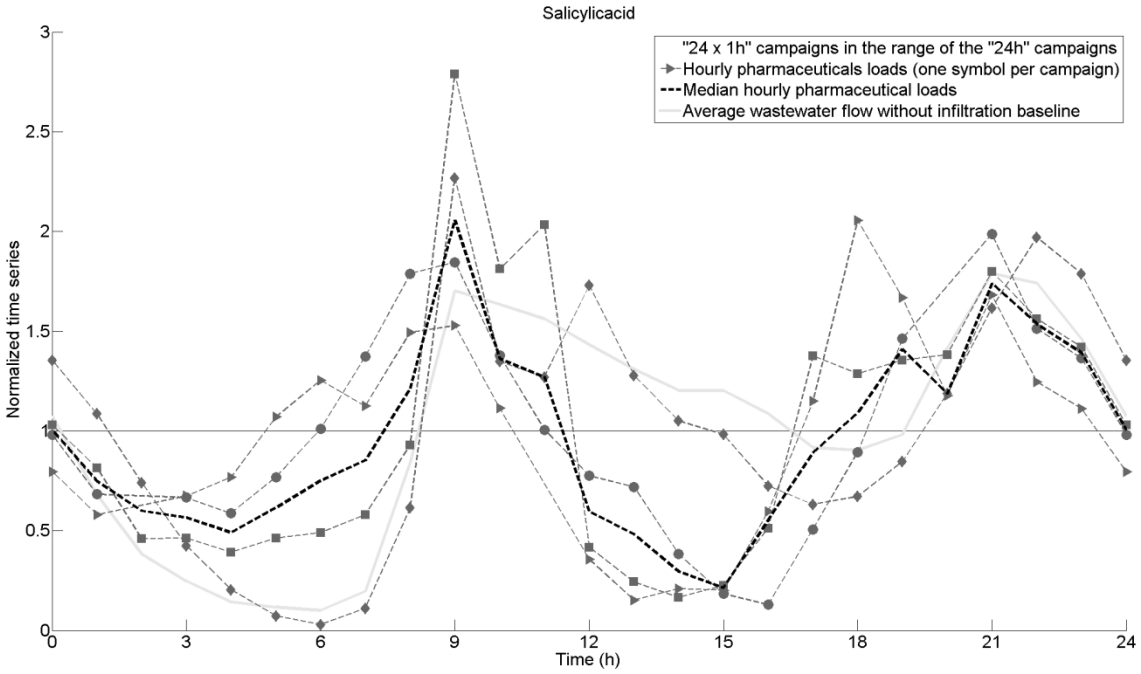

Figure 108: Time series of the hourly loads of the urban catchment for Salicylic acid.

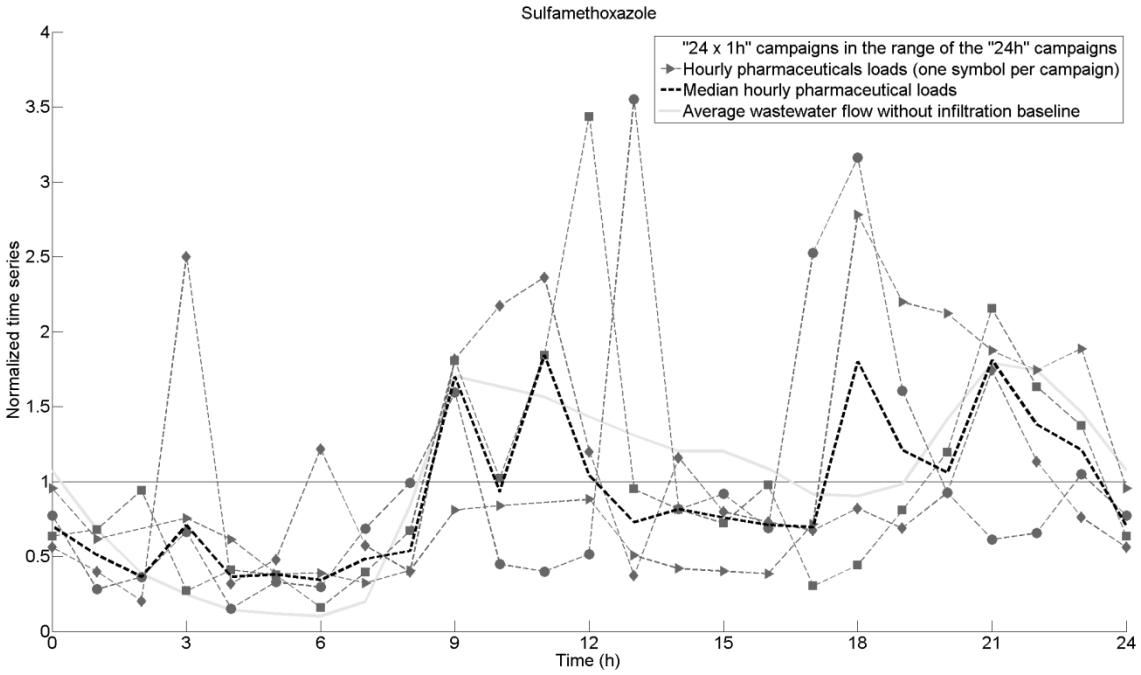

Figure 109: Time series of the hourly loads of the urban catchment for Sulfamethoxazole.

APPENDIX 12: DAILY LOADS OF THE "7 X 24 H" CAMPAIGNS IN THE URBAN CATCHMENT

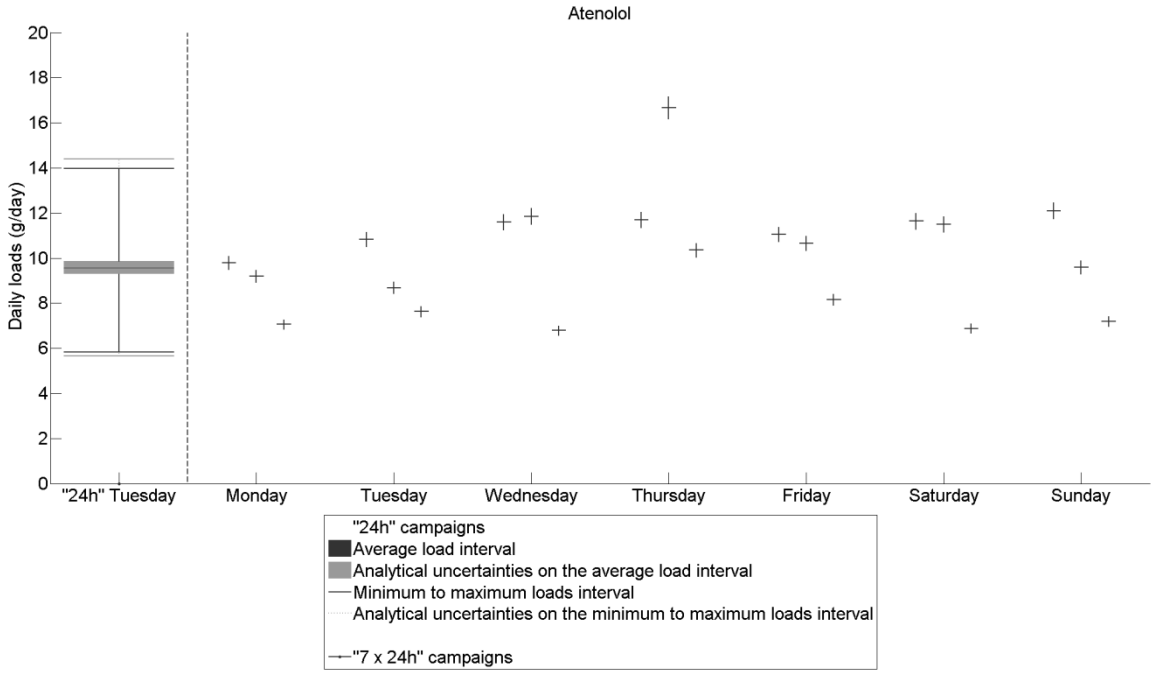

Figure 110: Time series of the daily loads for the "7 x 24h" of the urban catchment for Atenolol.

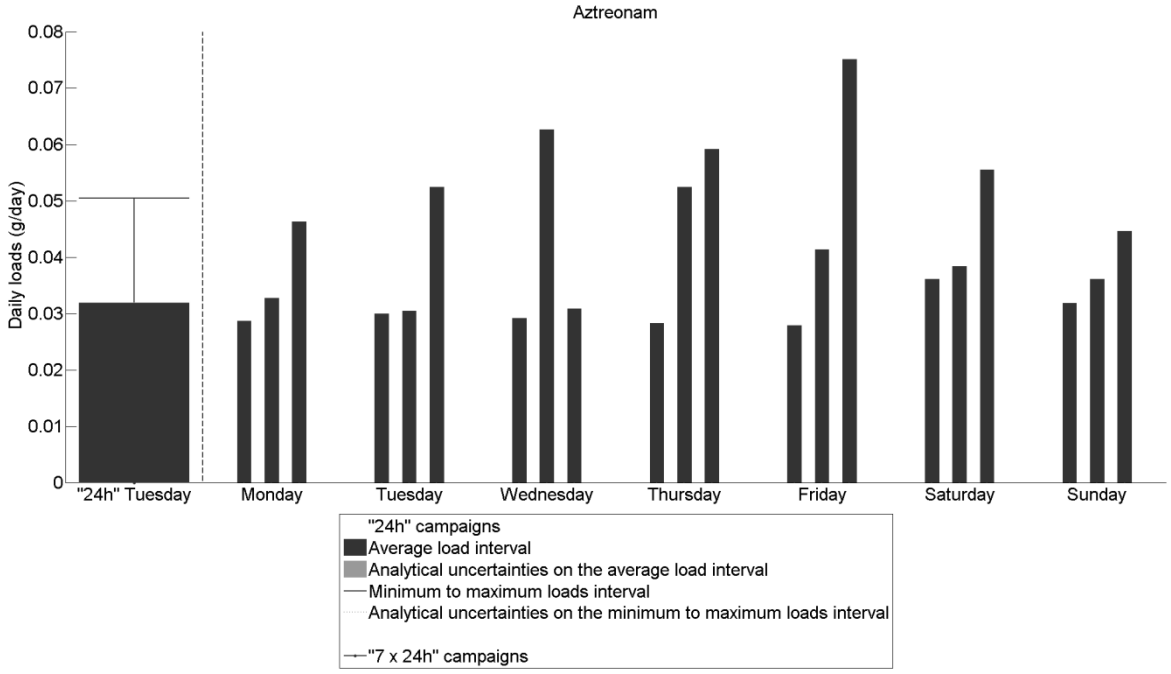

Figure 111: Time series of the daily loads for the "7 x 24h" of the urban catchment for Aztreonam.

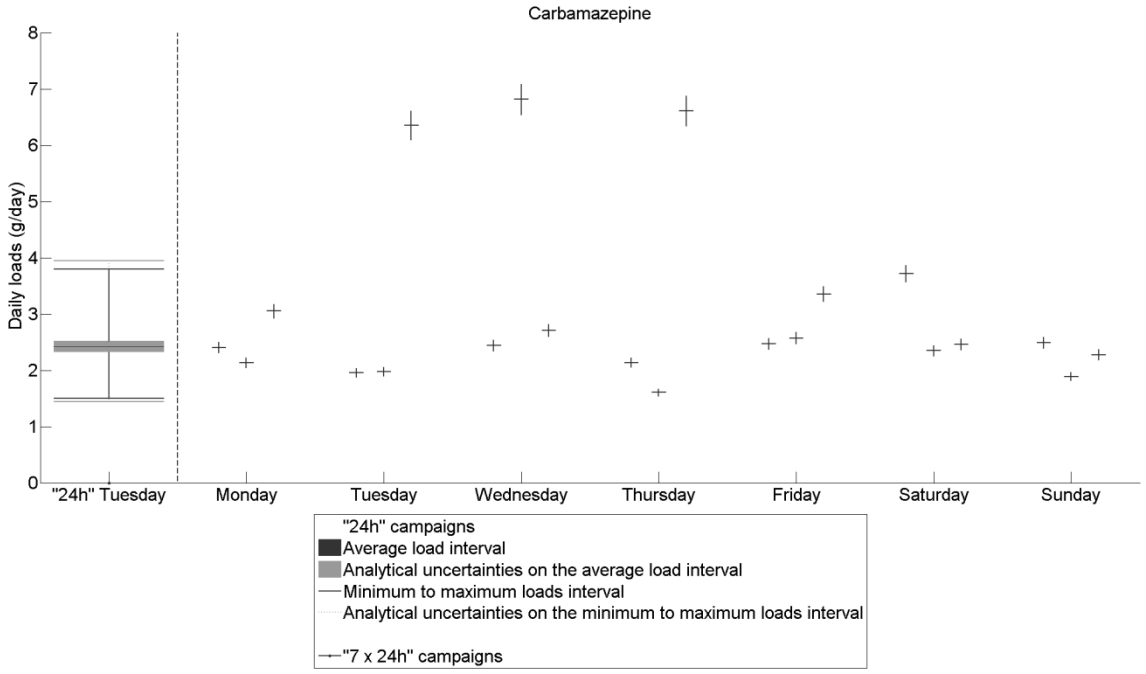

Figure 112: Time series of the daily loads for the "7 x 24h" of the urban catchment for Carbamazepine.

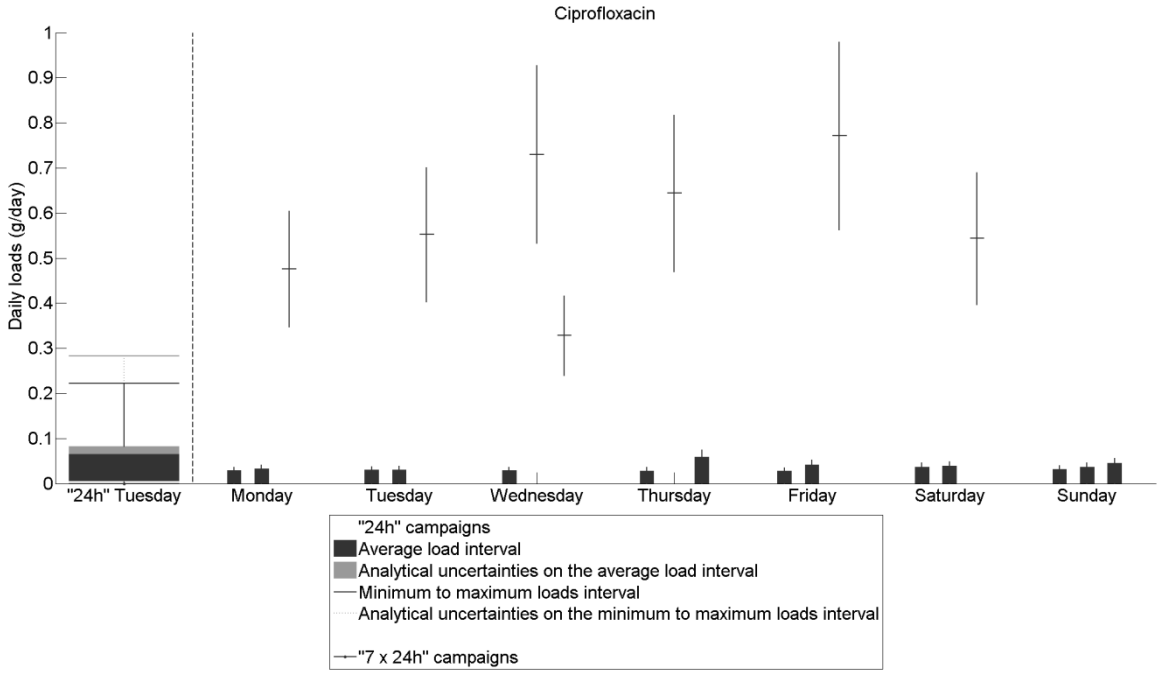

Figure 113: Time series of the daily loads for the "7 x 24h" of the urban catchment for Ciprofloxacin.

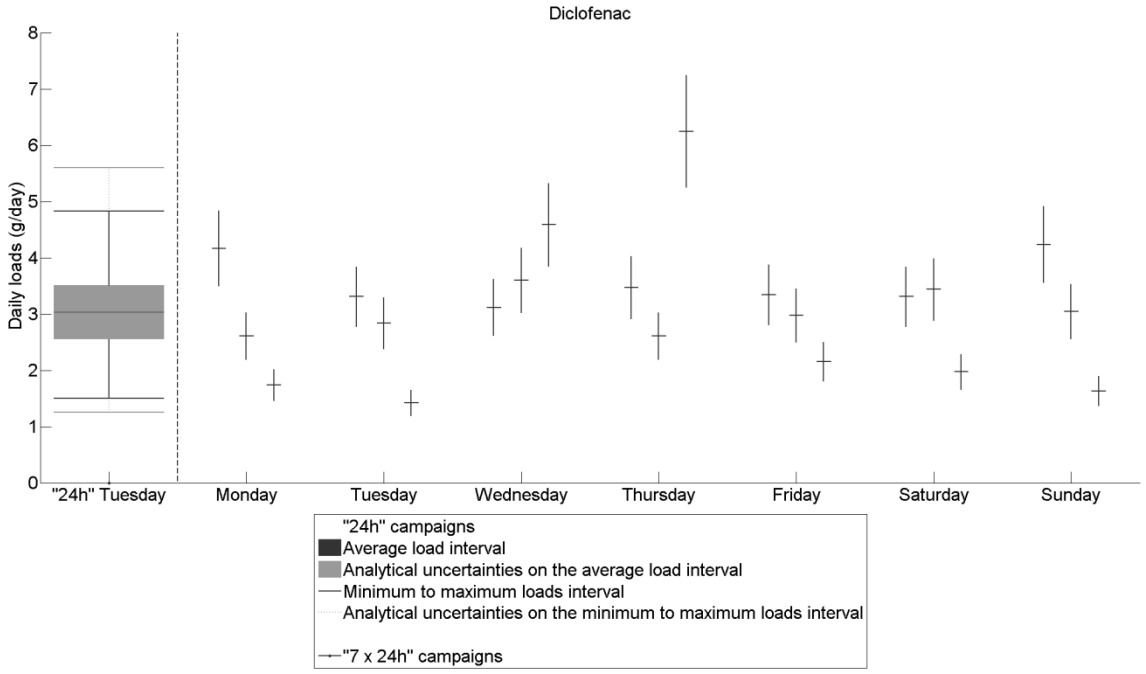

Figure 114: Time series of the daily loads for the "7 x 24h" of the urban catchment for Diclofenac.

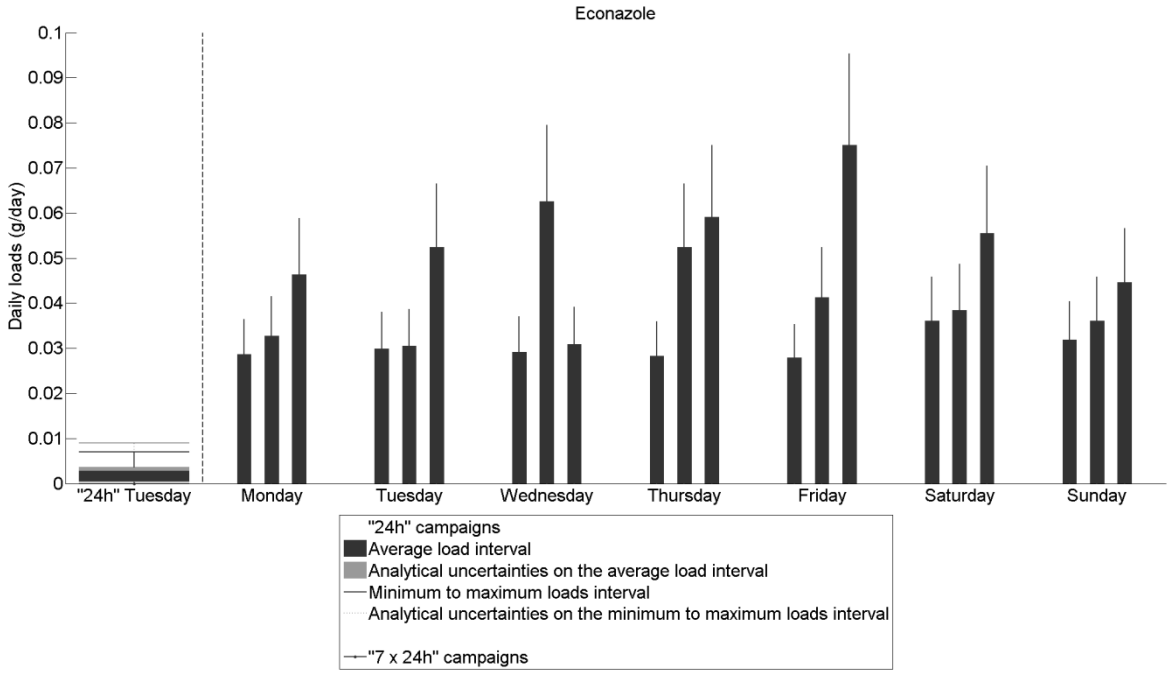

Figure 115: Time series of the daily loads for the "7 x 24h" of the urban catchment for Econazole.

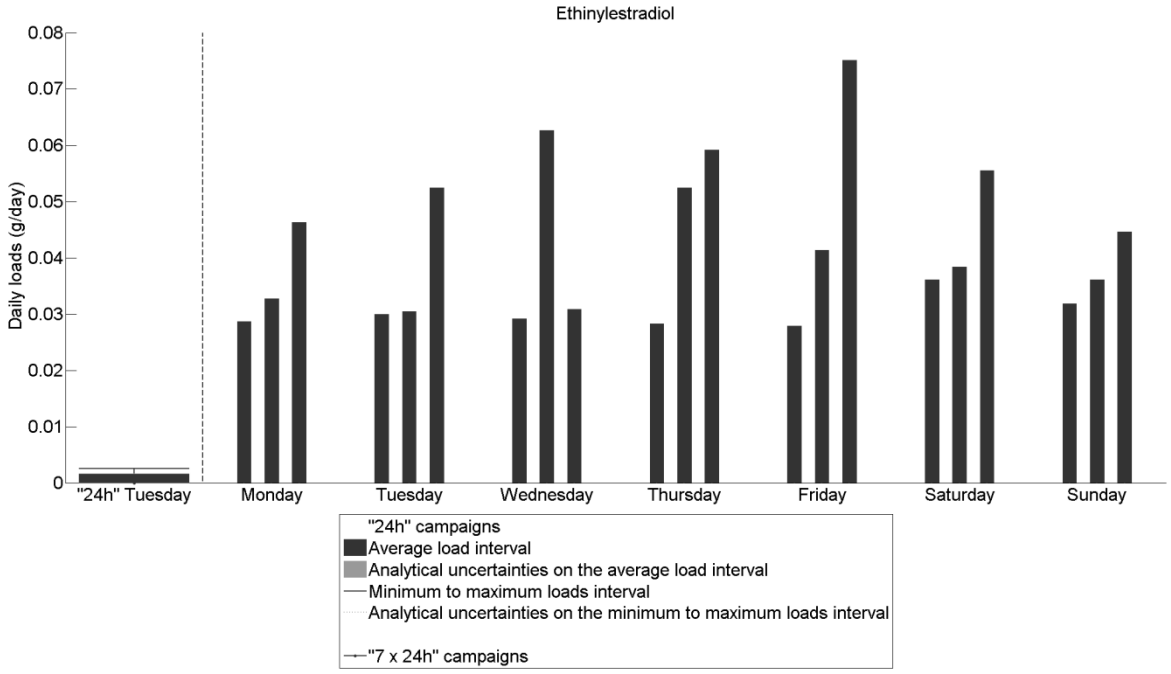

Figure 116: Time series of the daily loads for the "7 x 24h" of the urban catchment for Ethinylestradiol.

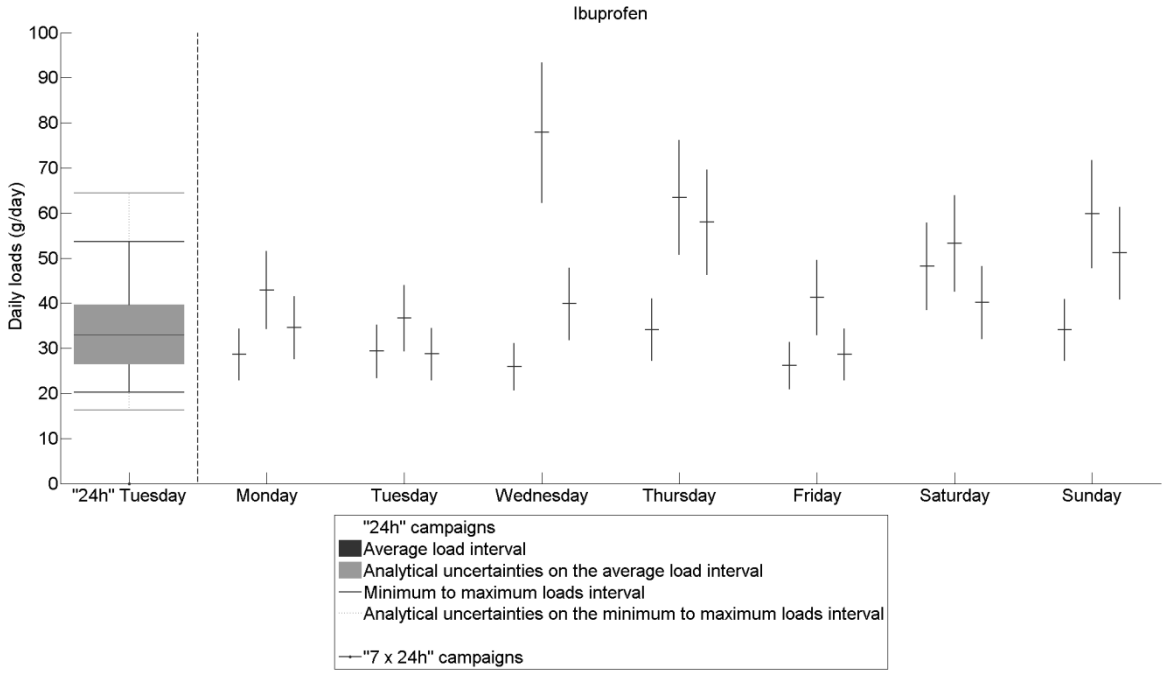

Figure 117: Time series of the daily loads for the "7 x 24h" of the urban catchment for Ibuprofen.

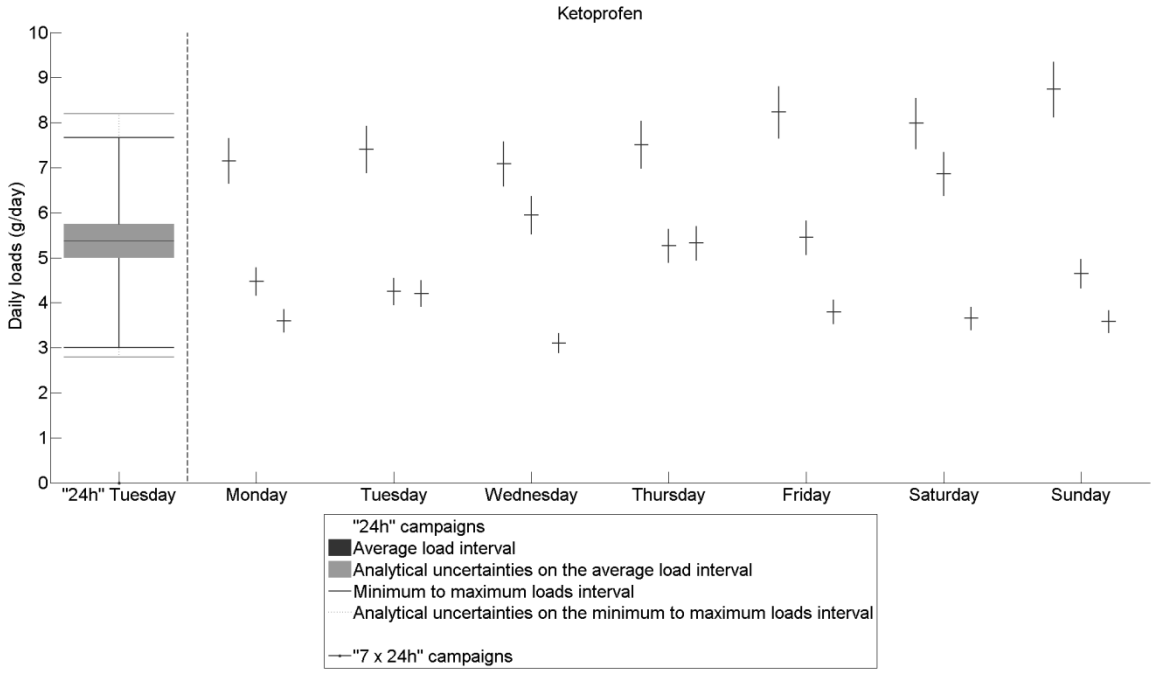

Figure 118: Time series of the daily loads for the "7 x 24h" of the urban catchment for Ketoprofen.

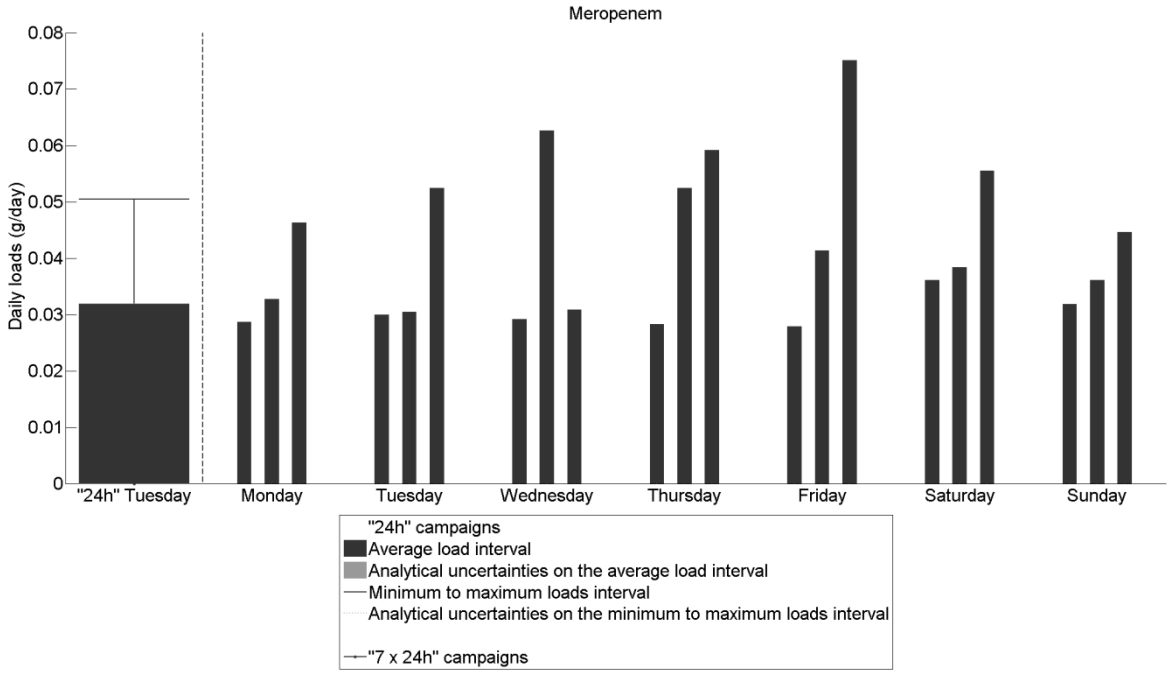

Figure 119: Time series of the daily loads for the "7 x 24h" of the urban catchment for Meropenem.

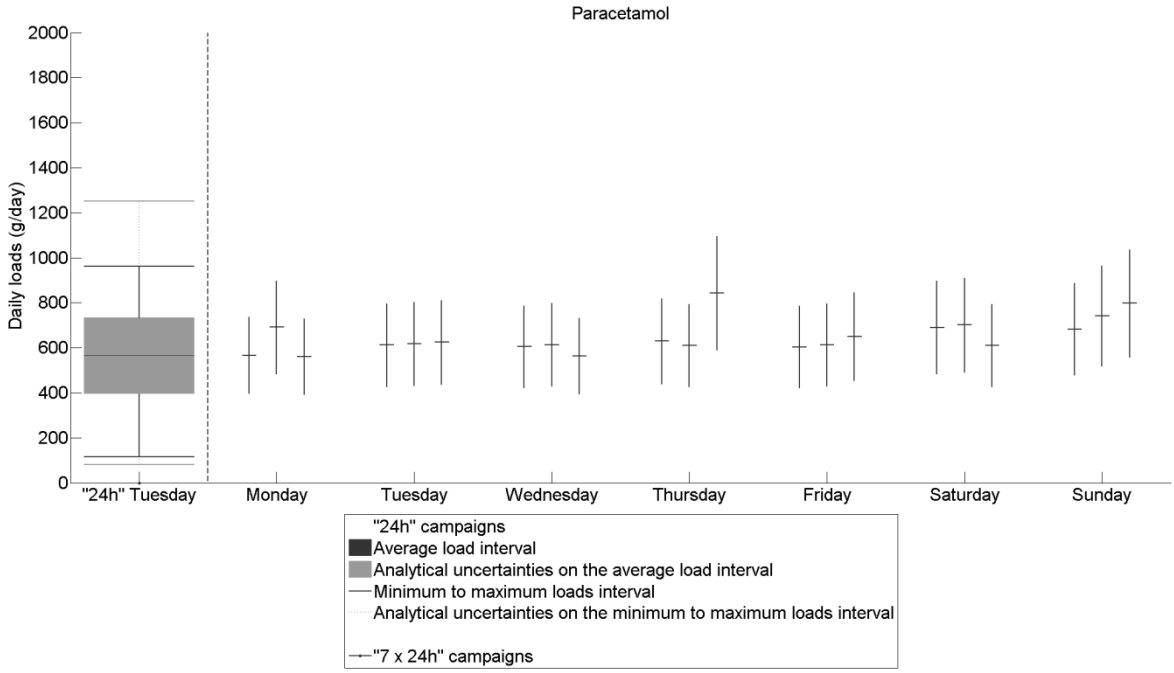

Figure 120: Time series of the daily loads for the "7 x 24h" of the urban catchment for Paracetamol.

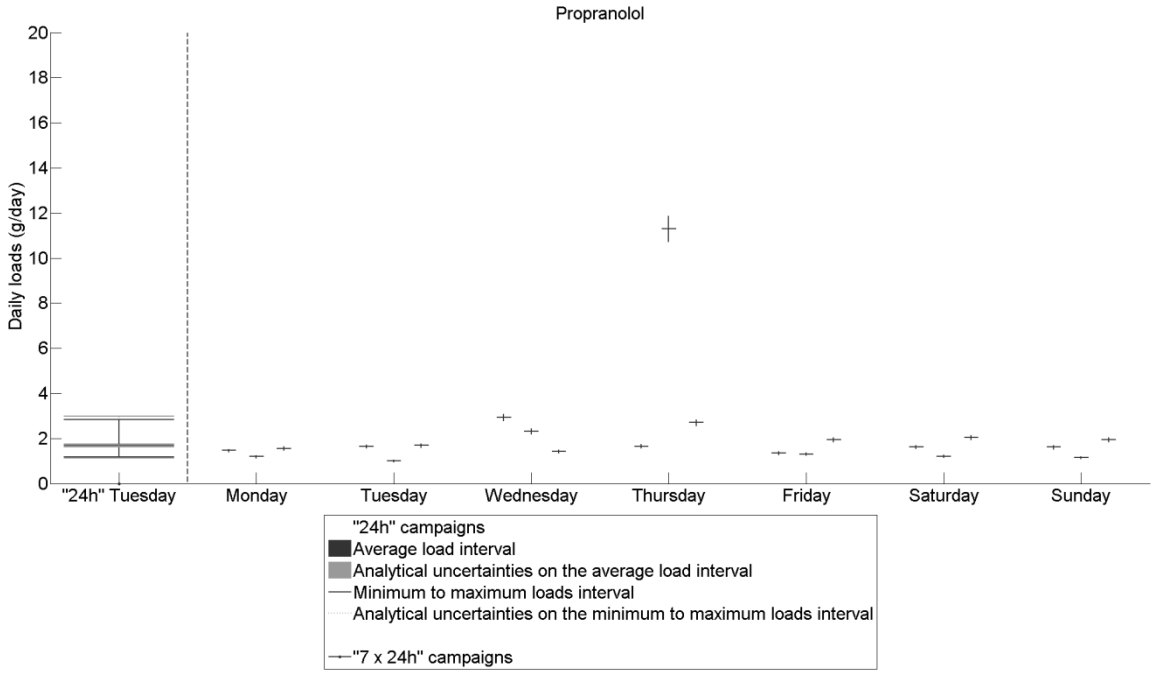

Figure 121: Time series of the daily loads for the "7 x 24h" of the urban catchment for Propranolol.

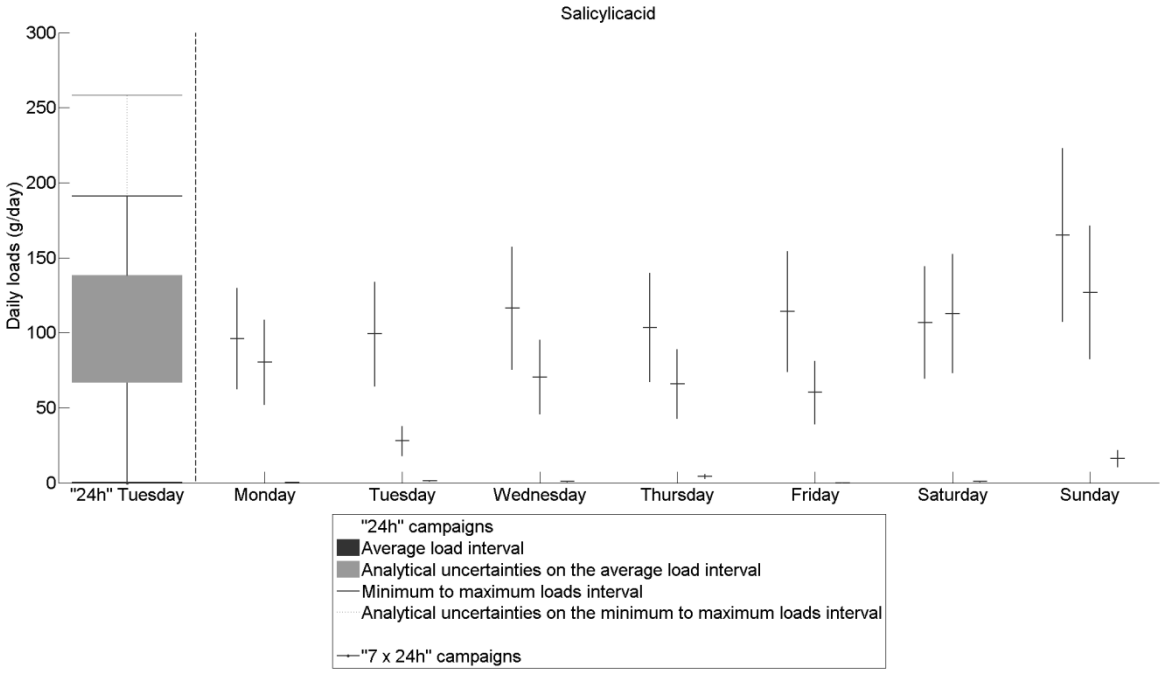

Figure 122: Time series of the daily loads for the "7 x 24h" of the urban catchment for Salicylic acid.

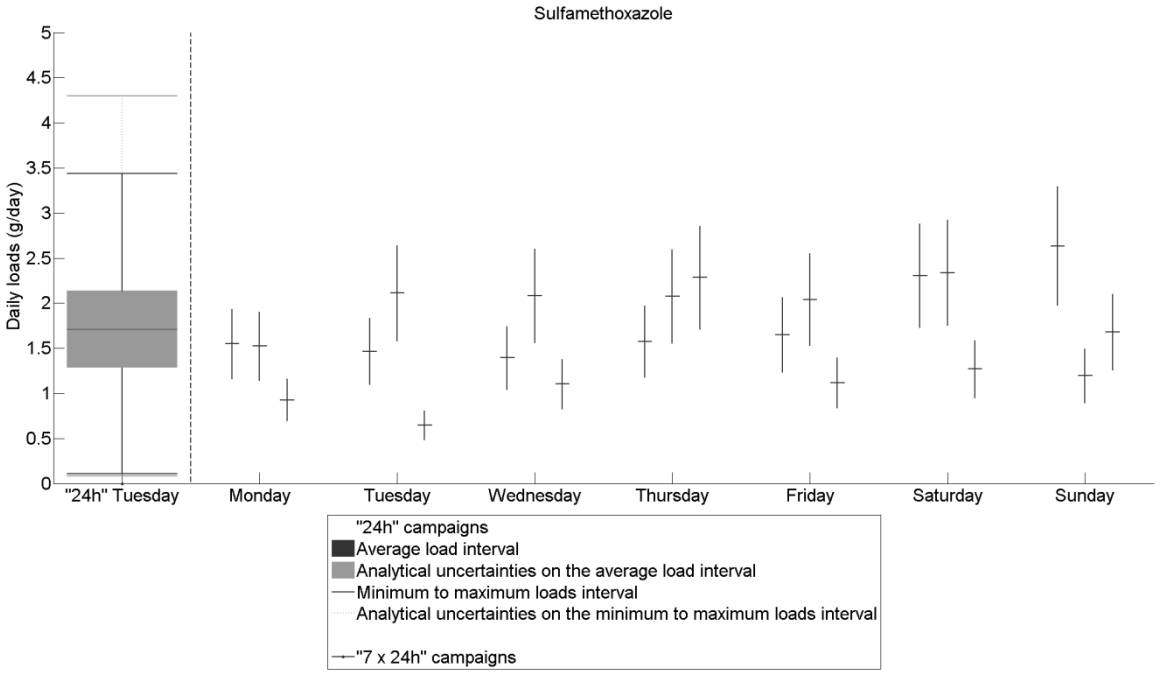

Figure 123: Time series of the daily loads for the "7 x 24h" of the urban catchment for Sulfamethoxazole.

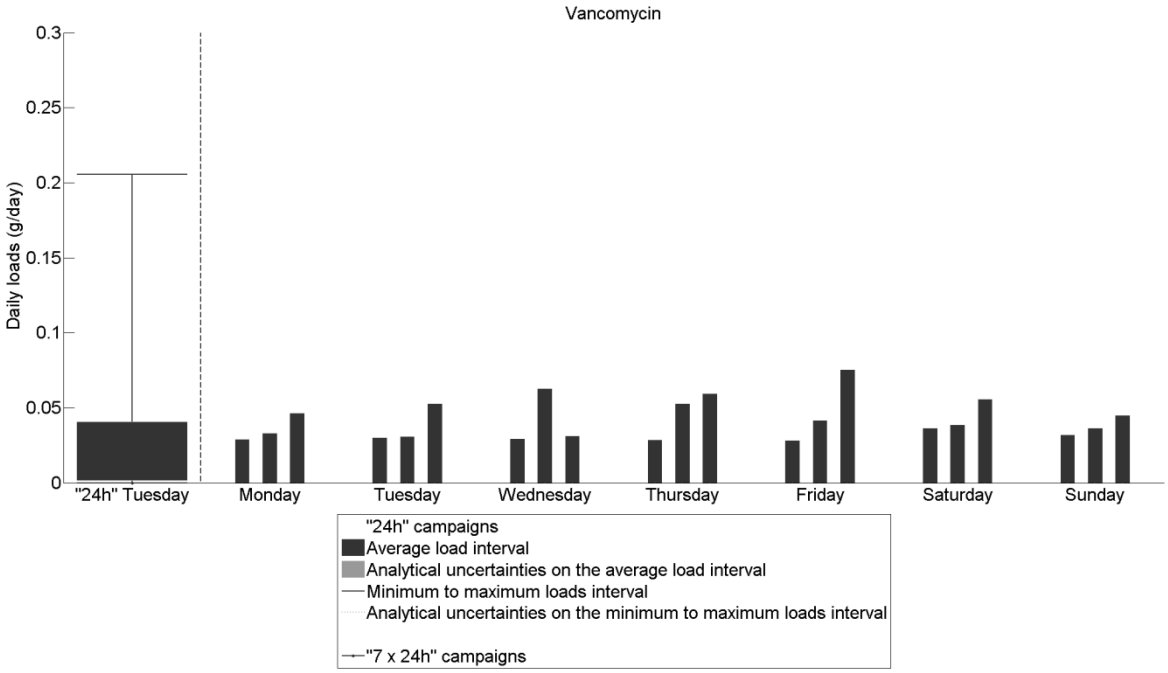

Figure 124: Time series of the daily loads for the "7 x 24h" of the urban catchment for Vancomycin.

APPENDIX 13: DAILY PHARMACEUTICALS CONCENTRATIONS AND LOADS OF THE CHAL HOSPITAL

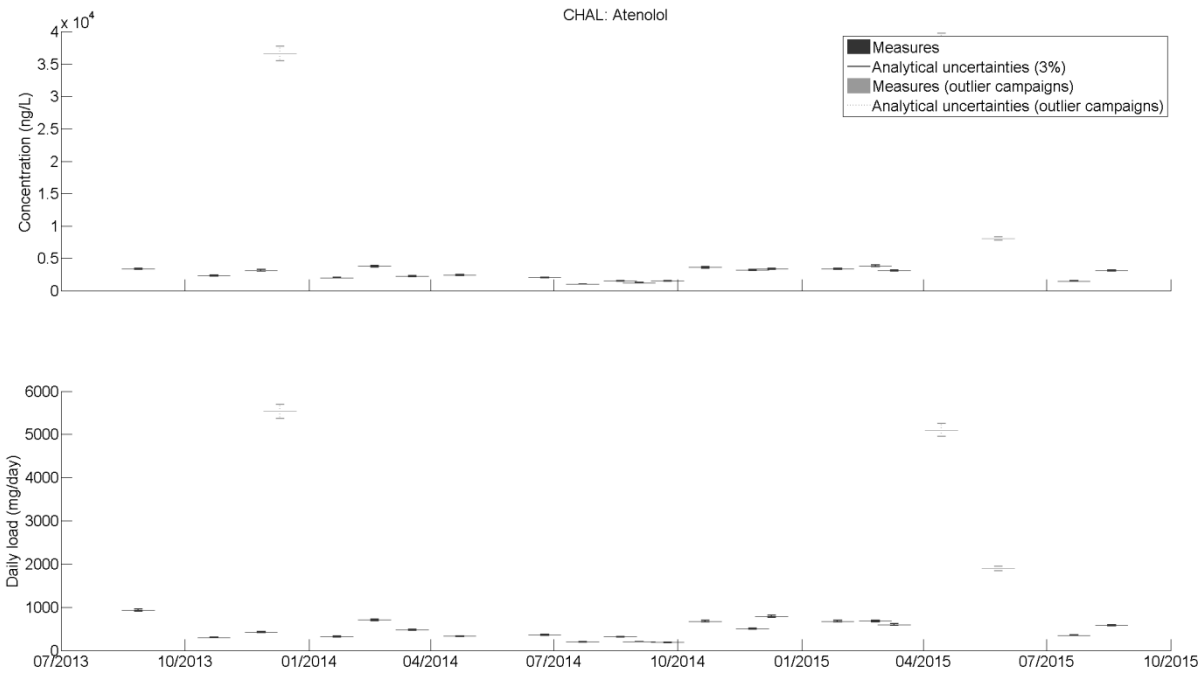

Figure 125: Time series of the daily concentrations and loads of the CHAL hospital for Atenolol.

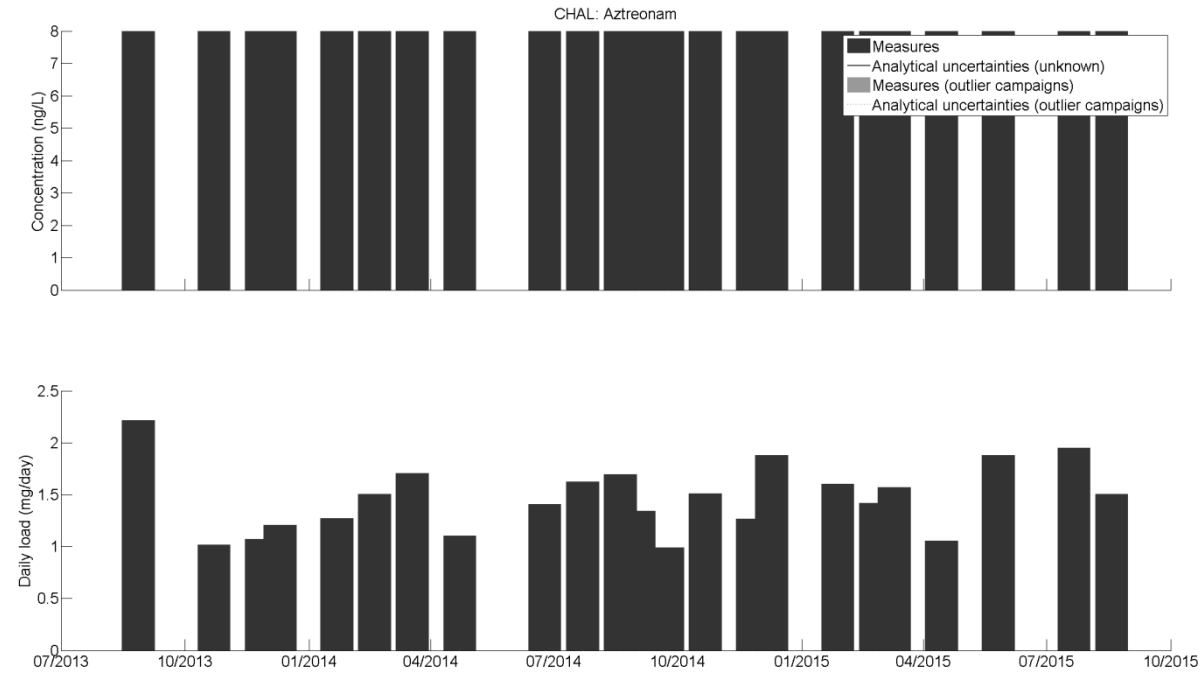

Figure 126: Time series of the daily concentrations and loads of the CHAL hospital for Aztreonam.

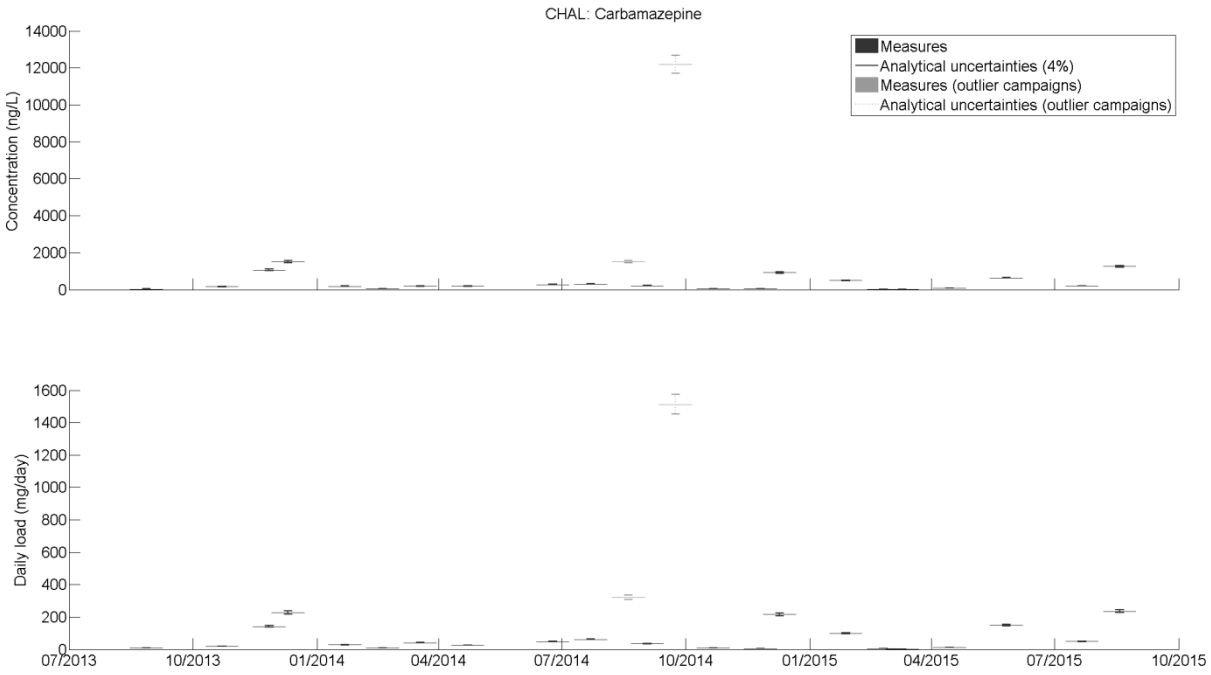

Figure 127: Time series of the daily concentrations and loads of the CHAL hospital for Carbamazepine.

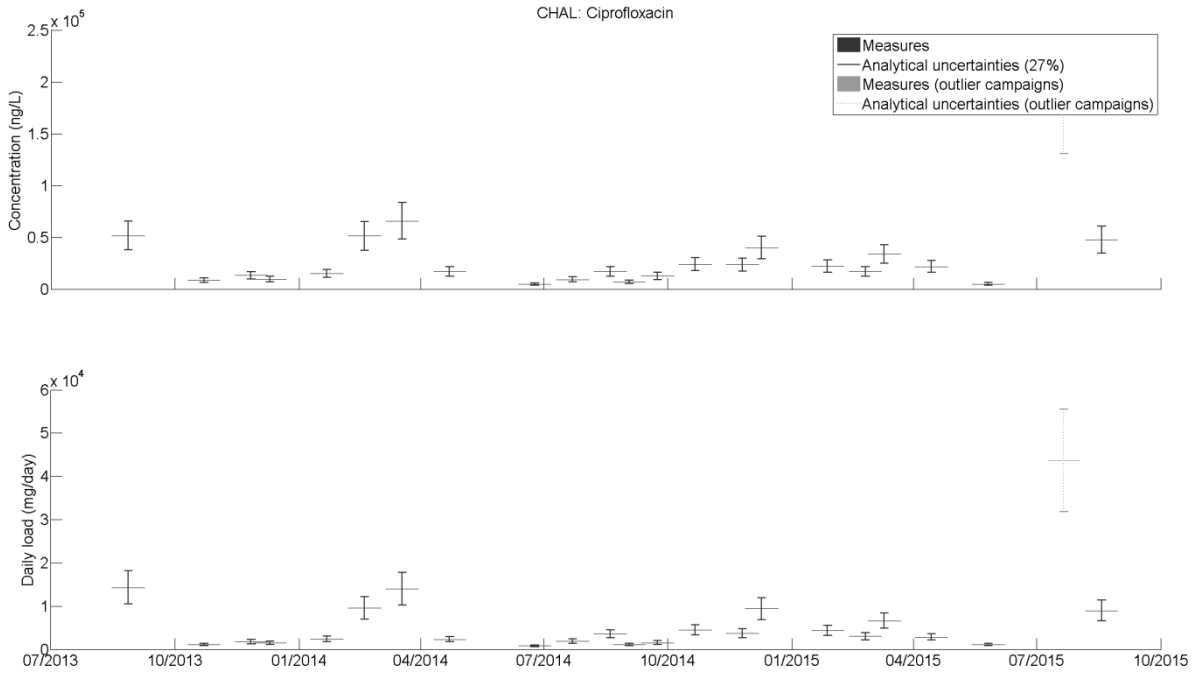

Figure 128: Time series of the daily concentrations and loads of the CHAL hospital for Ciprofloxacin.

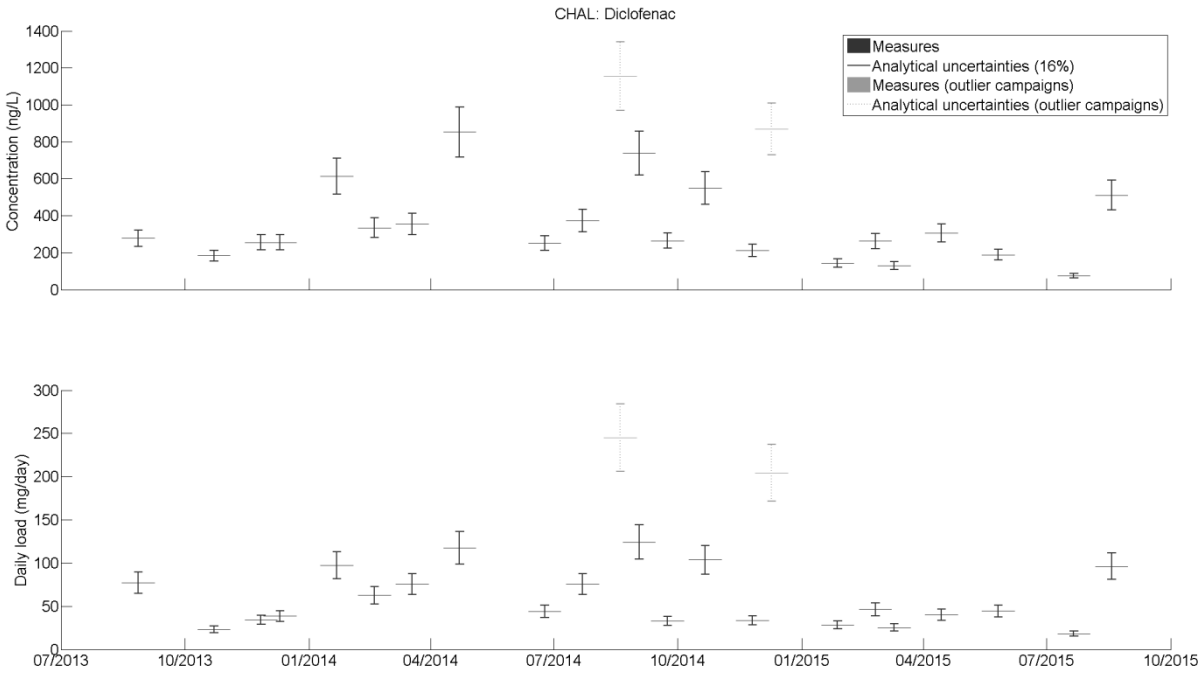

Figure 129: Time series of the daily concentrations and loads of the CHAL hospital for Diclofenac.

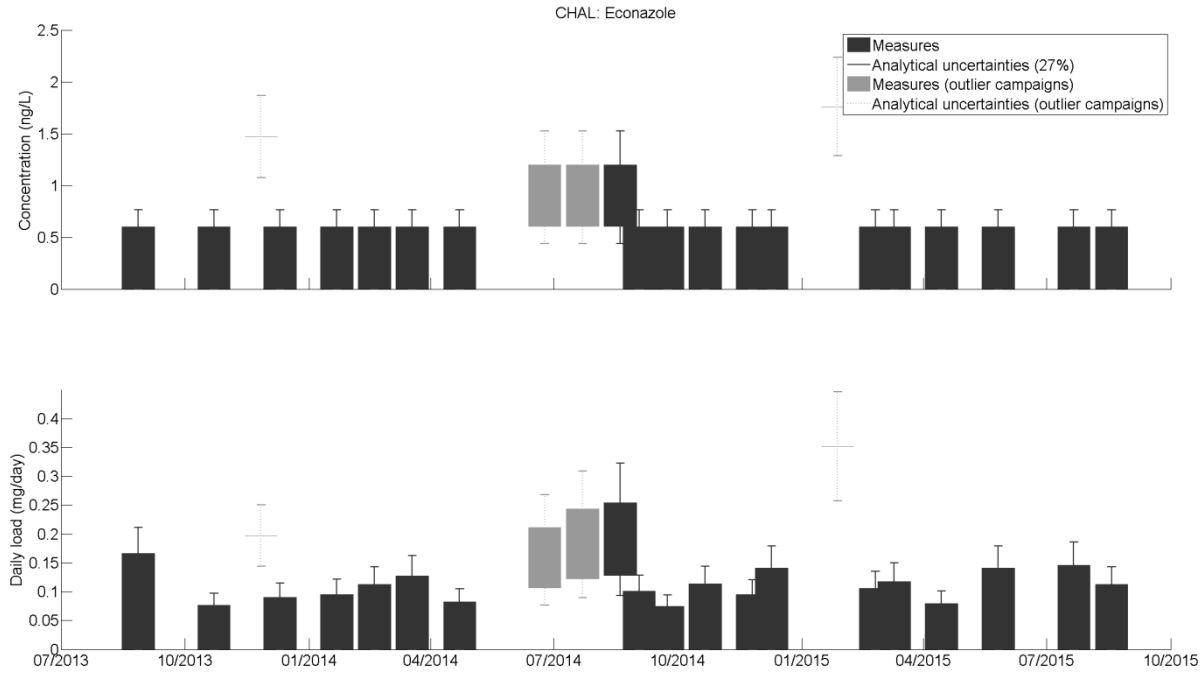

Figure 130: Time series of the daily concentrations and loads of the CHAL hospital for Econazole.

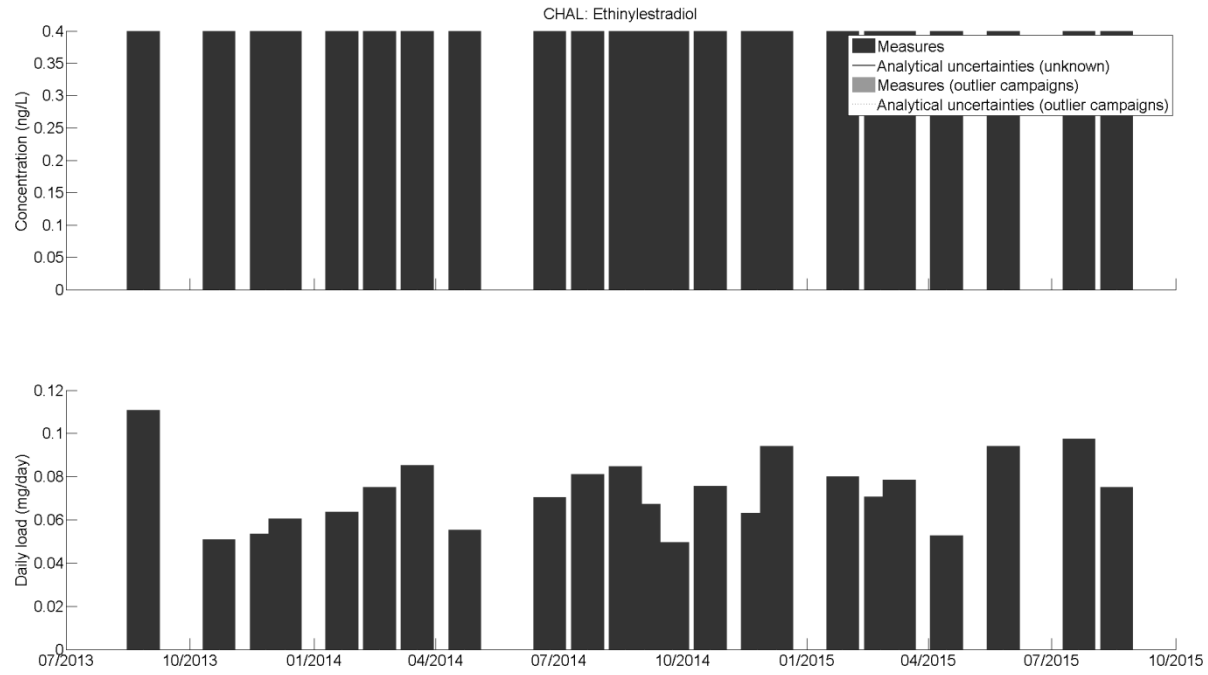

Figure 131: Time series of the daily concentrations and loads of the CHAL hospital for Ethinylestradiol.

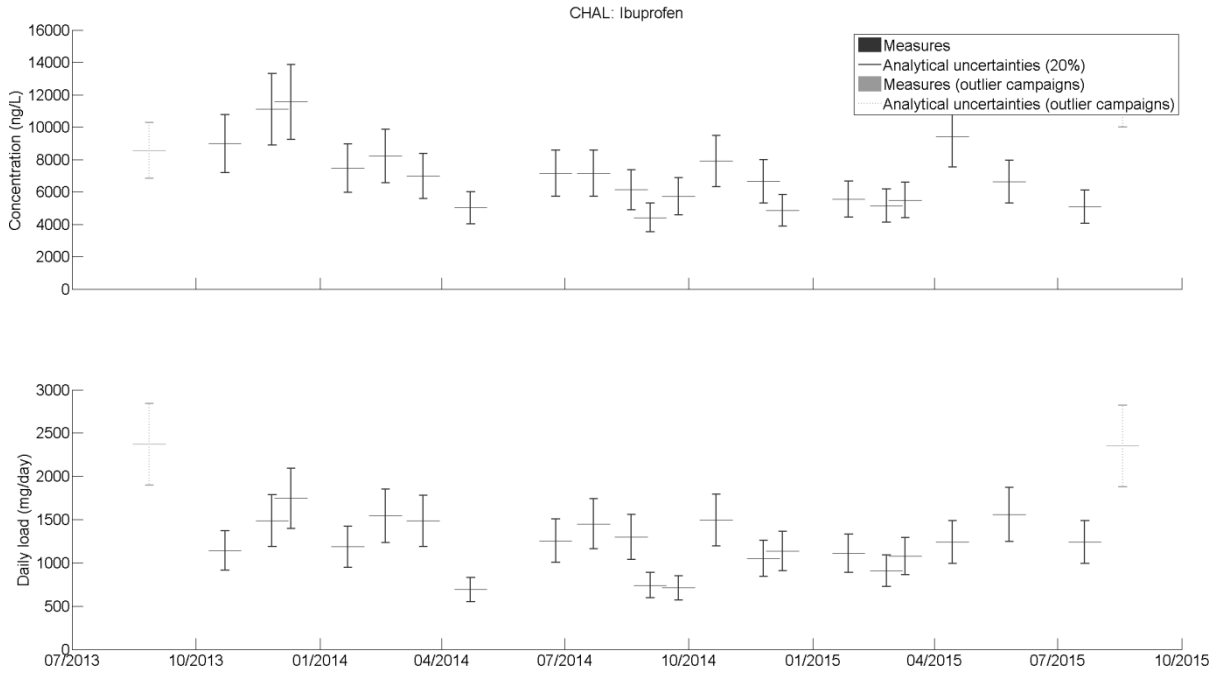

Figure 132: Time series of the daily concentrations and loads of the CHAL hospital for Ibuprofen.

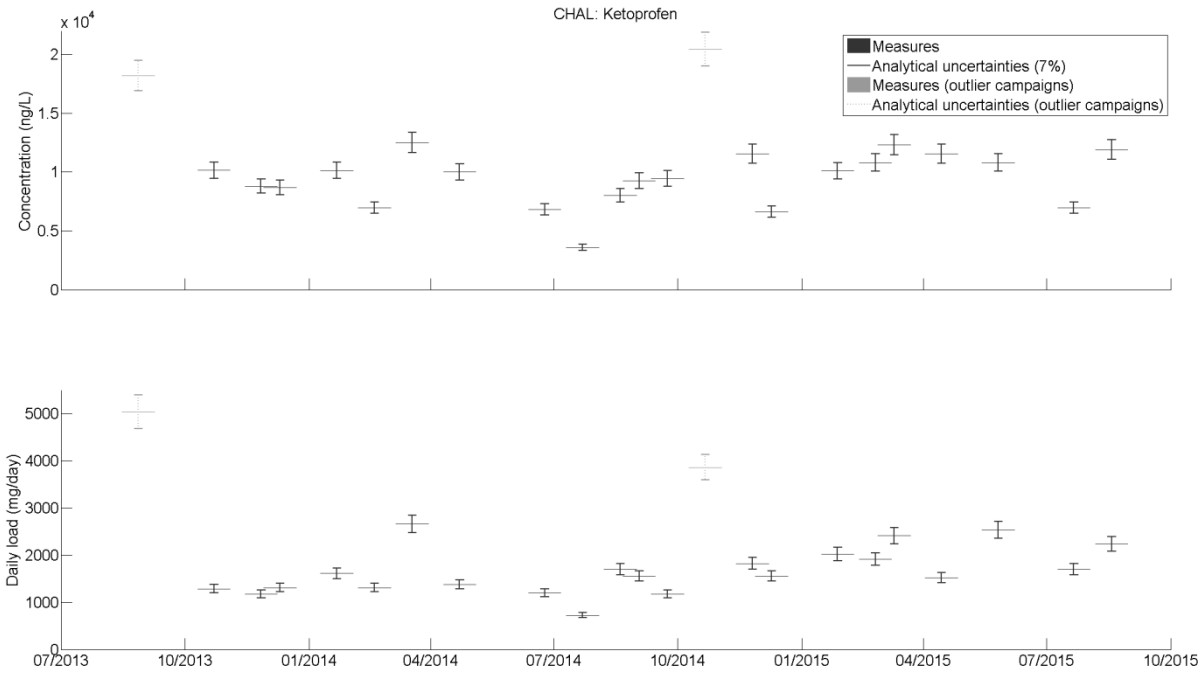

Figure 133: Time series of the daily concentrations and loads of the CHAL hospital for Ketoprofen.

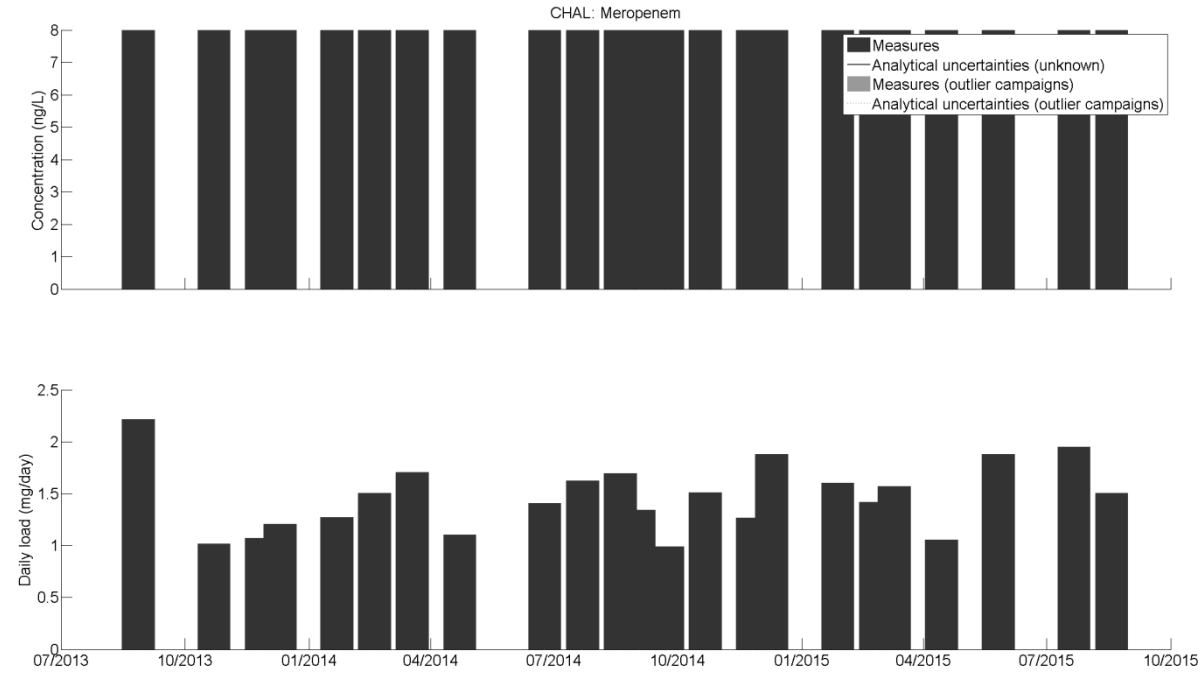

Figure 134: Time series of the daily concentrations and loads of the CHAL hospital for Meropenem.

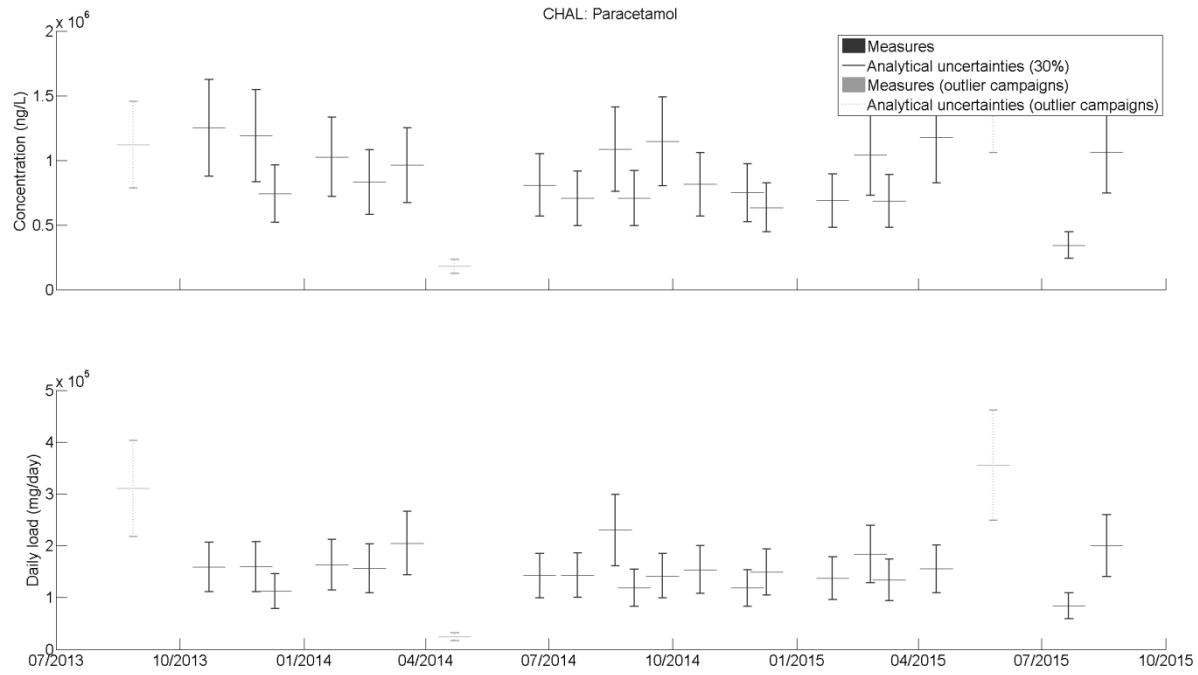

Figure 135: Time series of the daily concentrations and loads of the CHAL hospital for Paracetamol.

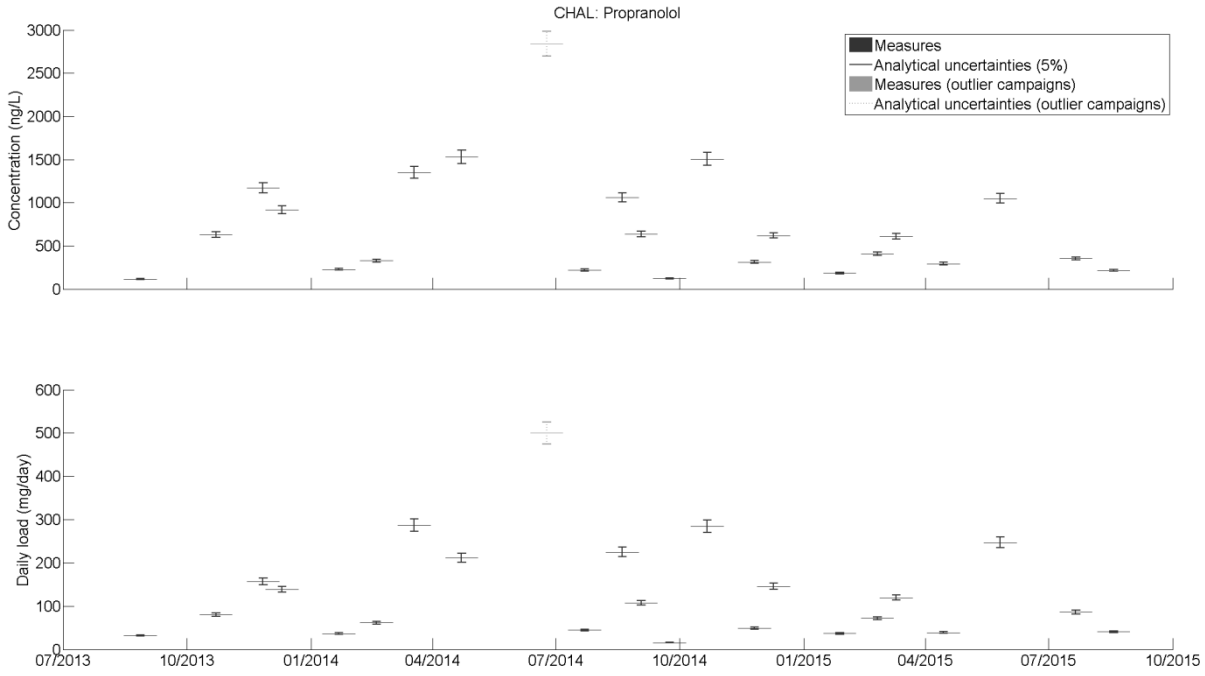

Figure 136: Time series of the daily concentrations and loads of the CHAL hospital for Propranolol.

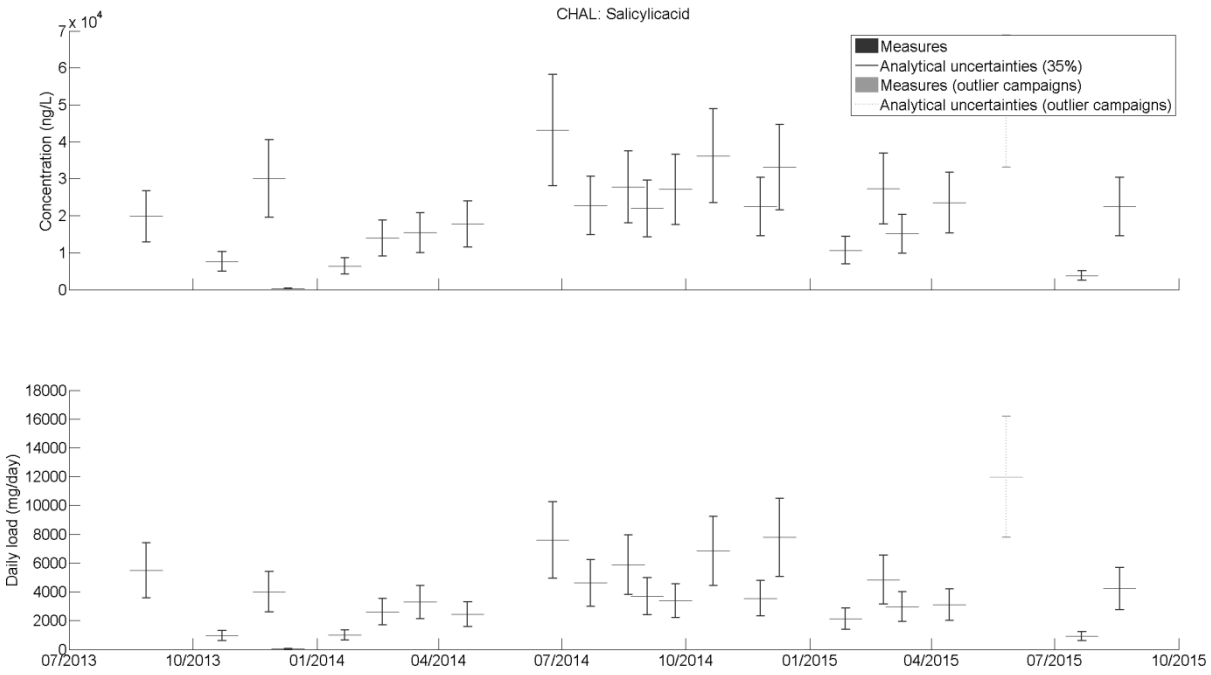

Figure 137: Time series of the daily concentrations and loads of the CHAL hospital for Salicylic acid.

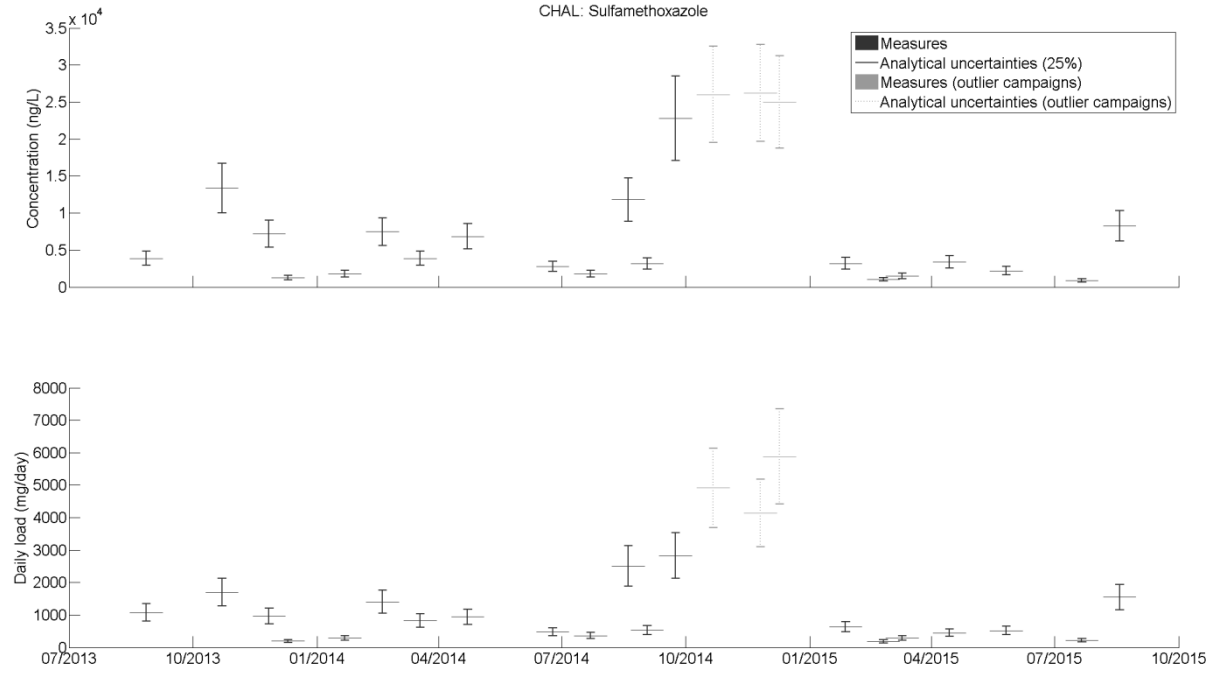

Figure 138: Time series of the daily concentrations and loads of the CHAL hospital for Sulfamethoxazole.

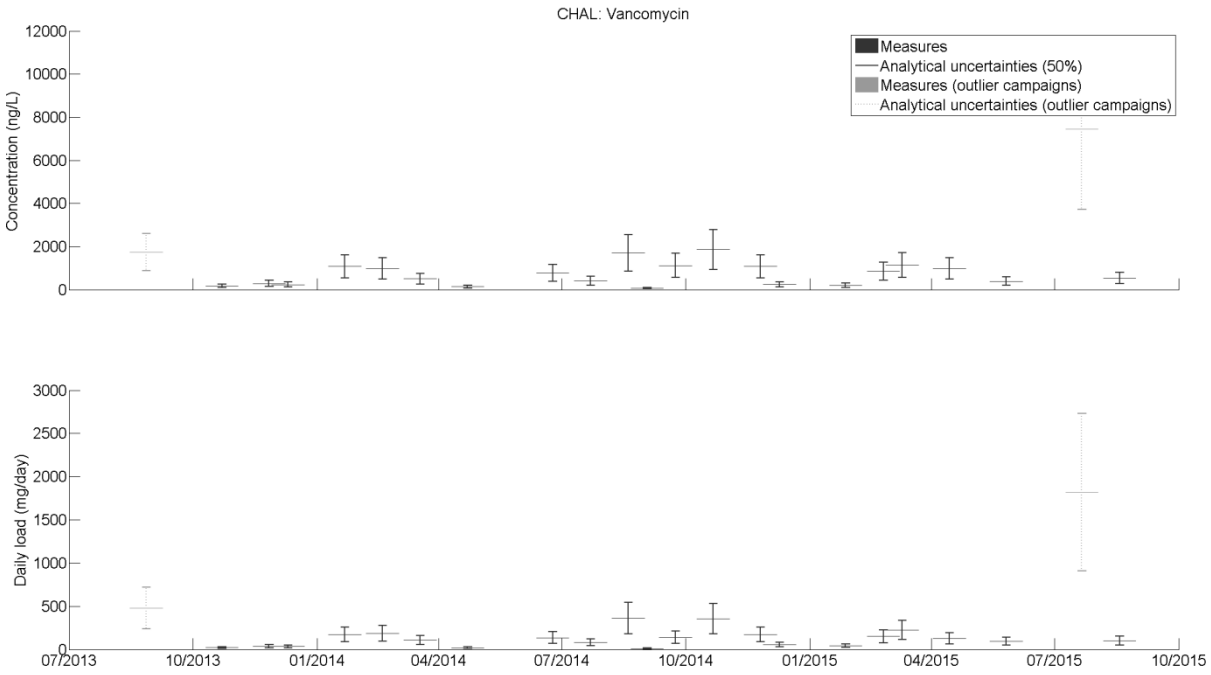

Figure 139: Time series of the daily concentrations and loads of the CHAL hospital for Vancomycin.

APPENDIX 14: HOURLY PHARMACEUTICALS LOADS OF THE CHAL HOSPITAL

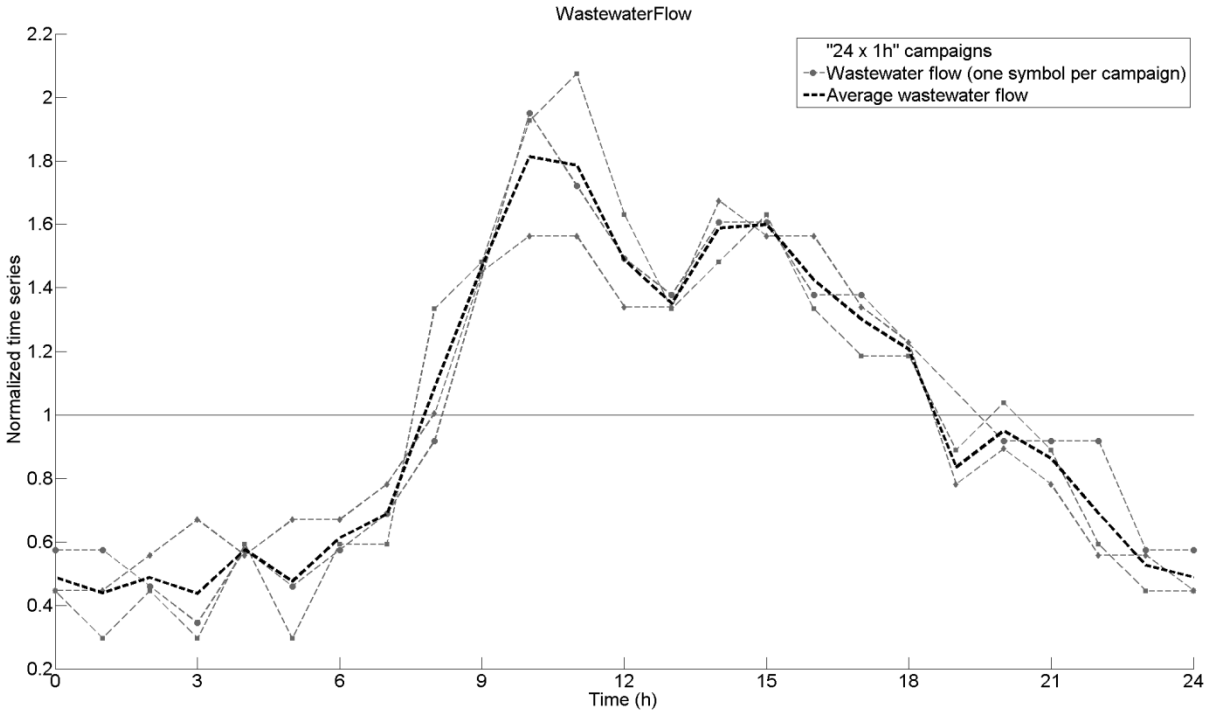

Figure 140: Time series of the hourly flow of the CHAL hospital for the wastewater without the infiltration baseline.

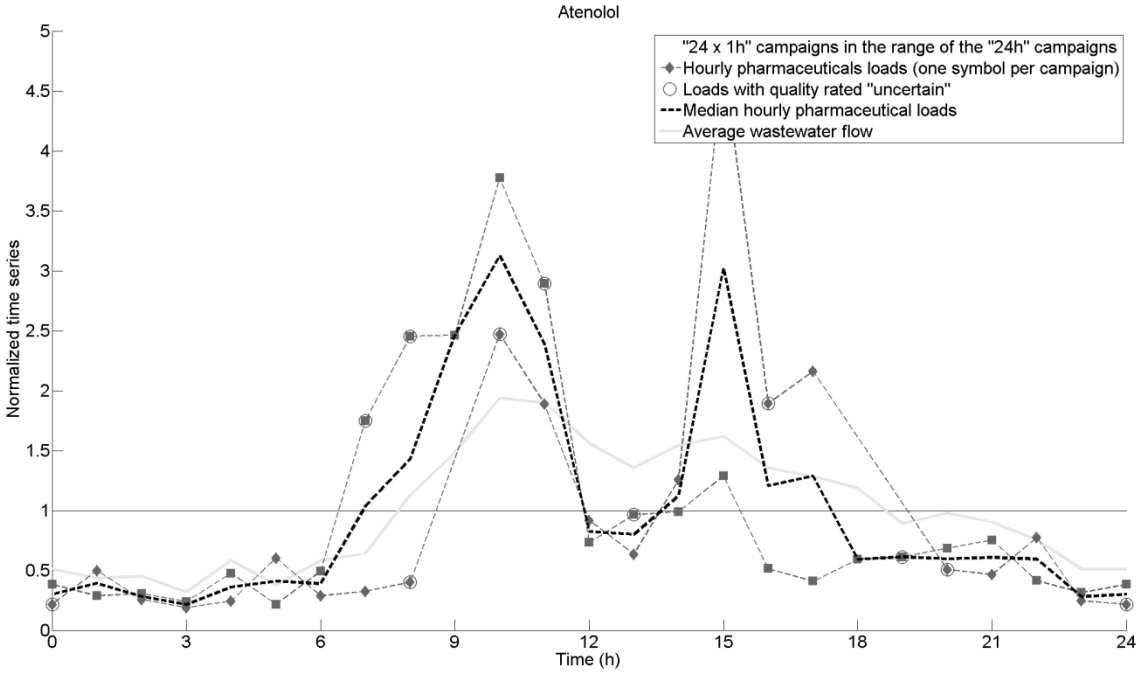

Figure 141: Time series of the hourly loads of the CHAL hospital for Atenolol.

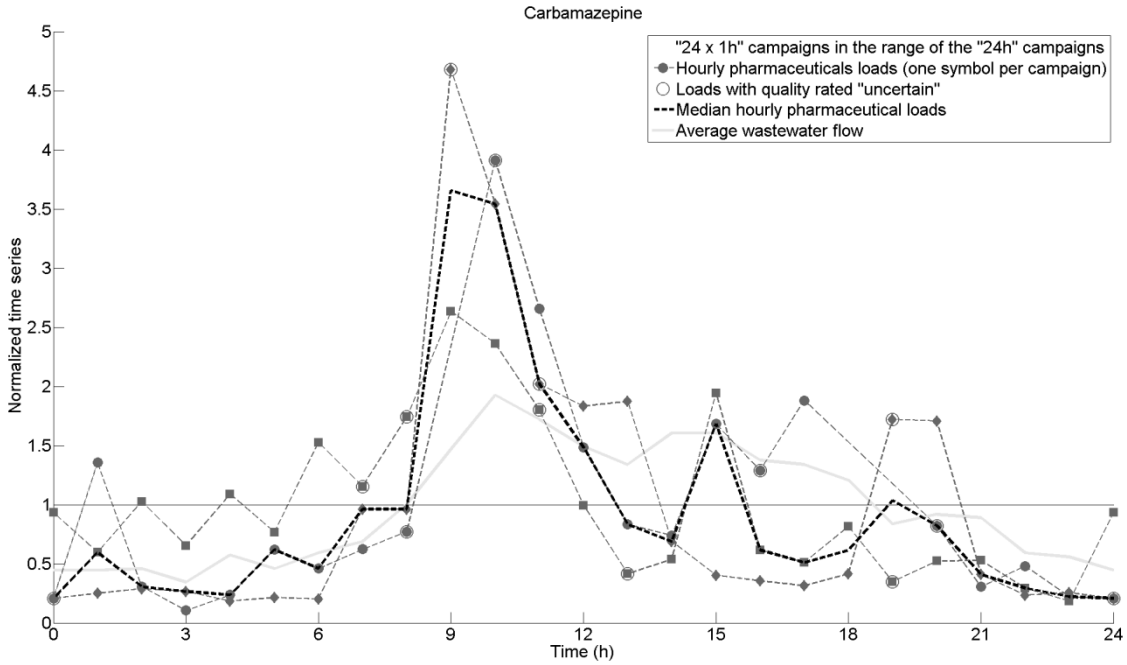

Figure 142: Time series of the hourly loads of the CHAL hospital for Carbamazepine.

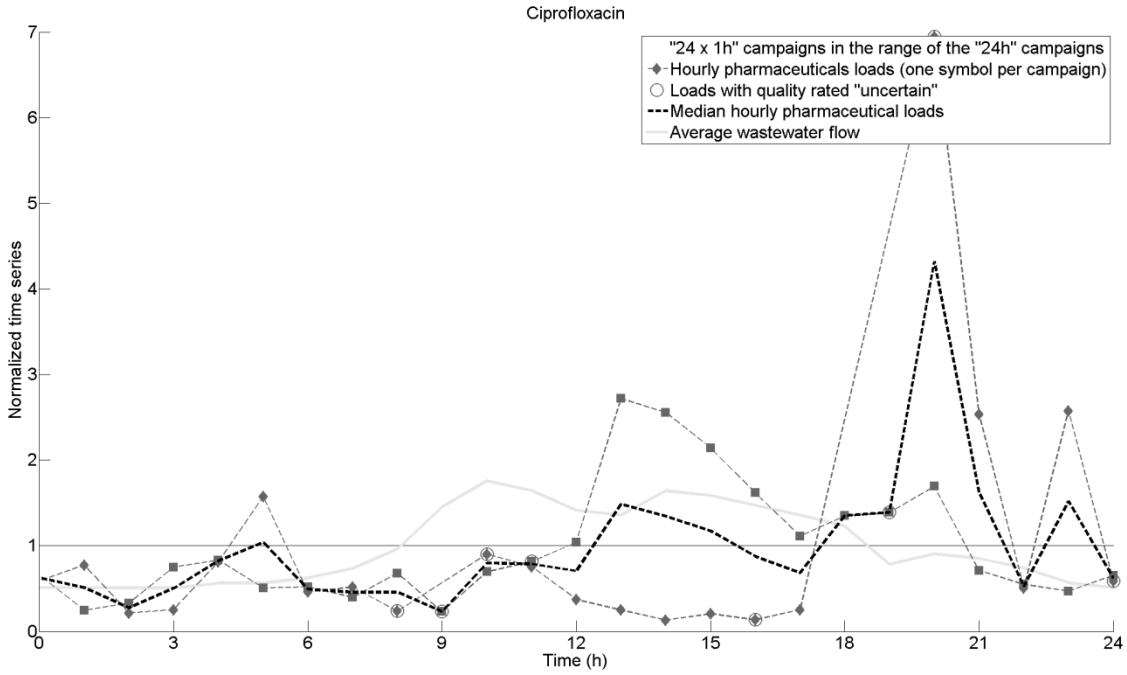

Figure 143: Time series of the hourly loads of the CHAL hospital for Ciprofloxacin.

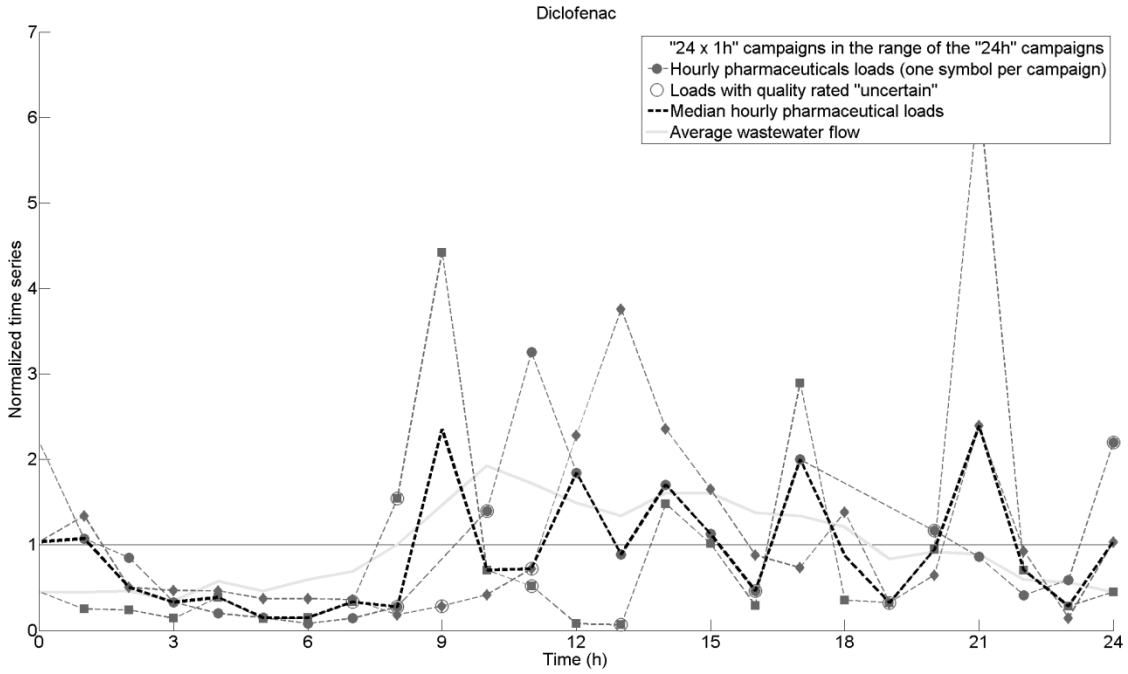

Figure 144: Time series of the hourly loads of the CHAL hospital for Diclofenac.

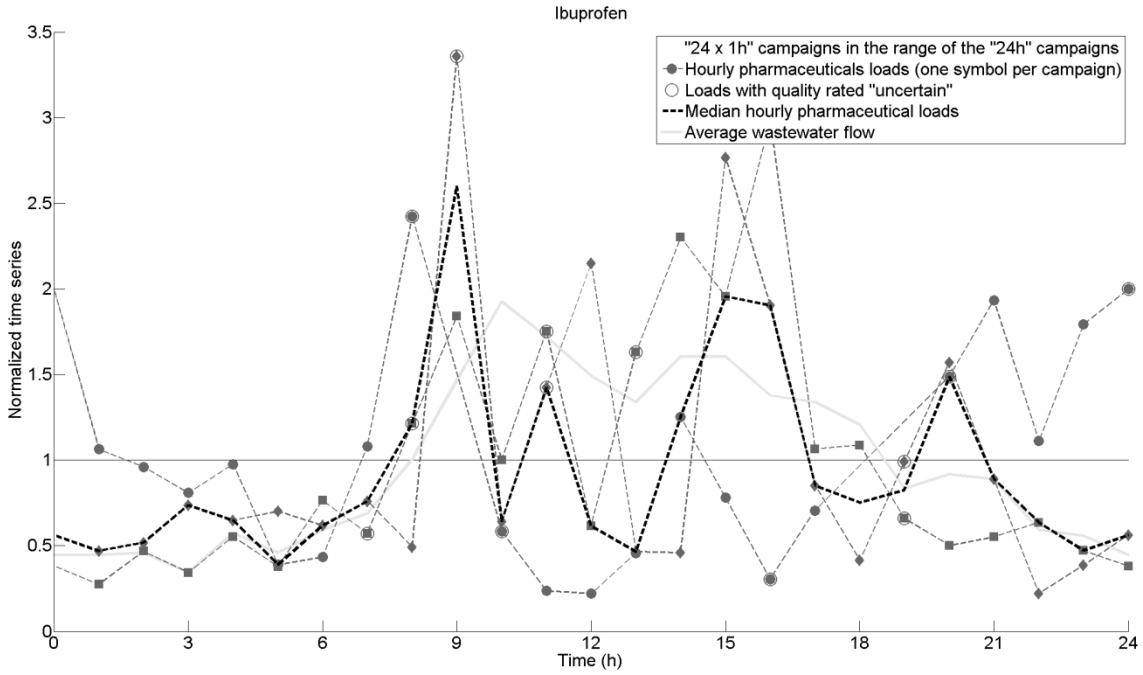

Figure 145: Time series of the hourly loads of the CHAL hospital for Ibuprofen.

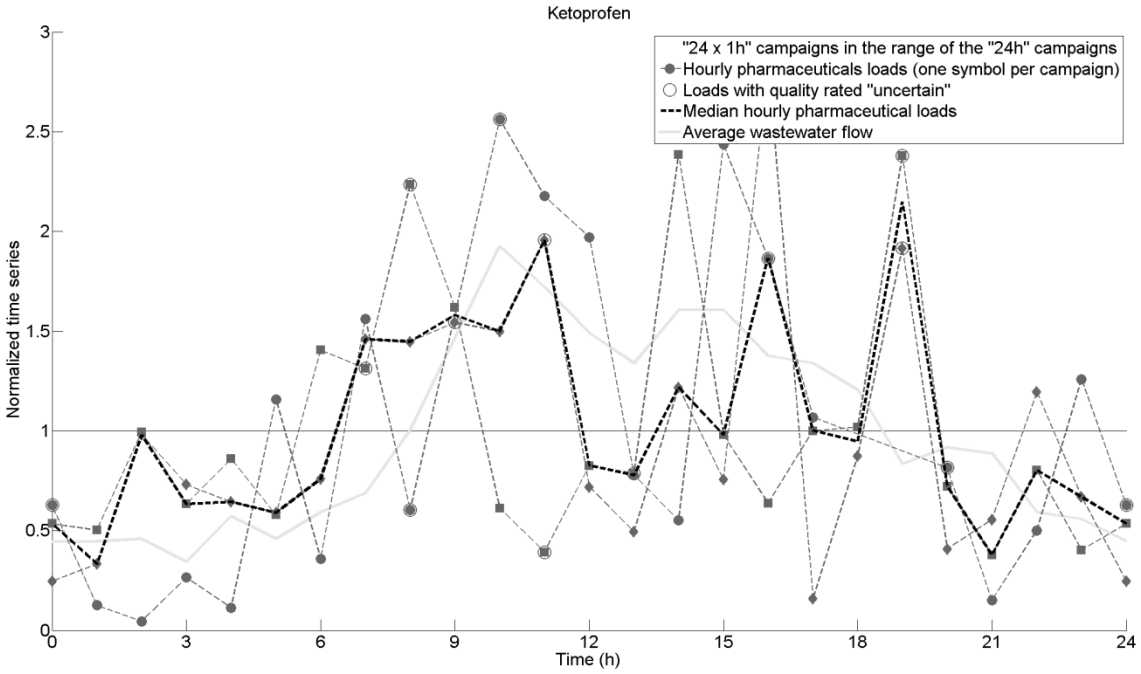

Figure 146: Time series of the hourly loads of the CHAL hospital for Ketoprofen.

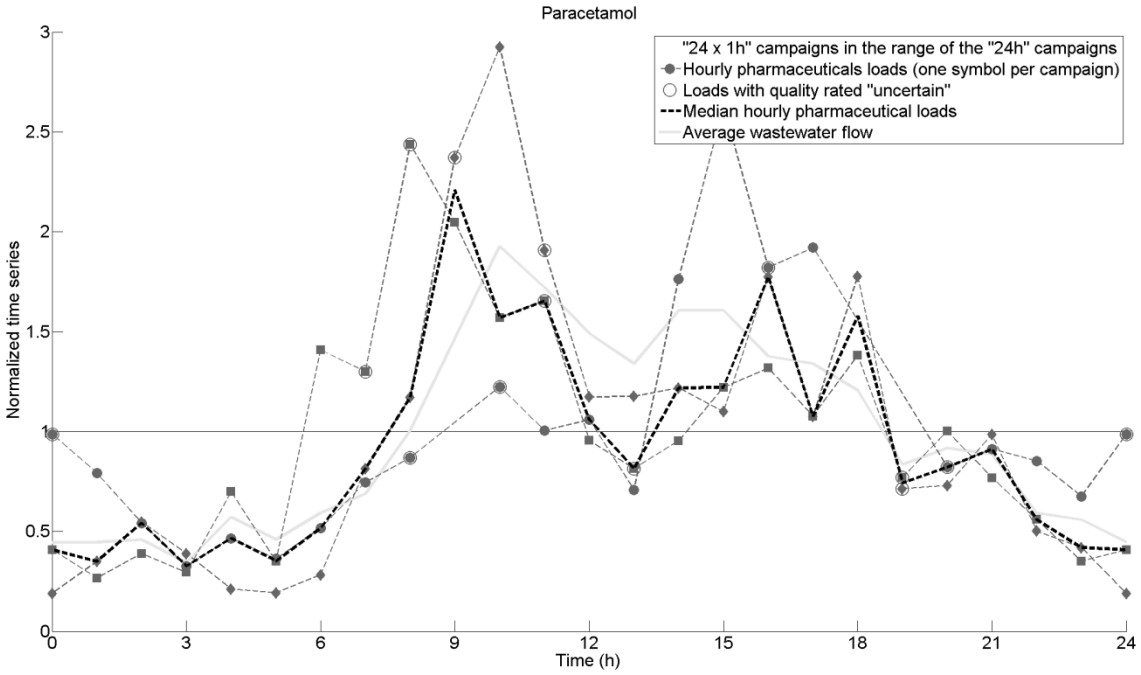

Figure 147: Time series of the hourly loads of the CHAL hospital for Paracetamol.

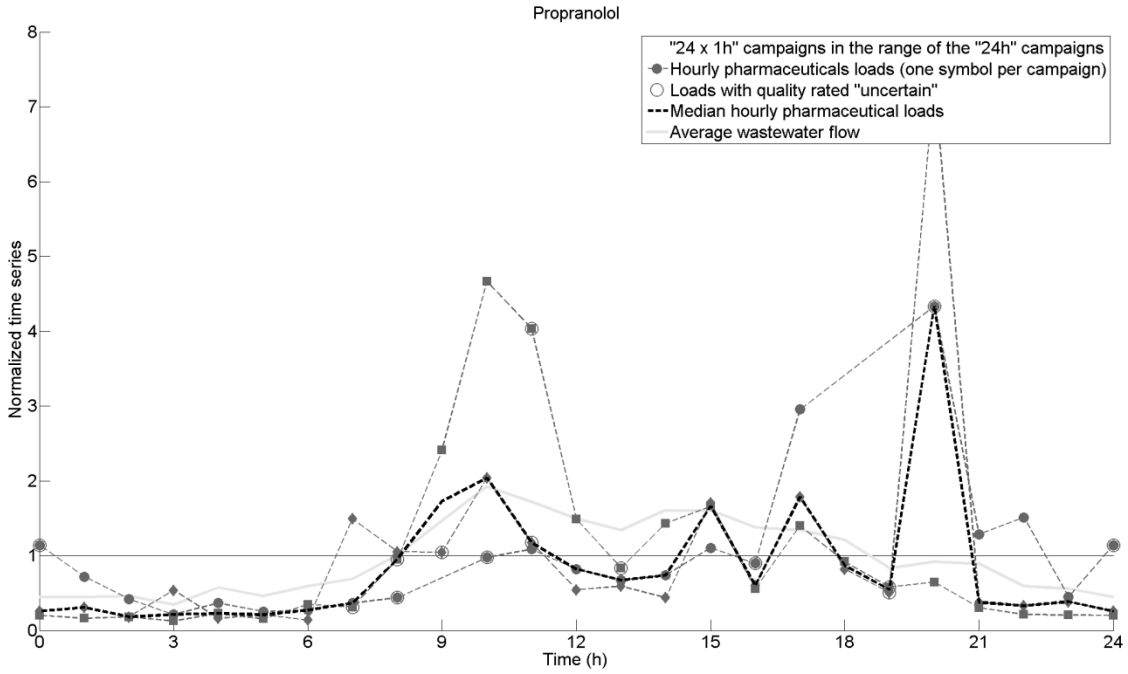

Figure 148: Time series of the hourly loads of the CHAL hospital for Propranolol.

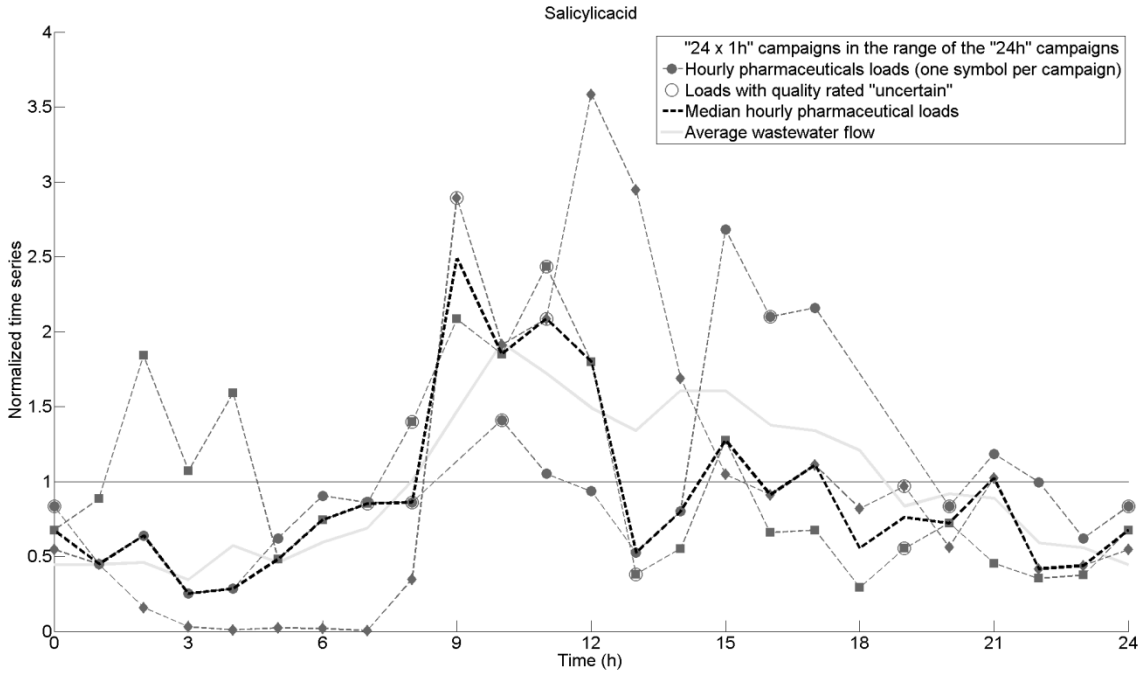

Figure 149: Time series of the hourly loads of the CHAL hospital for Salicylic acid.

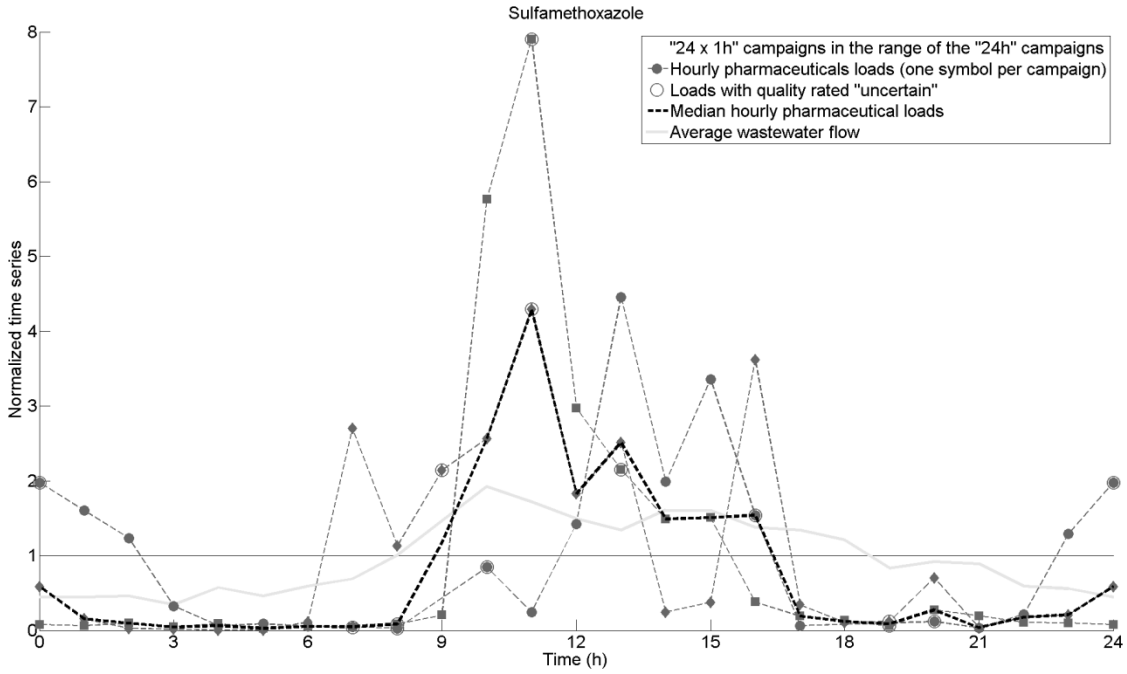

Figure 150: Time series of the hourly loads of the CHAL hospital for Sulfamethoxazole.

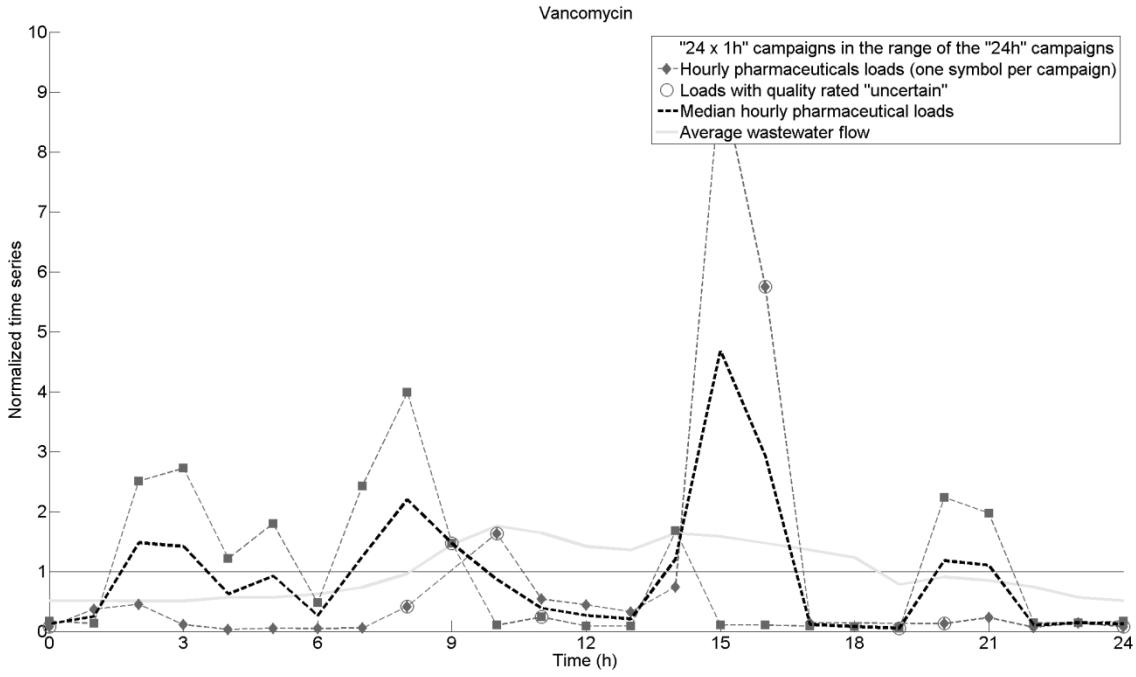

Figure 151: Time series of the hourly loads of the CHAL hospital for Vancomycin.

APPENDIX 15: DAILY LOADS OF THE “7 X 24H” CAMPAIGNS IN THE CHAL HOSPITAL

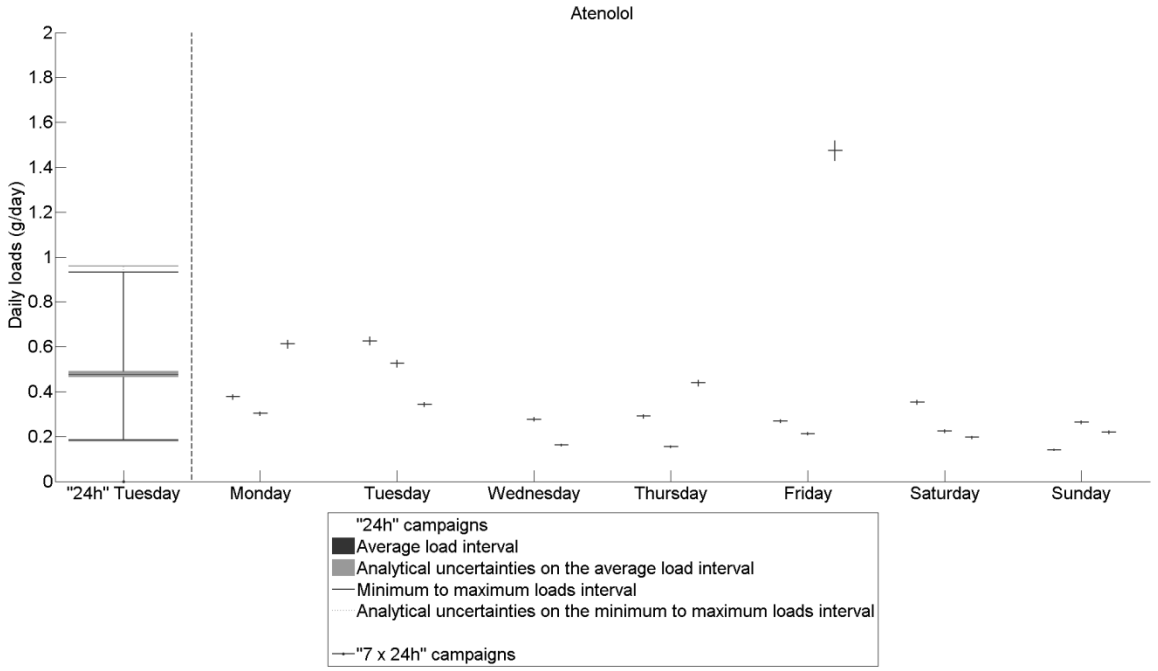

Figure 152: Time series of the daily loads for the “7 x 24h” of the CHAL hospital for Atenolol.

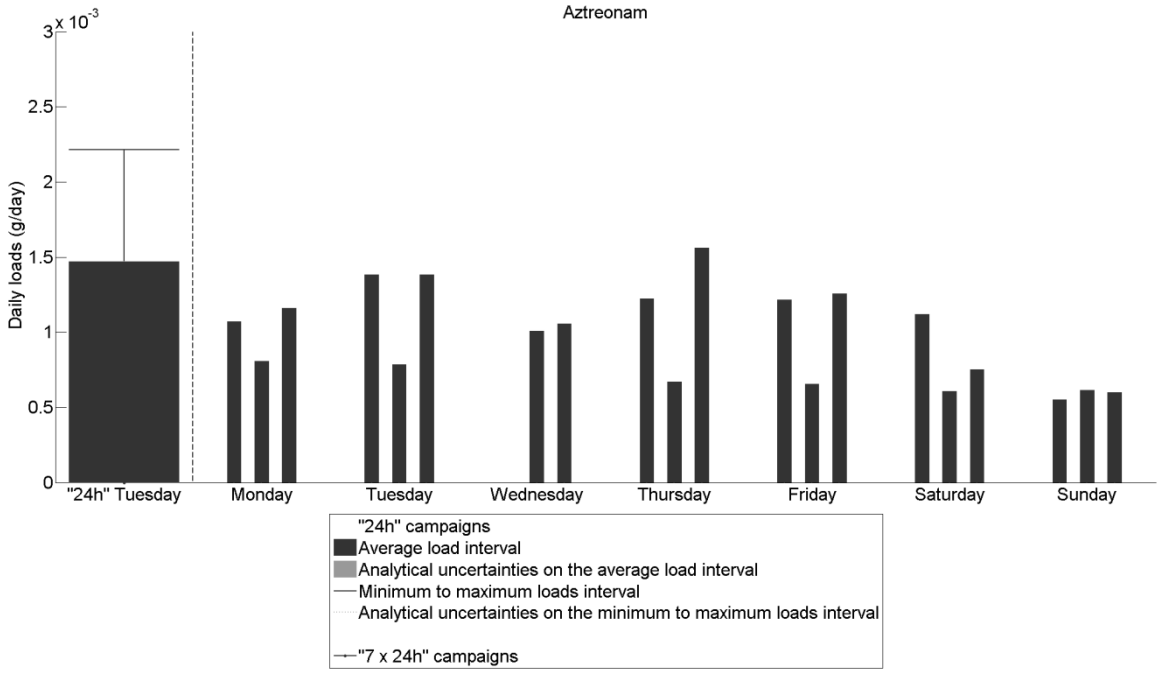

Figure 153: Time series of the daily loads for the “7 x 24h” of the CHAL hospital for Aztreonam.

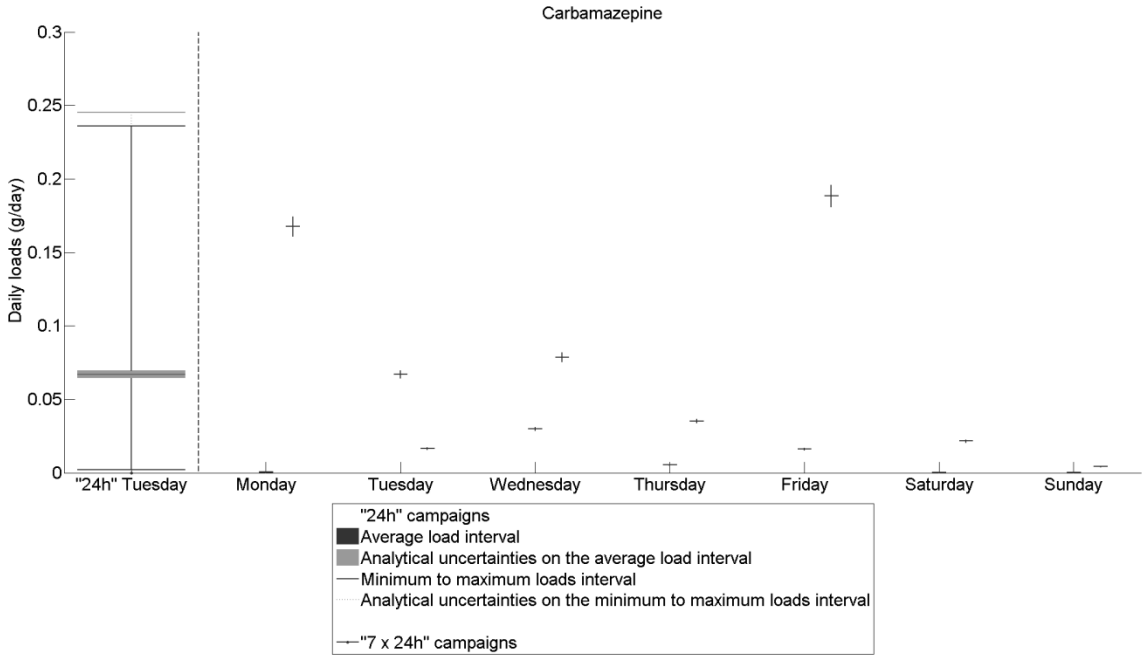

Figure 154: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Carbamazepine.

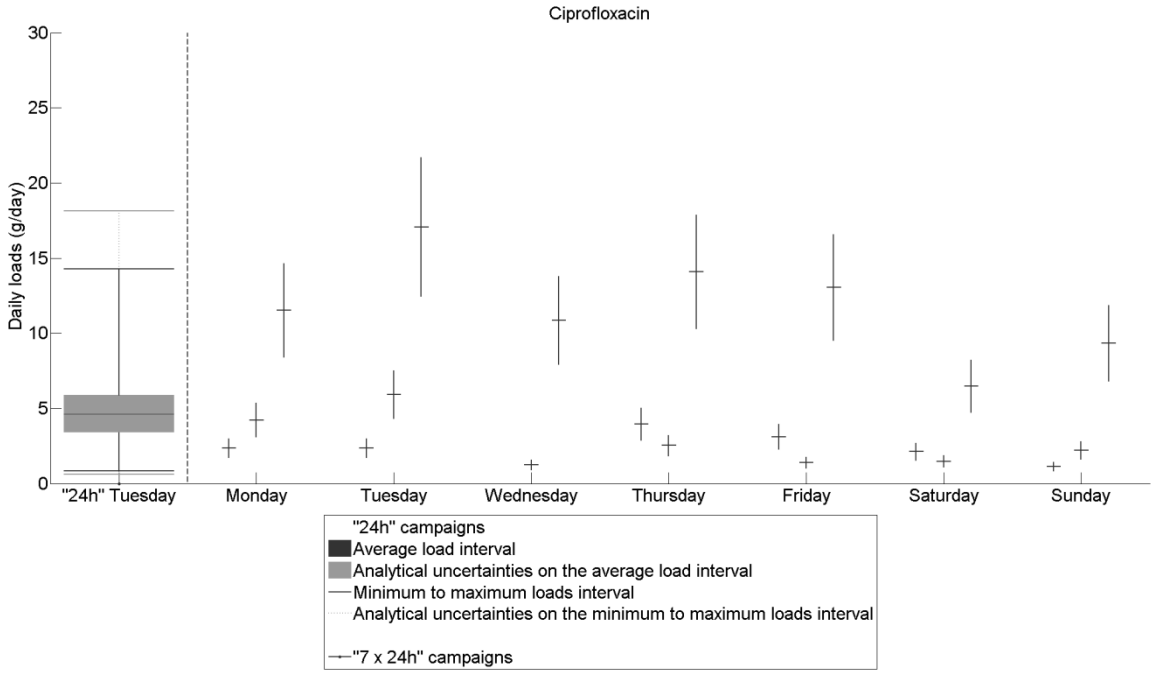

Figure 155: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Ciprofloxacin.

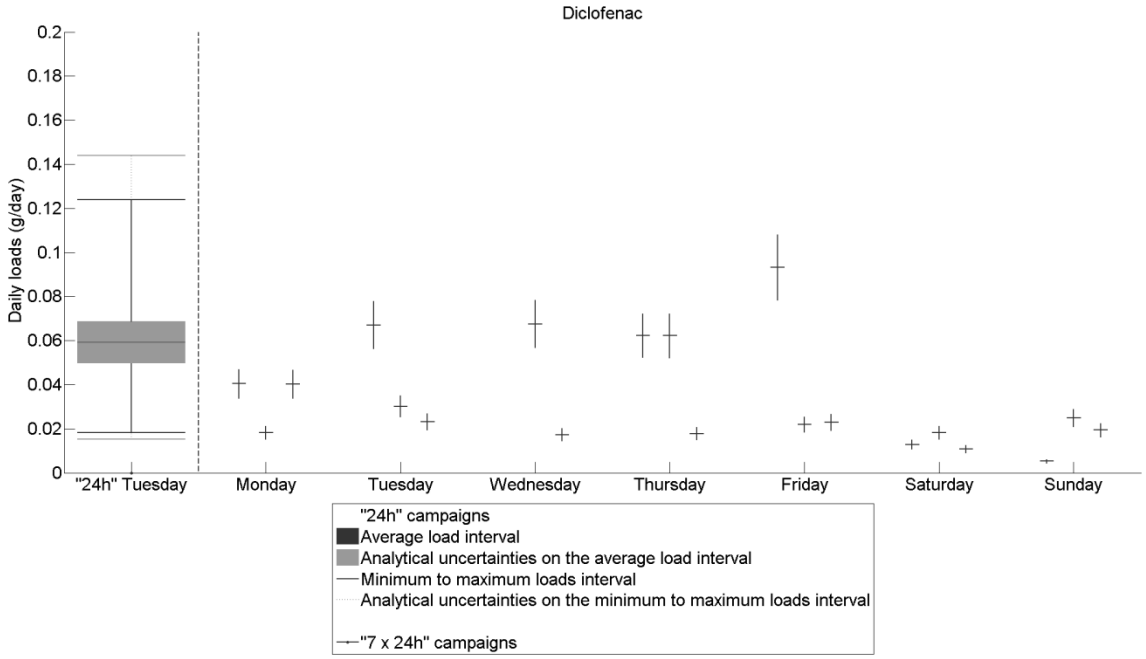

Figure 156: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Diclofenac.

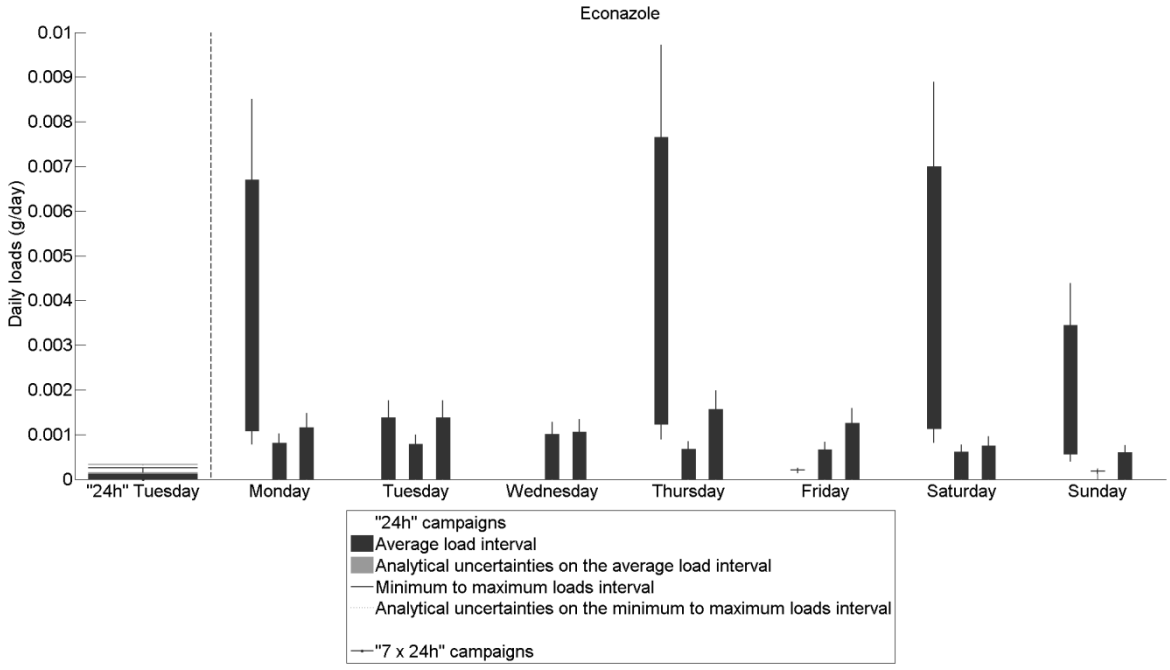

Figure 157: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Econazole.

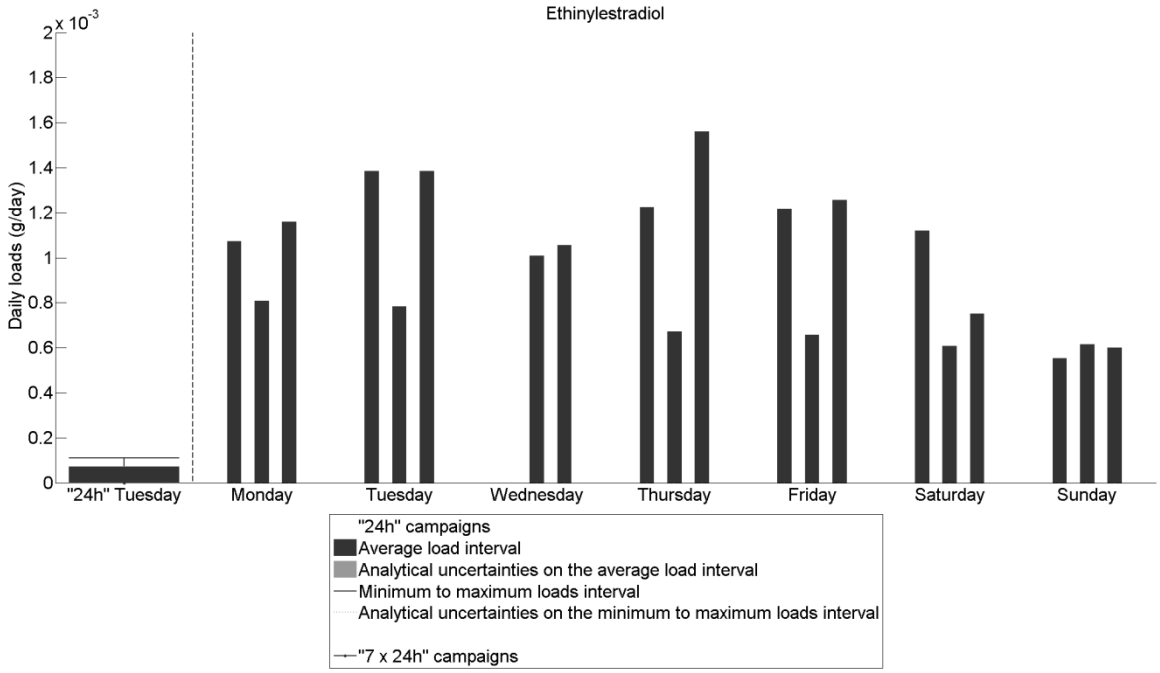

Figure 158: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Ethinylestradiol.

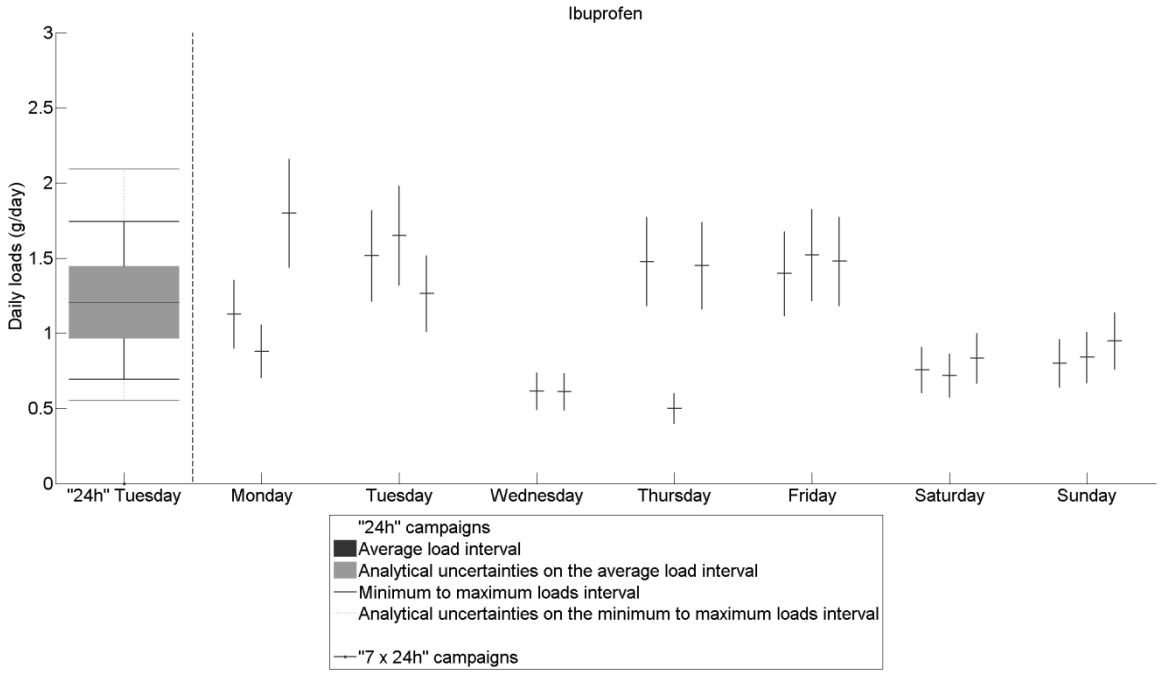

Figure 159: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Ibuprofen.

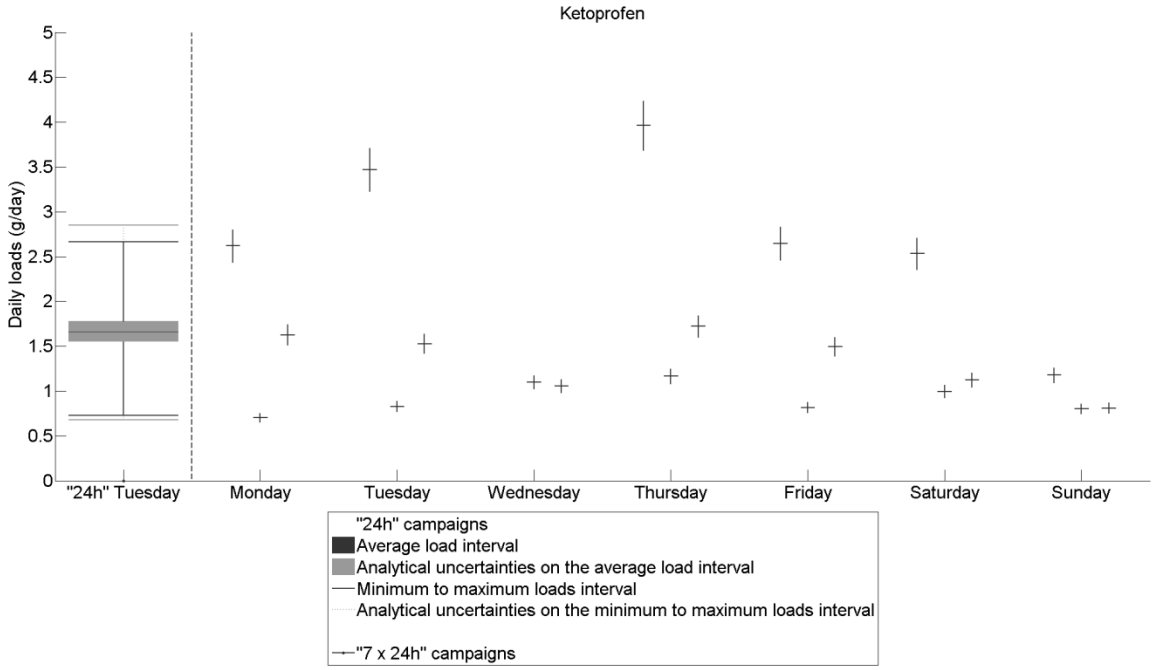

Figure 160: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Ketoprofen.

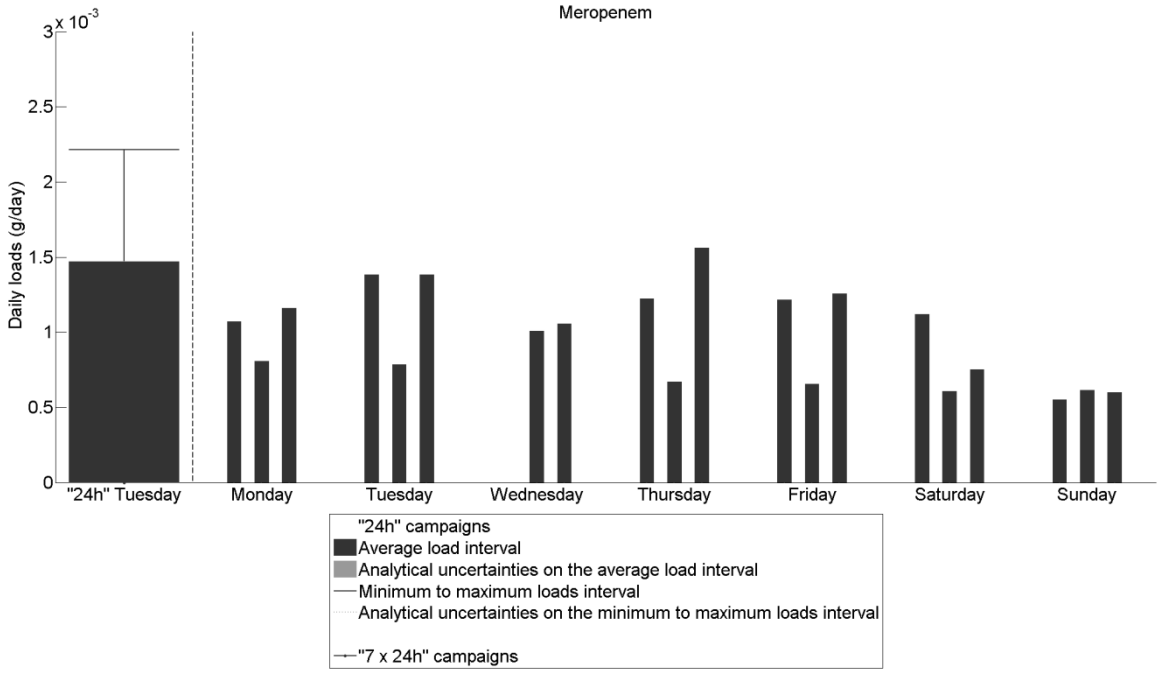

Figure 161: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Meropenem.

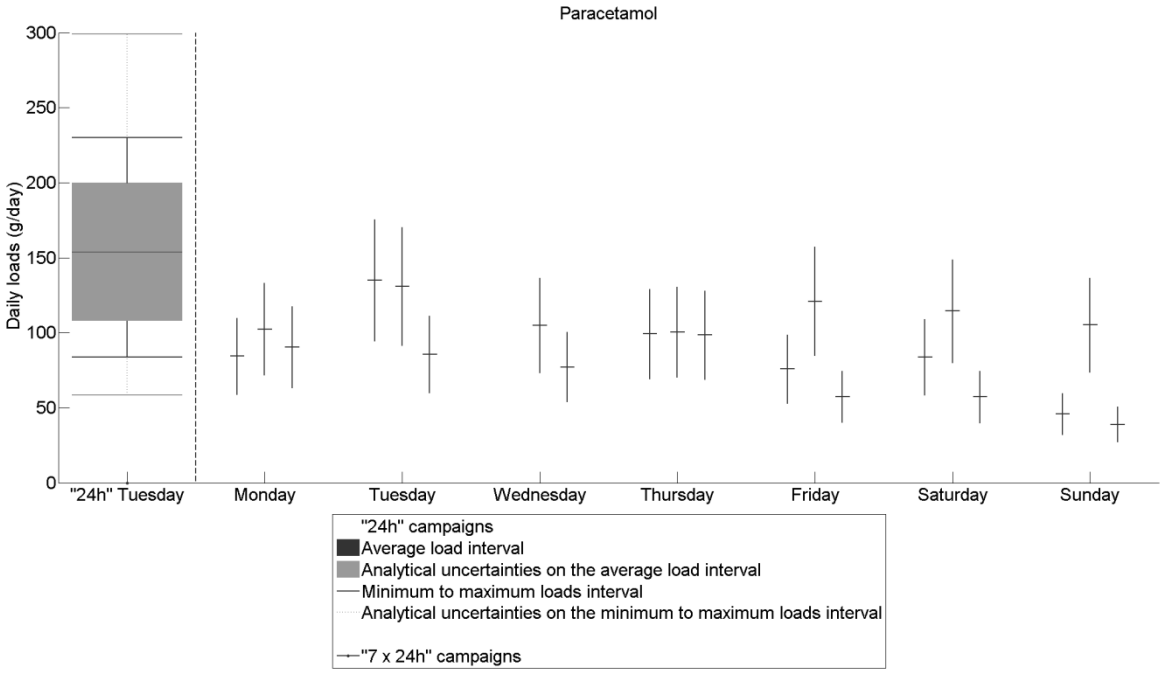

Figure 162: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Paracetamol.

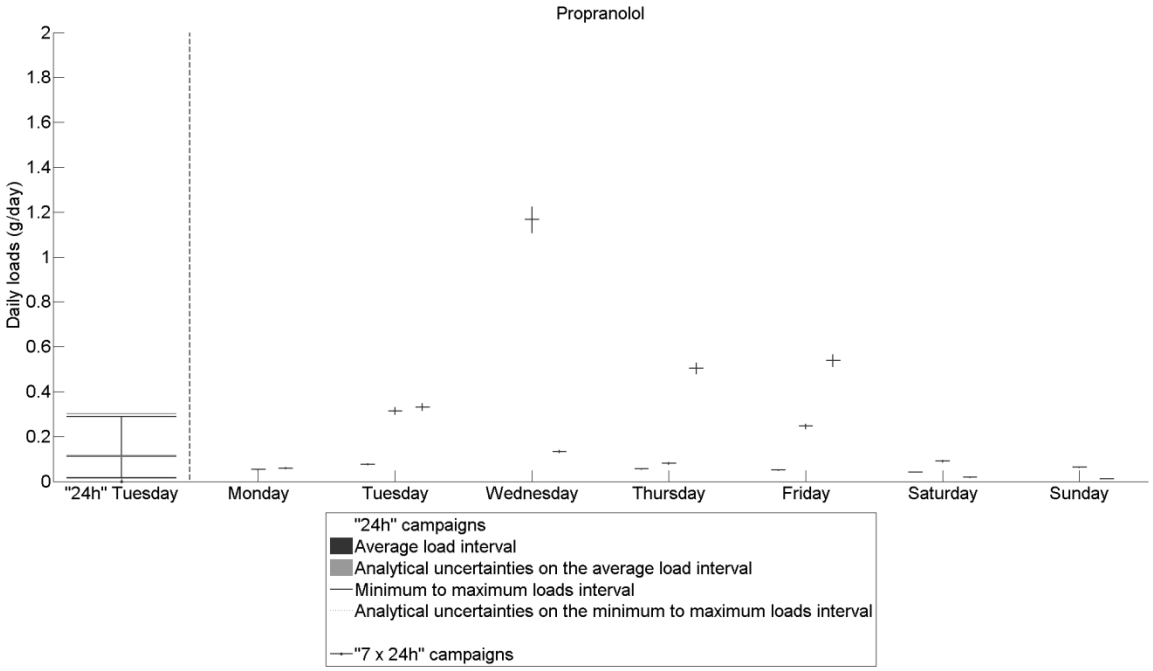

Figure 163: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Propranolol.

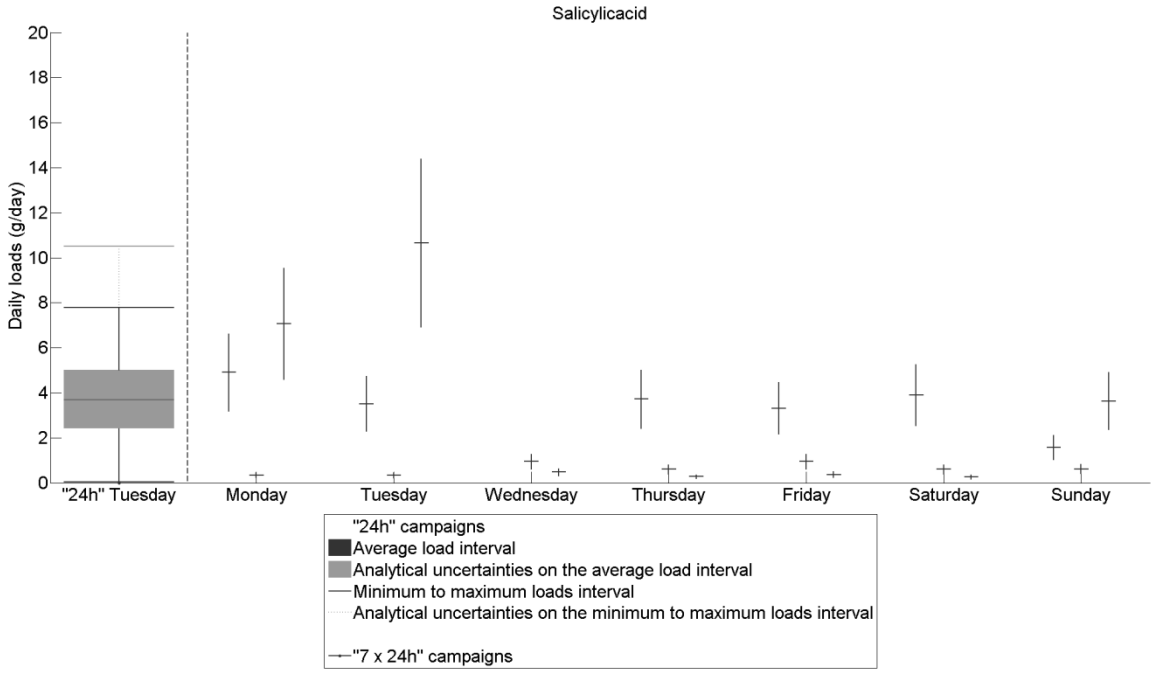

Figure 164: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Salicylic acid.

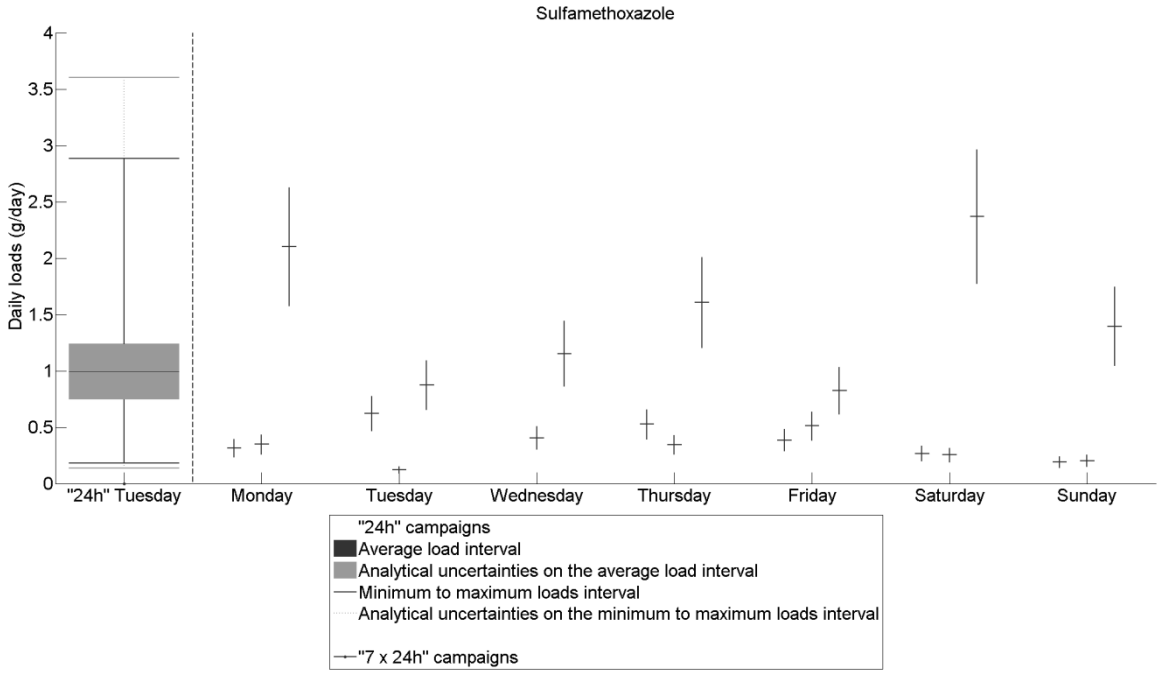

Figure 165: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Sulfamethoxazole.

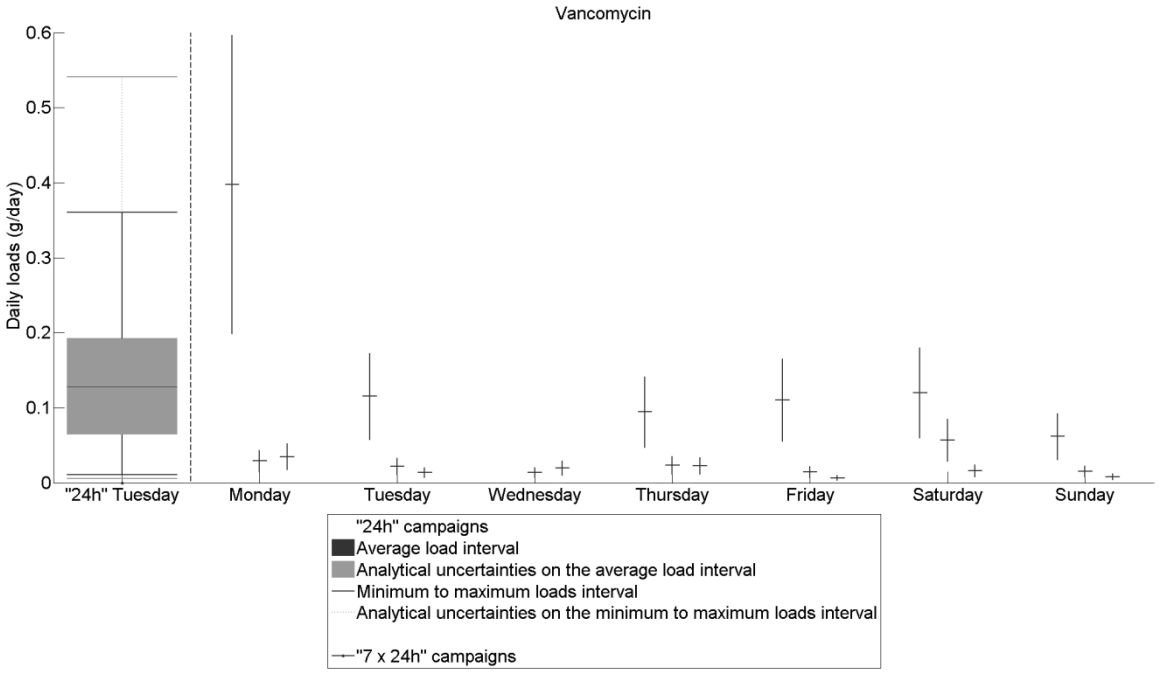

Figure 166: Time series of the daily loads for the "7 x 24h" of the CHAL hospital for Vancomycin.

APPENDIX 16: COMPARISON OF THE DAILY CONCENTRATIONS AND LOADS OF THE TWO SITES

Table 51: Comparison of the daily pharmaceuticals concentrations and loads between the two sites.

Molecule	Average daily concentration (ng/L)			Average daily load (mg/day)			Average daily load per capita (µg/day/capita)		
	Urban	Hospital	Hospital/ Urban	Urban	Hospital	Hospital/ Urban	Urban (15 733 inhabitants)	Hospital (450 beds)	Hospital/ Urban
Atenolol	2 533	2 553	1	9 578	477	0.05	609	1 061	1.74
Aztreonam	Not detected	Not detected	-	-	-	-	-	-	-
Carbamazepine	648	368	0.57	2 422	67	0.03	154	149	0.97
Ciprofloxacin	1 to 16	23 845	1 490 to ∞	6 to 65	4 635	71 to 834	0 to 4	10 301	2498 to 29 172
Diclofenac	818	339	0.41	3 030	59	0.02	193	132	0.68
Econazole	0 to 1	0 to 1	-	-	-	-	-	-	-
Ethinylestradiol	Not detected	Not detected	-	-	-	-	-	-	-
Ibuprofen	8 813	6 885	0.78	33 043	1 204	0.04	2 100	2 676	1.27
Ketoprofen	1 423	9 385	6.60	5 376	1 665	0.31	342	3 699	11
Meropenem	Not detected	Not detected	-	-	-	-	-	-	-
Paracetamol	146 619	886 733	6	564 429	153 881	0.27	35 876	341 958	10
Propranolol	464	621	1.34	1 683	113	0.07	107	251	2.34
Salicylic acid	28 727	20 377	0.71	102 397	3 704	0.04	6 508	8 231	1.26
Sulfamethoxazole	453	5 885	13	1 709	991	0.58	109	2 201	20
Vancomycin	0 to 10	719	72 to ∞	2 to 41	128	3.17 to 78	0 to 3	285	111 to 2 730

APPENDIX 17: CORRELATION BETWEEN SALES AND DAILY LOADS FOR THE URBAN CATCHMENT

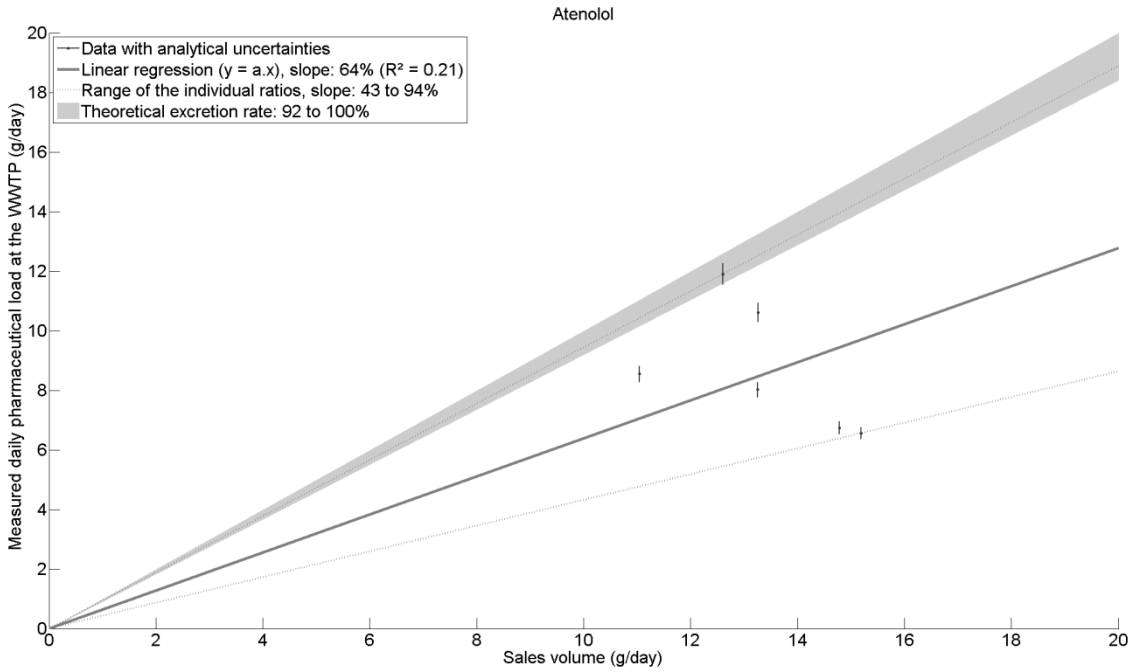

Figure 167: Correlation between sales and daily loads of Atenolol for the urban catchment.

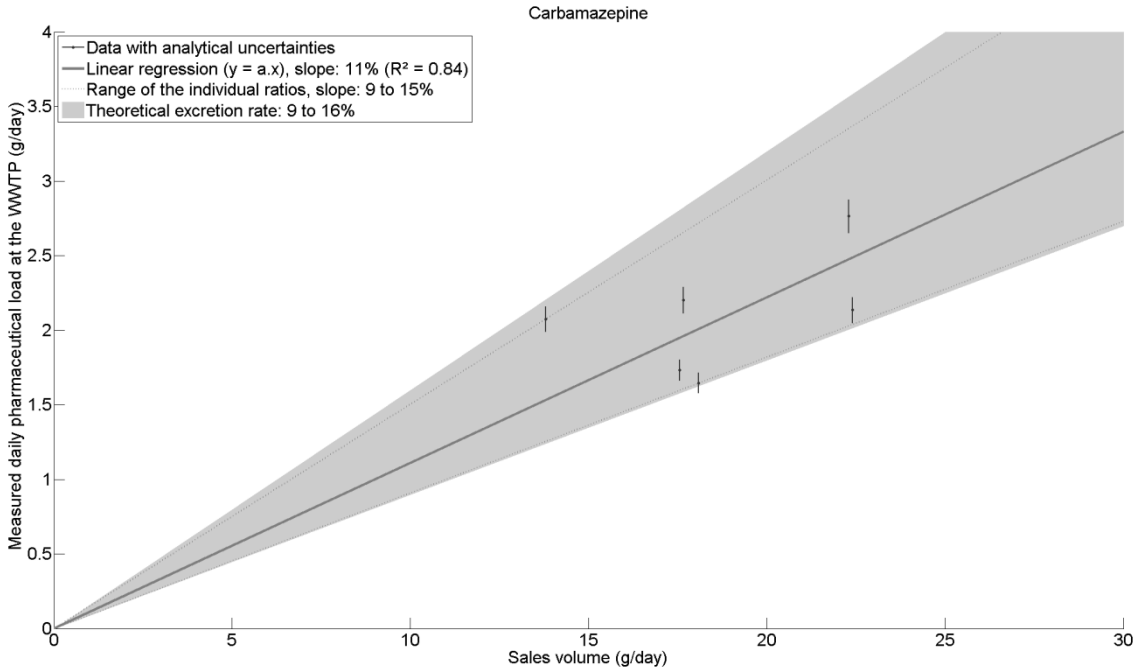

Figure 168: Correlation between sales and daily loads of Carbamazepine for the urban catchment.

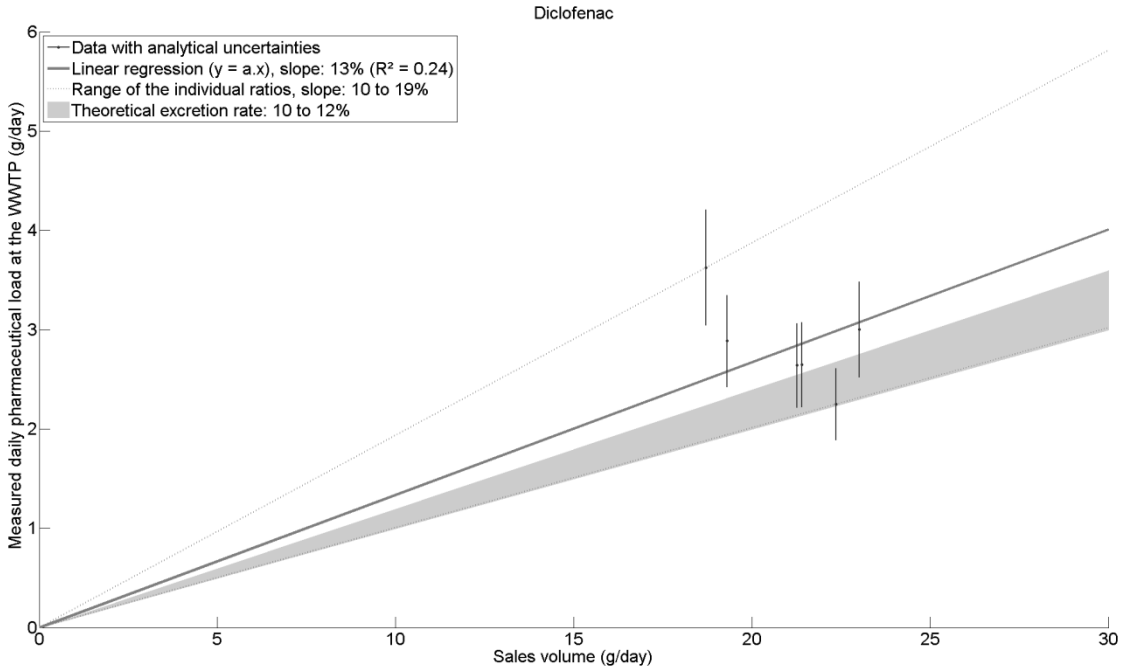

Figure 169: Correlation between sales and daily loads of Diclofenac for the urban catchment.

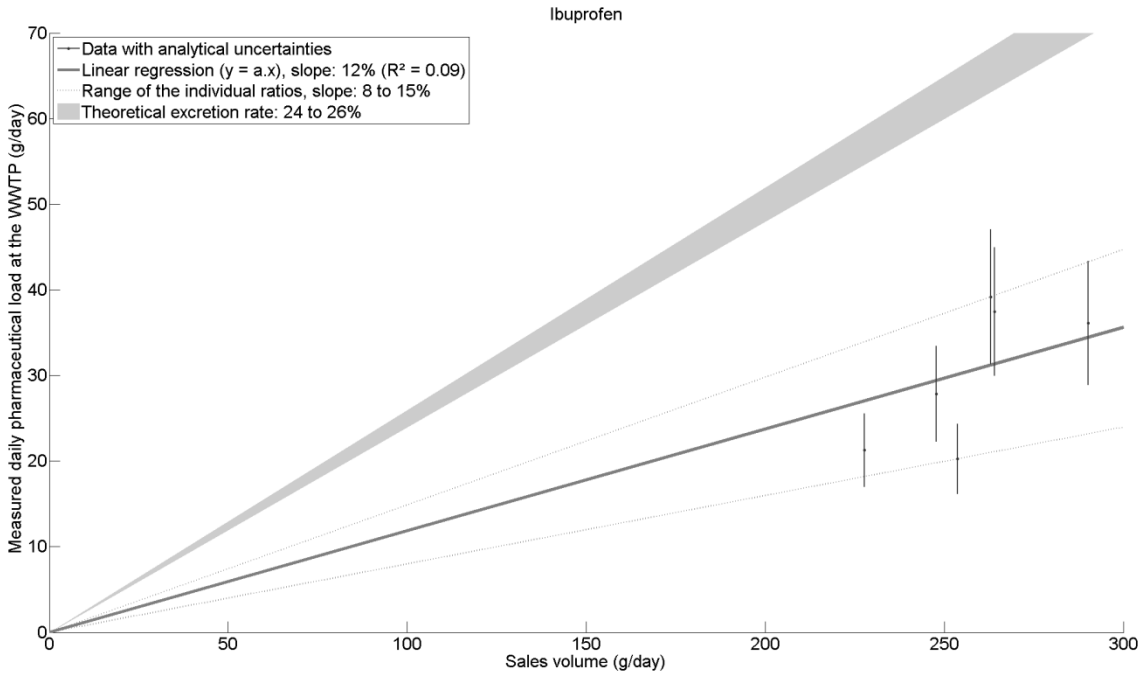

Figure 170: Correlation between sales and daily loads of Ibuprofen for the urban catchment.

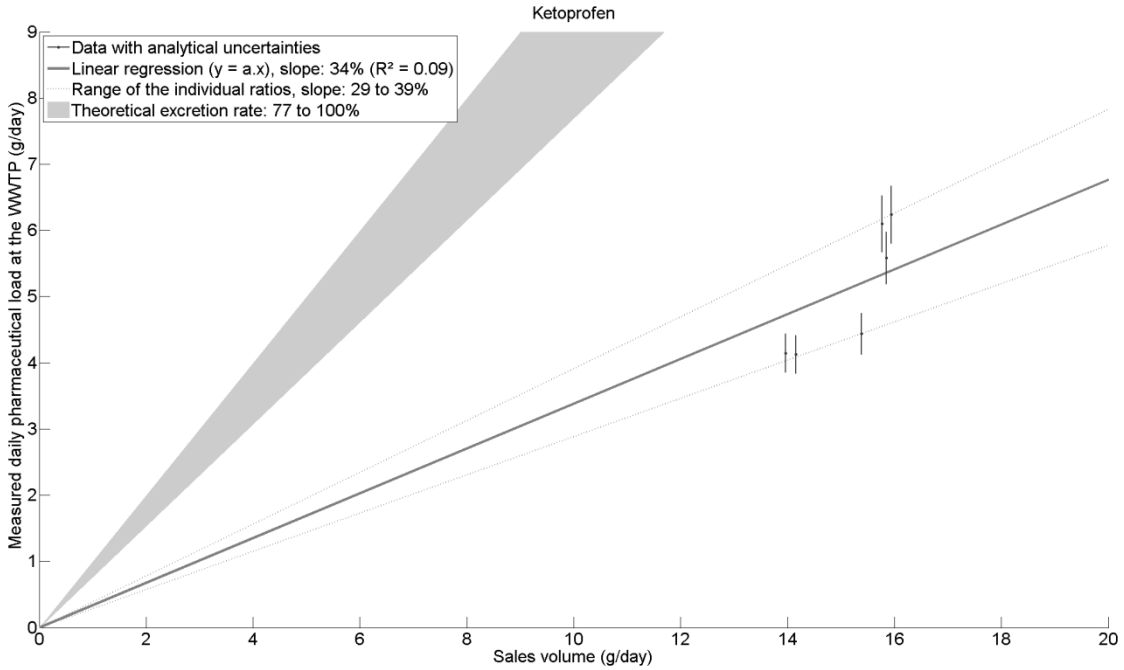

Figure 171: Correlation between sales and daily loads of Ketoprofen for the urban catchment.

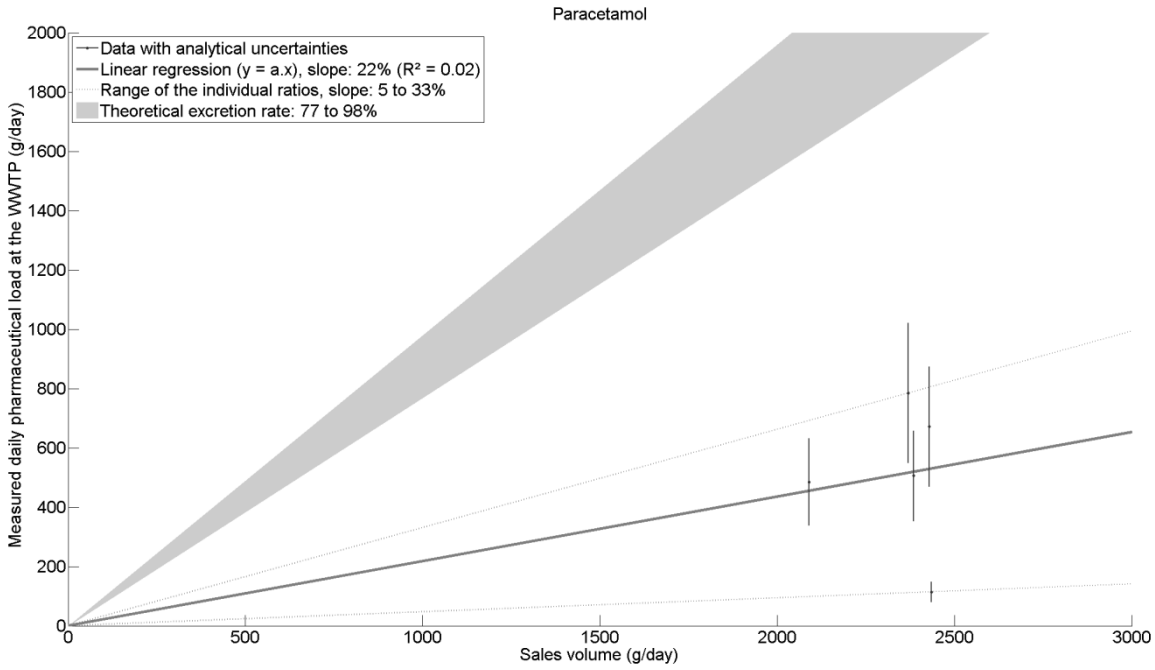

Figure 172: Correlation between sales and daily loads of Paracetamol for the urban catchment.

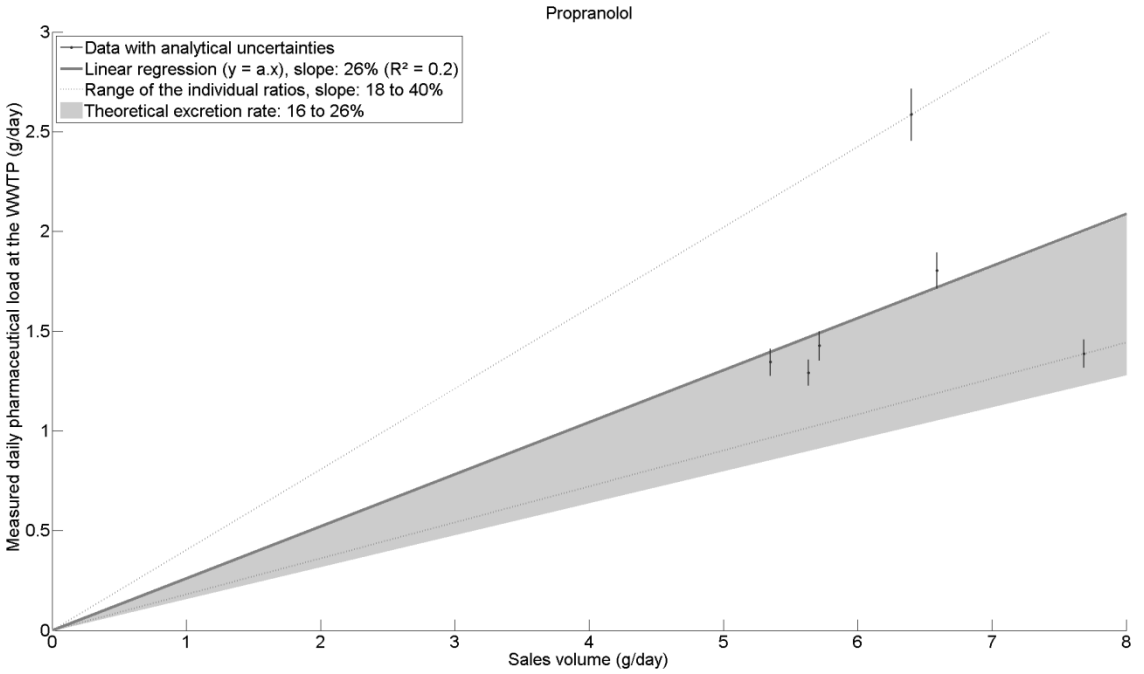

Figure 173: Correlation between sales and daily loads of Propranolol for the urban catchment.

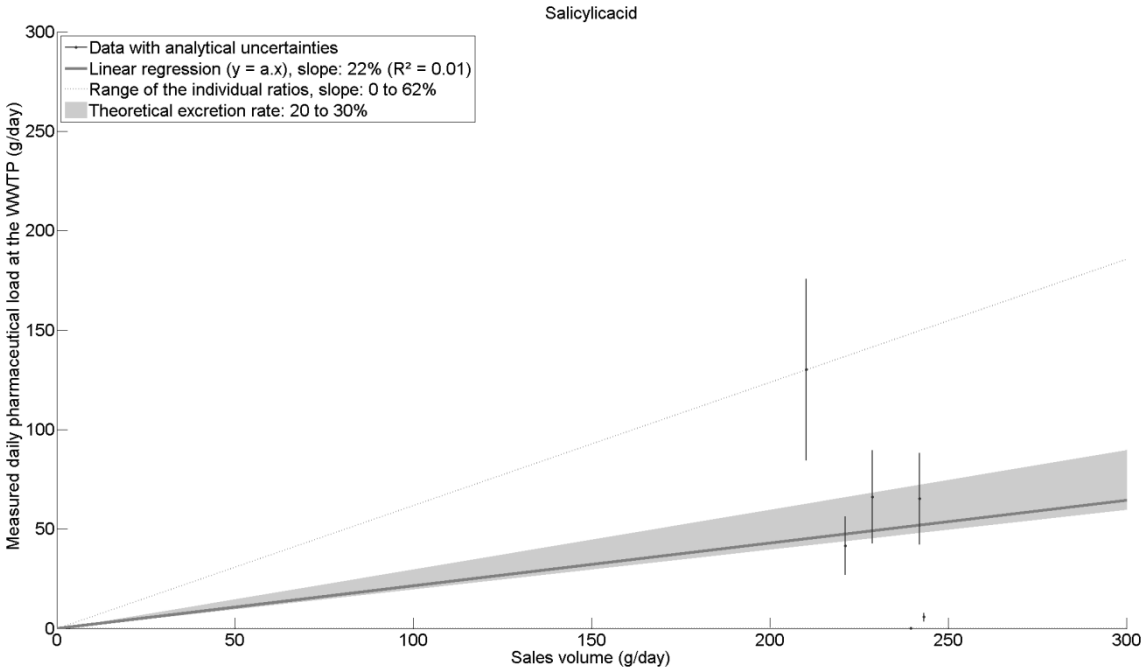

Figure 174: Correlation between sales and daily loads of Salicylic acid for the urban catchment.

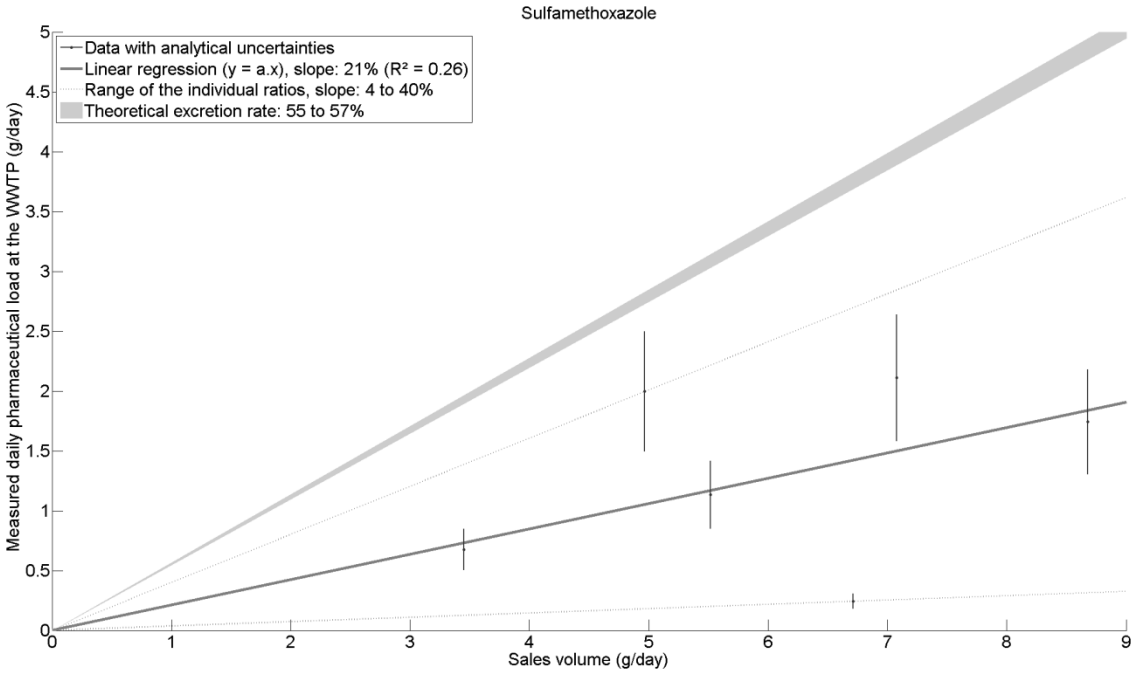

Figure 175: Correlation between sales and daily loads of Sulfamethoxazole for the urban catchment.

APPENDIX 18: CORRELATION BETWEEN DISTRIBUTIONS AND DAILY LOADS FOR THE CHAL HOSPITAL

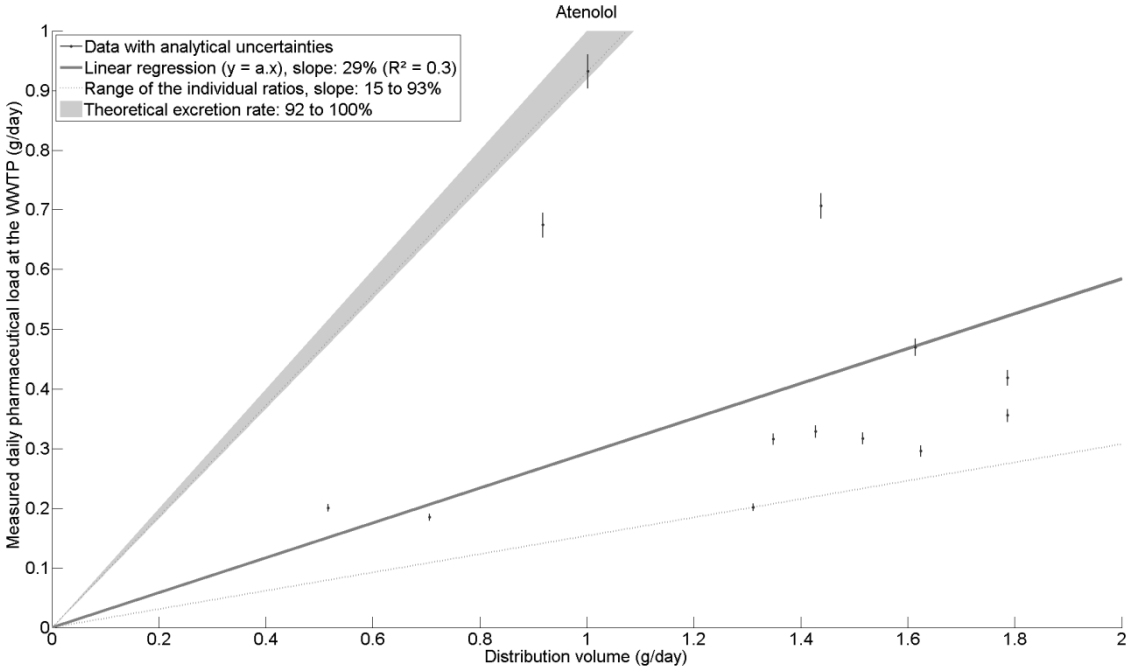

Figure 176: Correlation between distributions and daily loads of Atenolol for the CHAL hospital.

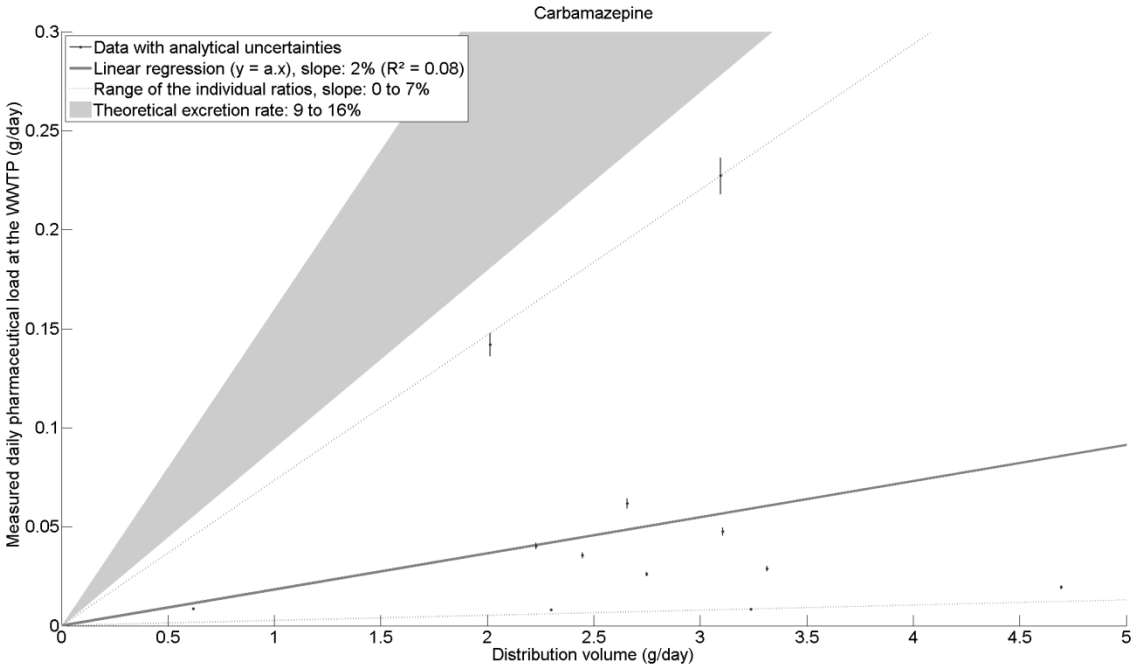

Figure 177: Correlation between distributions and daily loads of Carbamazepine for the CHAL hospital.

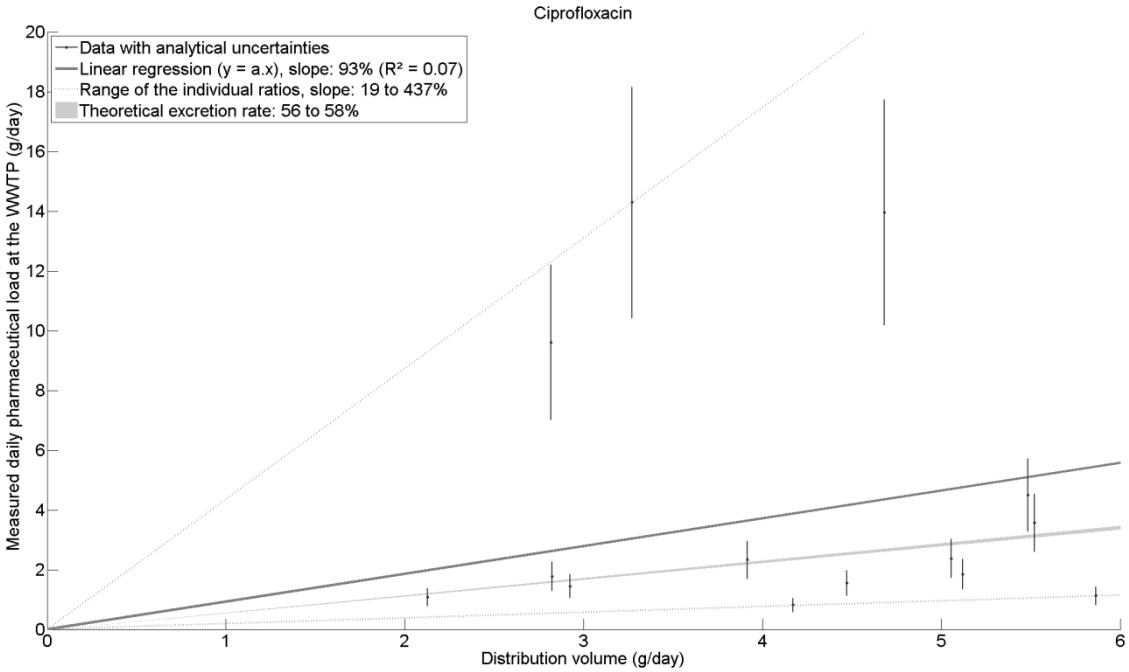

Figure 178: Correlation between distributions and daily loads of Ciprofloxacin for the CHAL hospital.

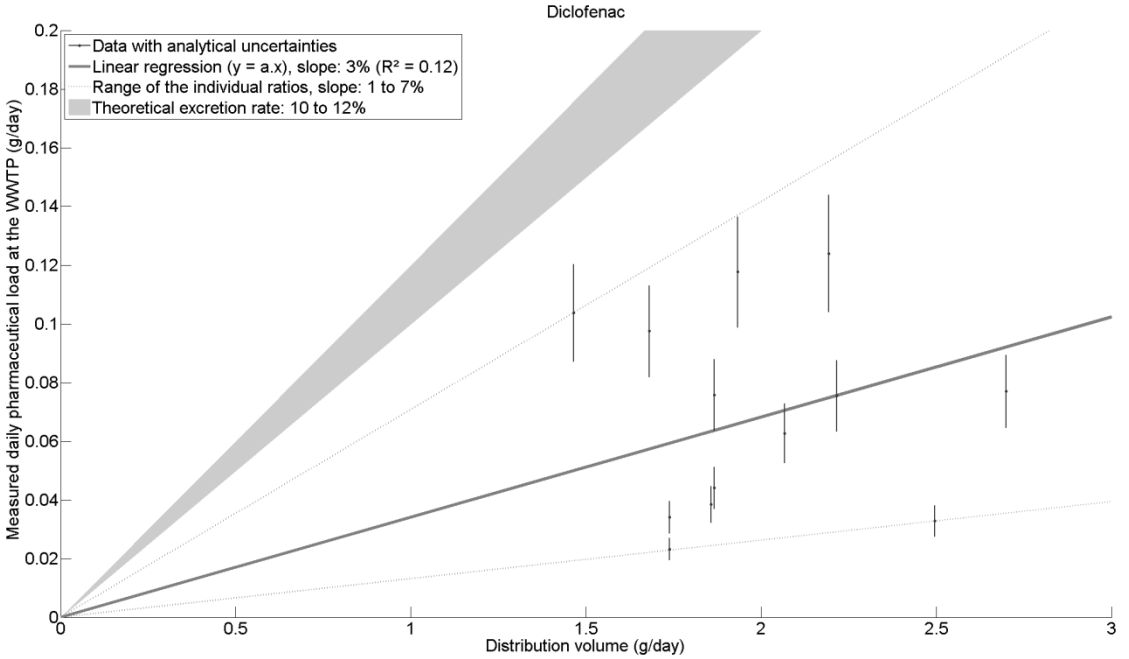

Figure 179: Correlation between distributions and daily loads of Diclofenac for the CHAL hospital.

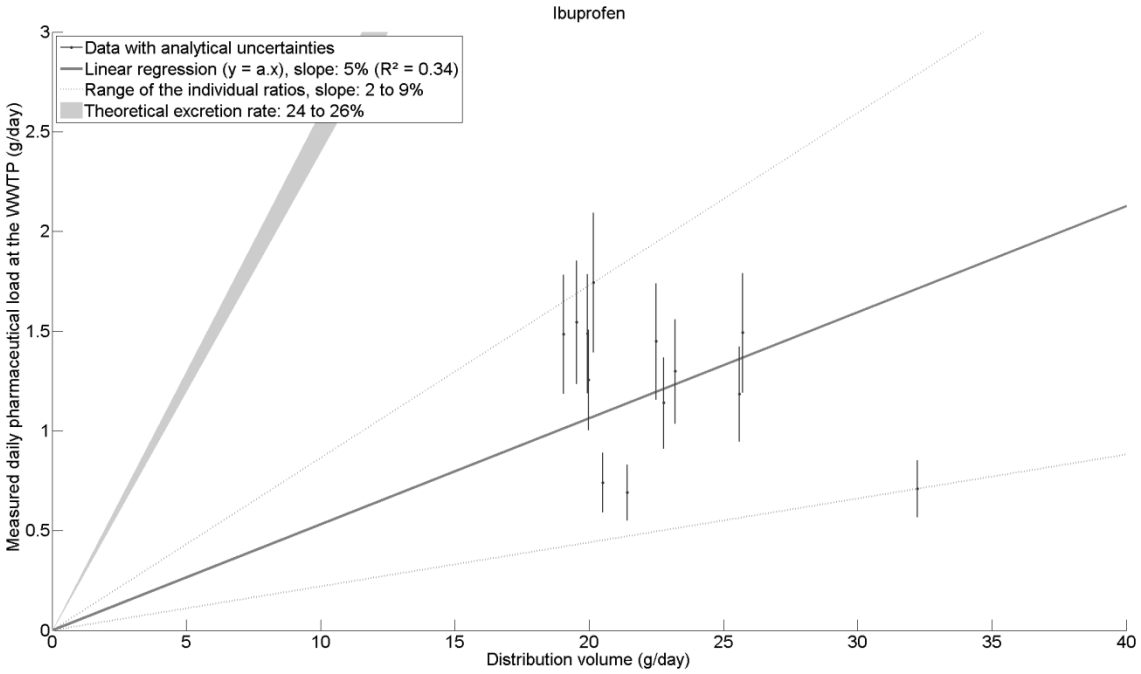

Figure 180: Correlation between distributions and daily loads of Ibuprofen for the CHAL hospital.

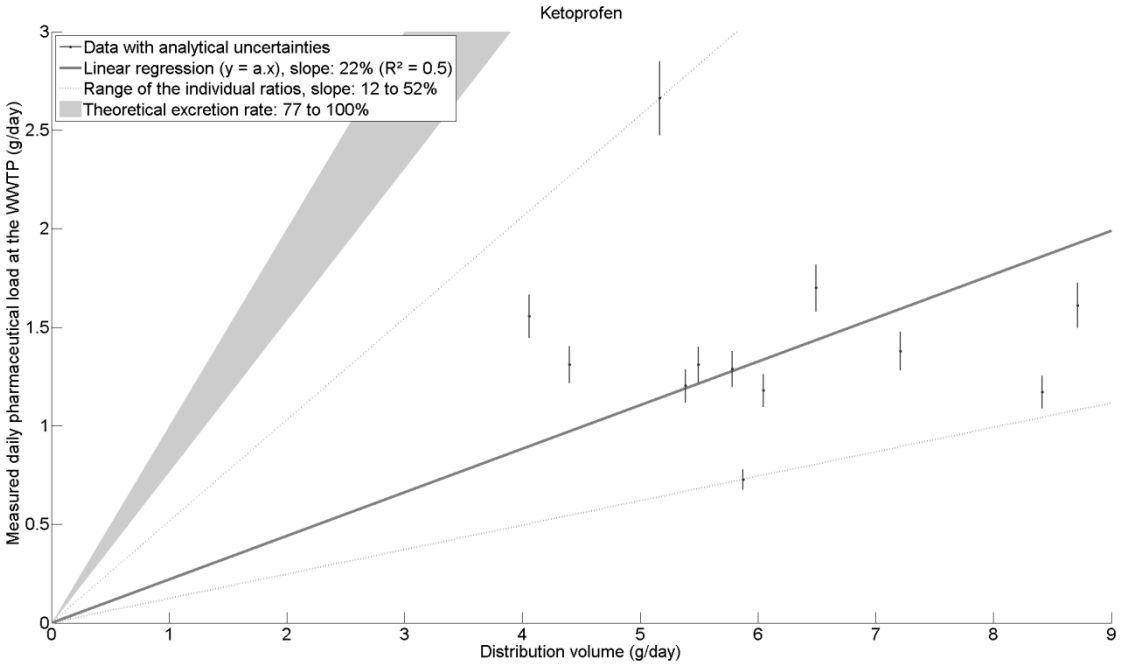

Figure 181: Correlation between distributions and daily loads of Ketoprofen for the CHAL hospital.

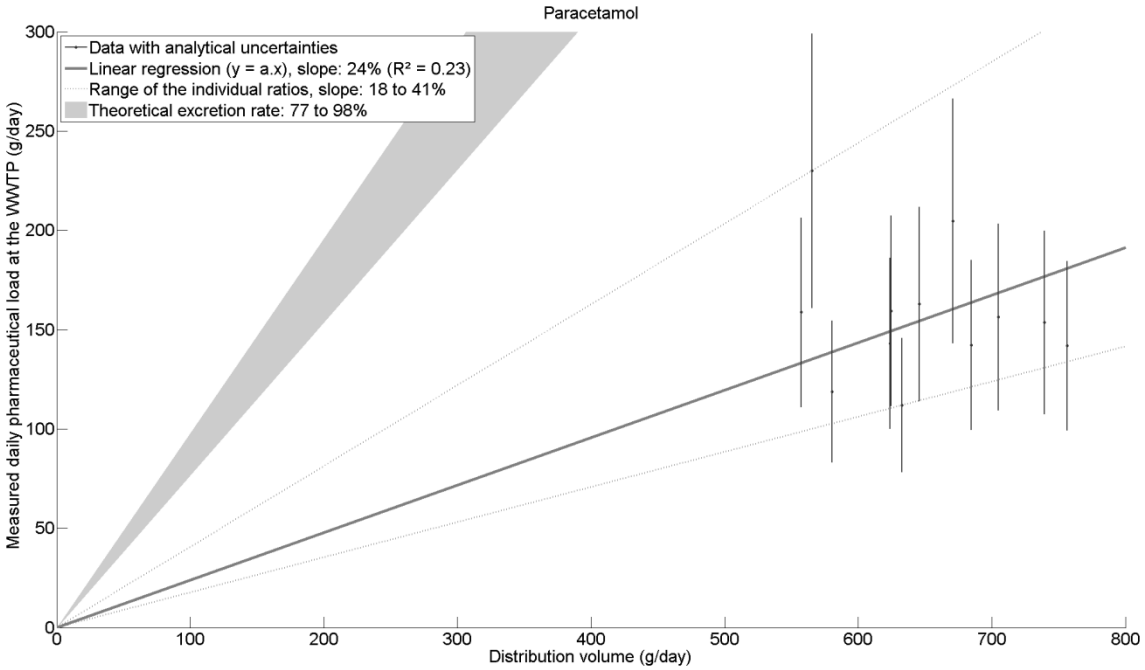

Figure 182: Correlation between distributions and daily loads of Paracetamol for the CHAL hospital.

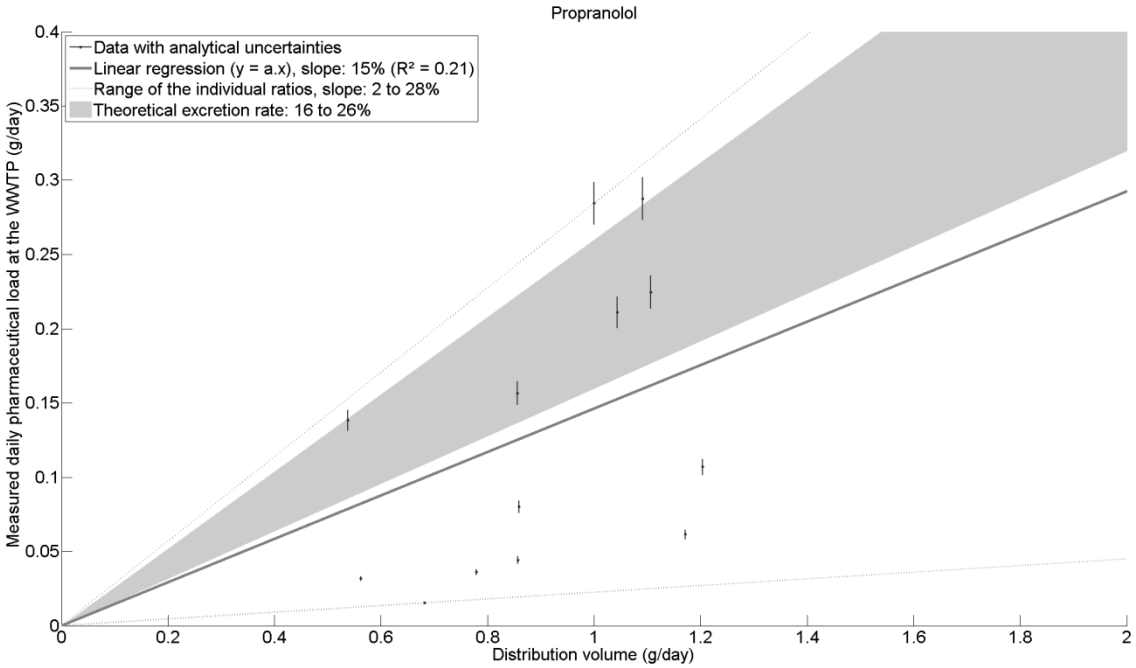

Figure 183: Correlation between distributions and daily loads of Propranolol for the CHAL hospital.

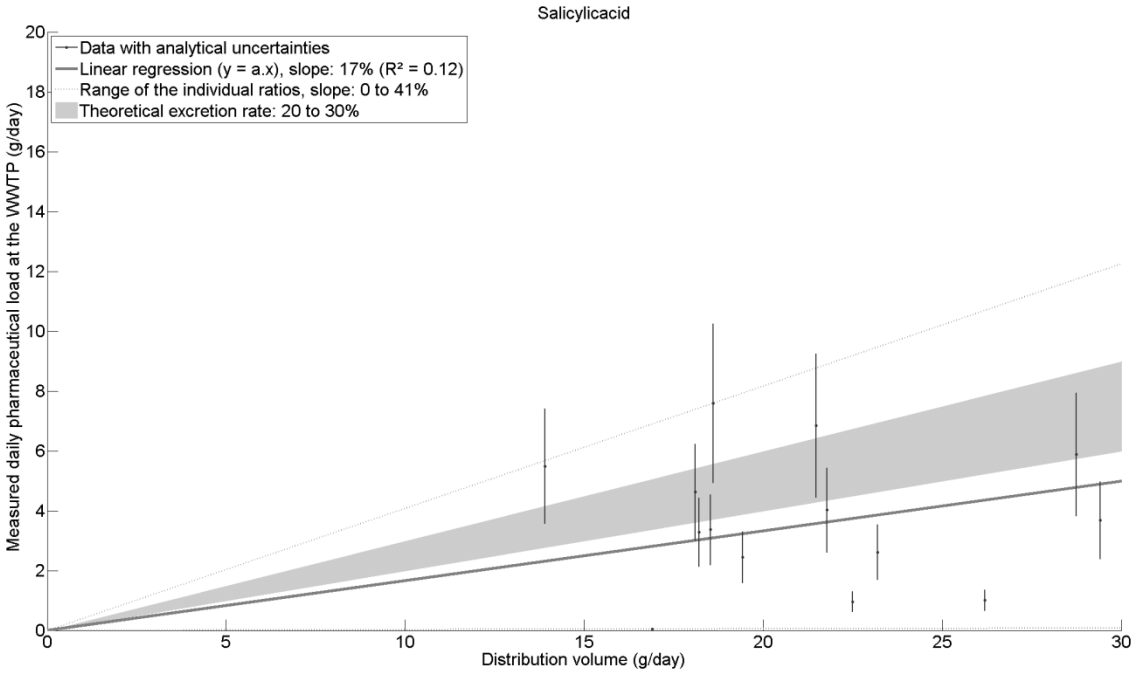

Figure 184: Correlation between distributions and daily loads of Salicylic acid for the CHAL hospital.

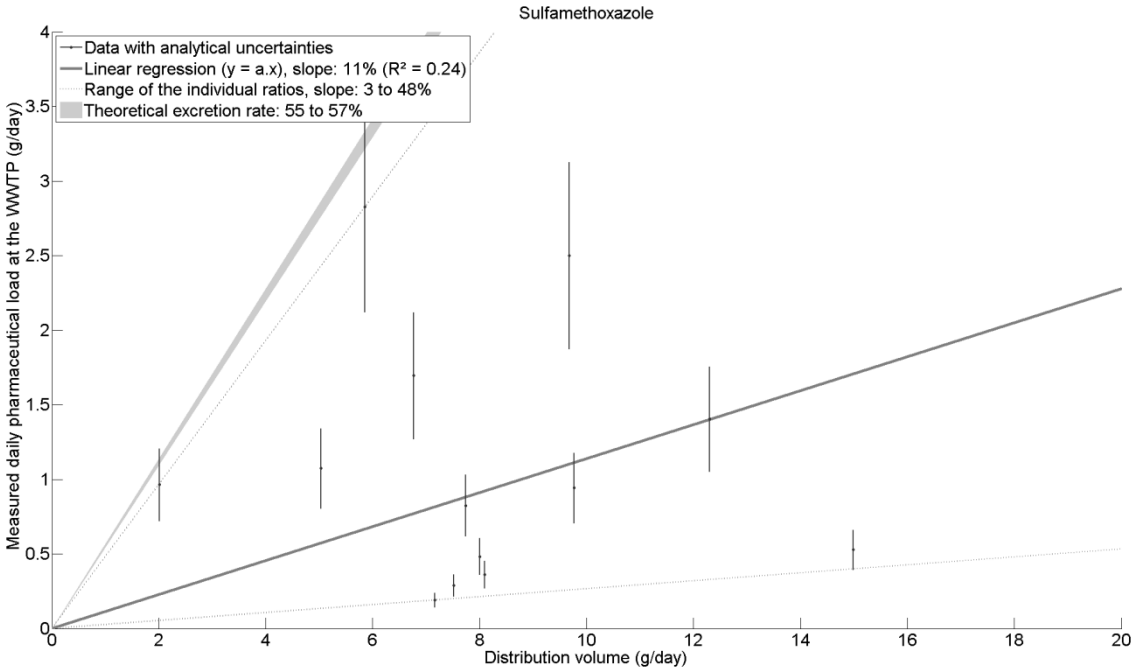

Figure 185: Correlation between distributions and daily loads of Sulfamethoxazole for the CHAL hospital.

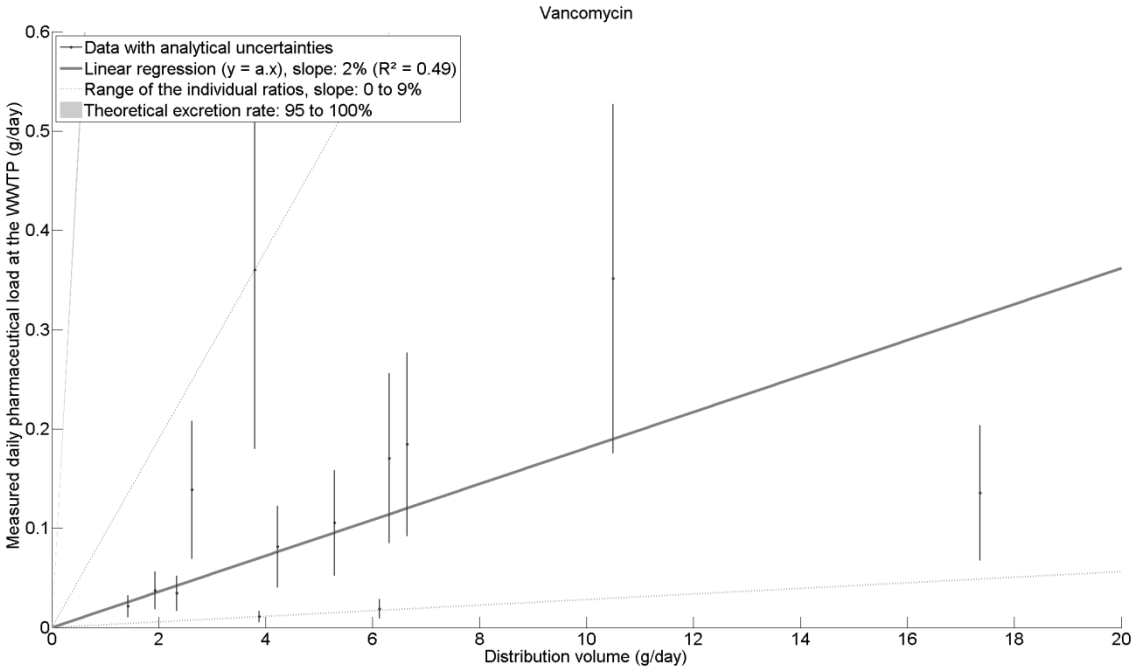

Figure 186: Correlation between distributions and daily loads of Vancomycin for the CHAL hospital.

APPENDIX 19: MODELLED HOURLY PHARMACEUTICALS LOADS OF THE URBAN CATCHMENT

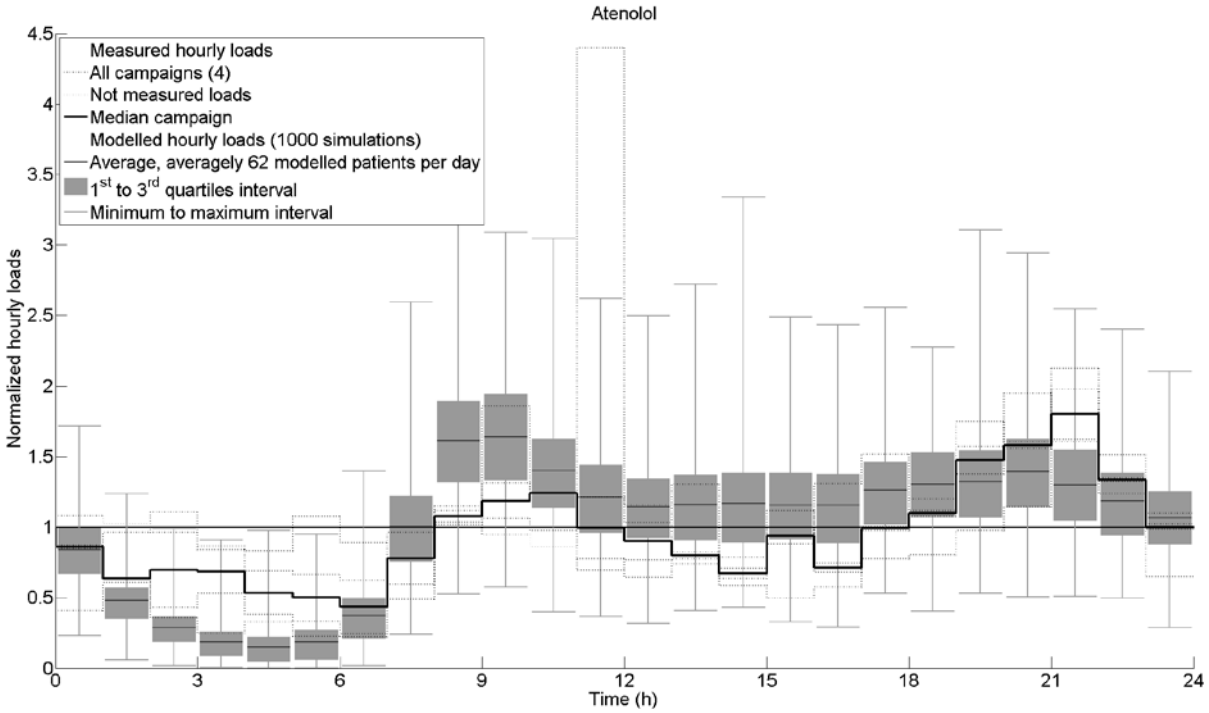

Figure 187: Comparison of the dynamics of the measured and modelled hourly loads of Atenolol in the urban catchment.

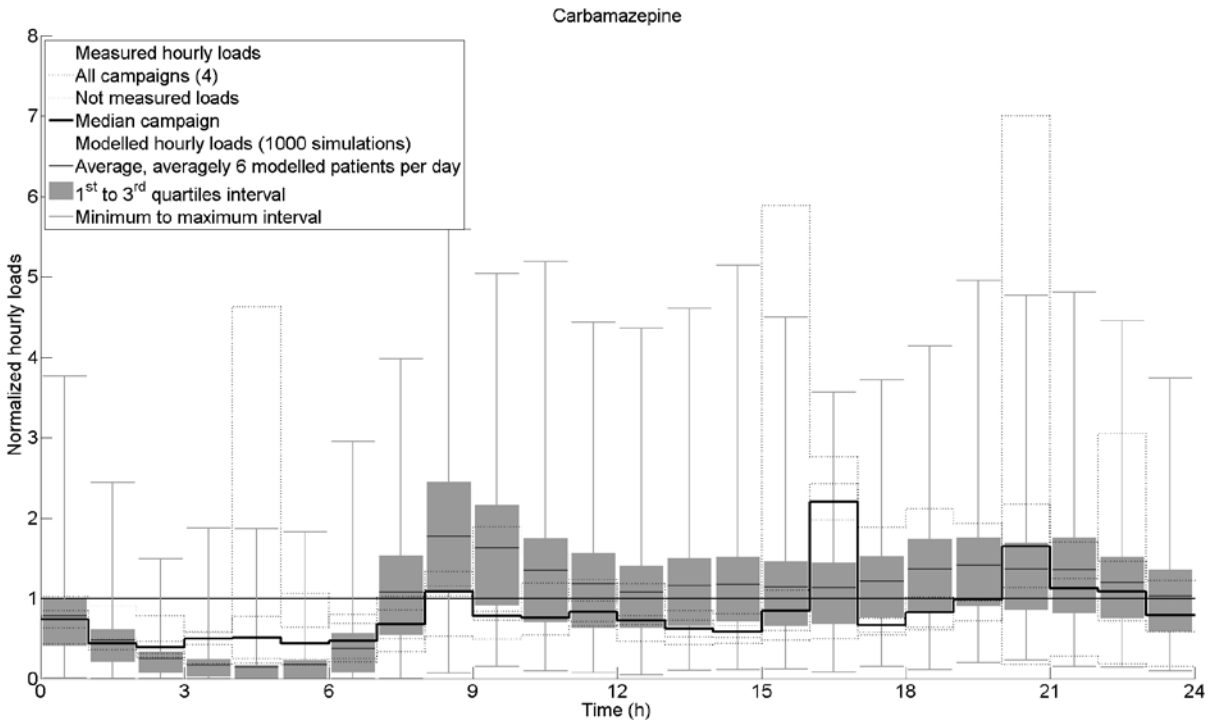

Figure 188: Comparison of the dynamics of the measured and modelled hourly loads of Carbamazepine in the urban catchment.

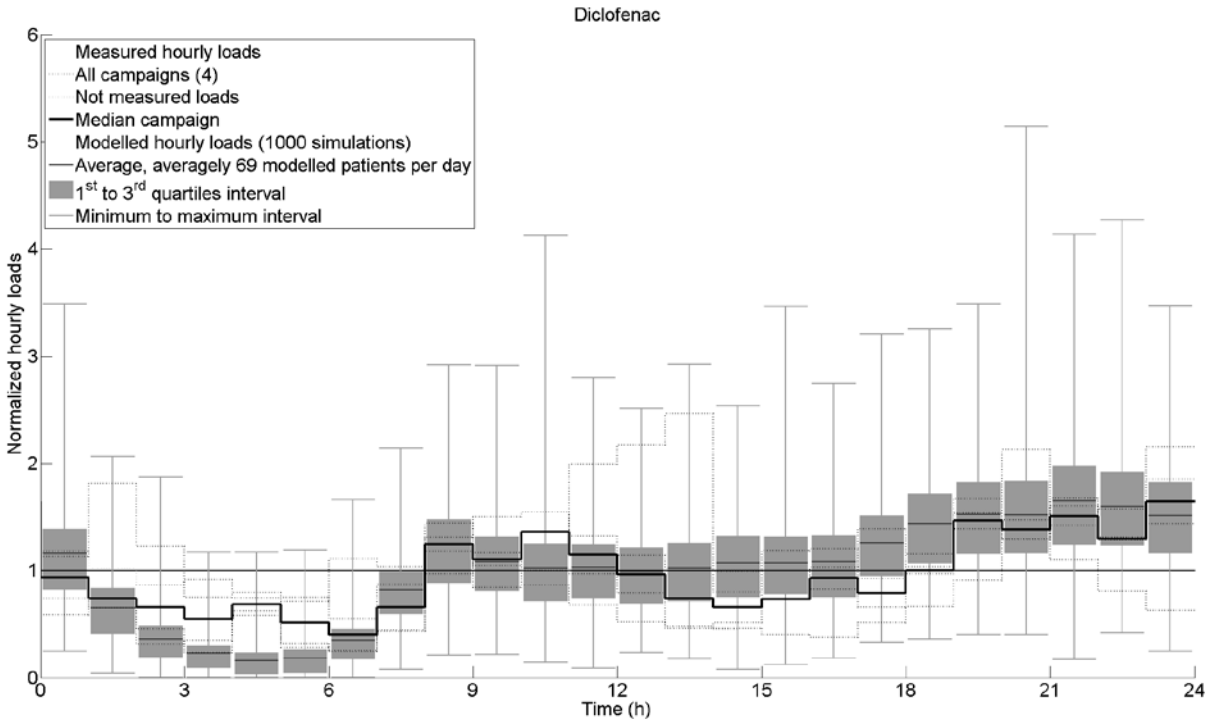

Figure 189: Comparison of the dynamics of the measured and modelled hourly loads of Diclofenac in the urban catchment.

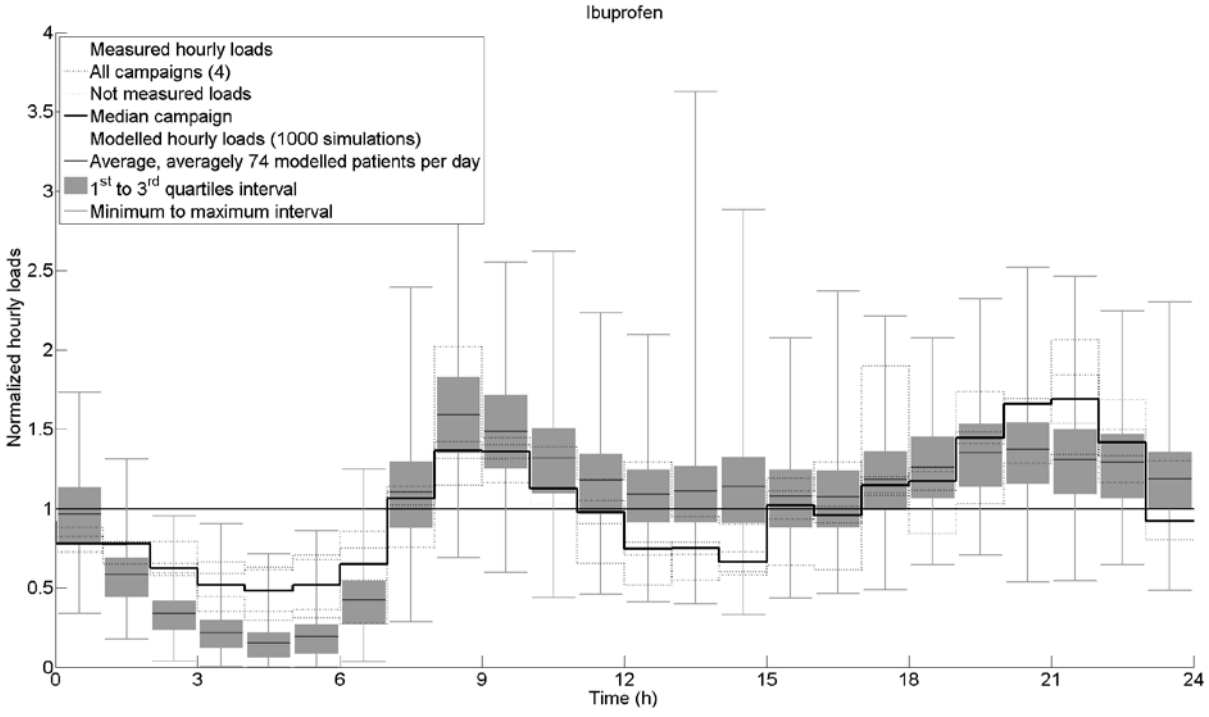

Figure 190: Comparison of the dynamics of the measured and modelled hourly loads of Ibuprofen in the urban catchment.

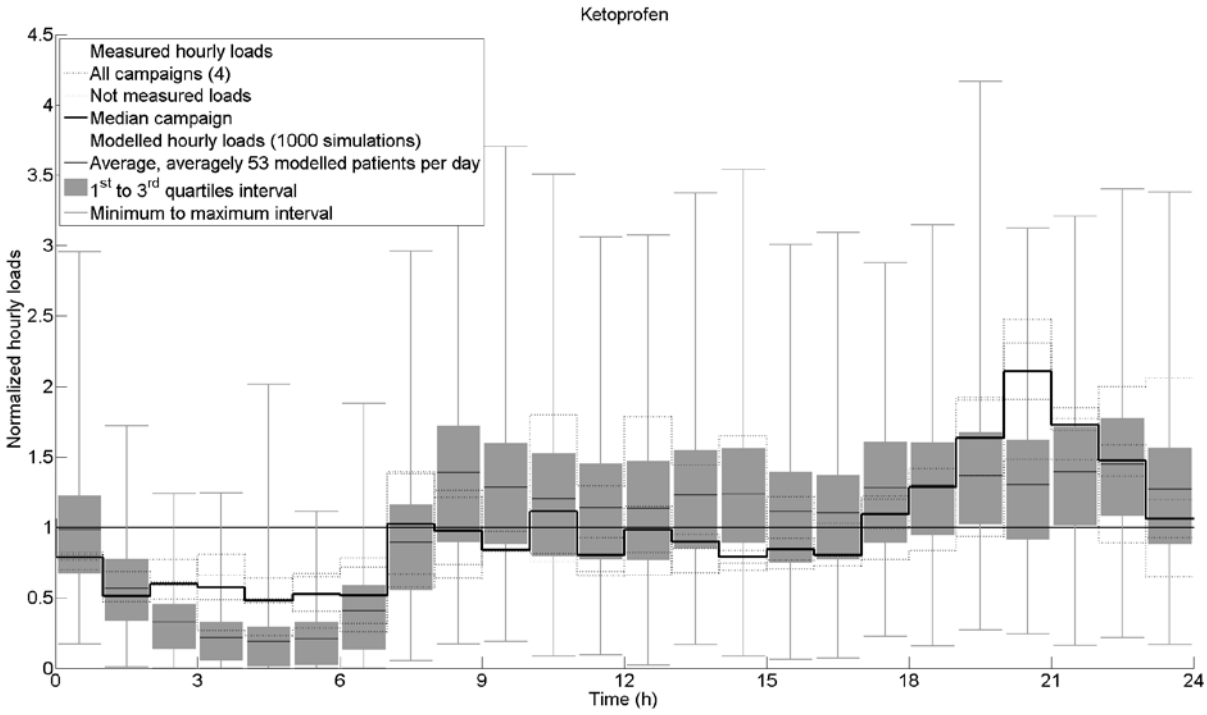

Figure 191: Comparison of the dynamics of the measured and modelled hourly loads of Ketoprofen in the urban catchment.

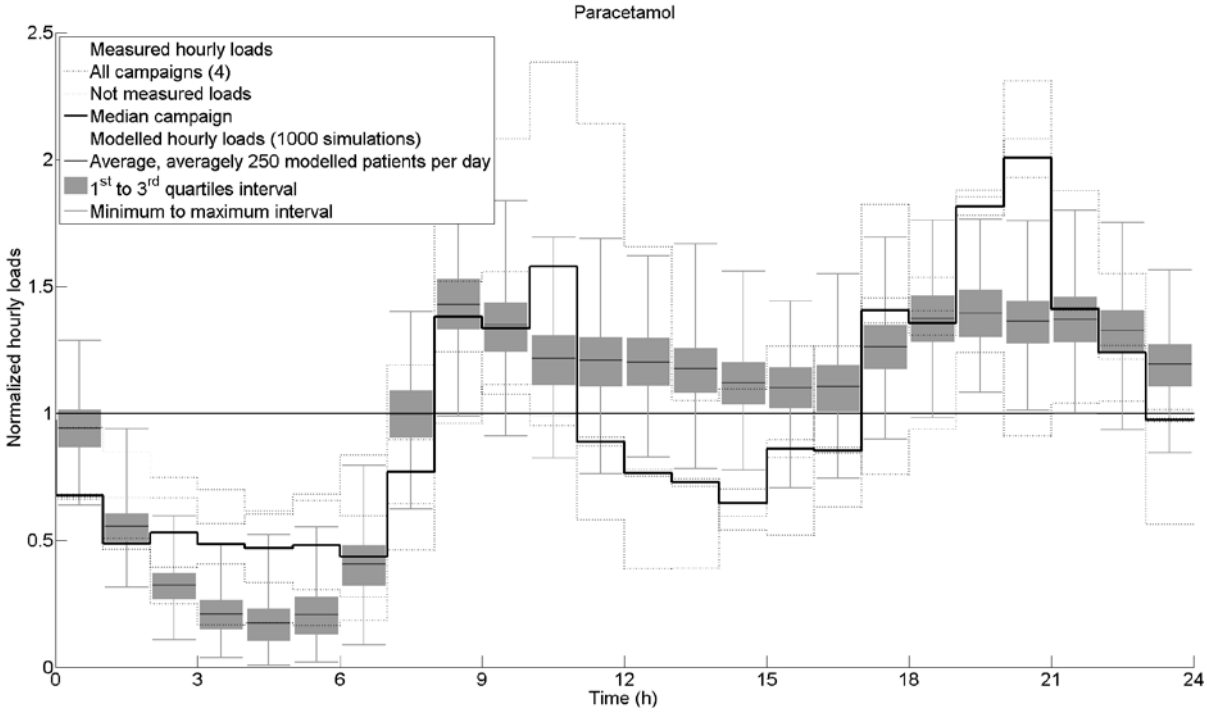

Figure 192: Comparison of the dynamics of the measured and modelled hourly loads of Paracetamol in the urban catchment.

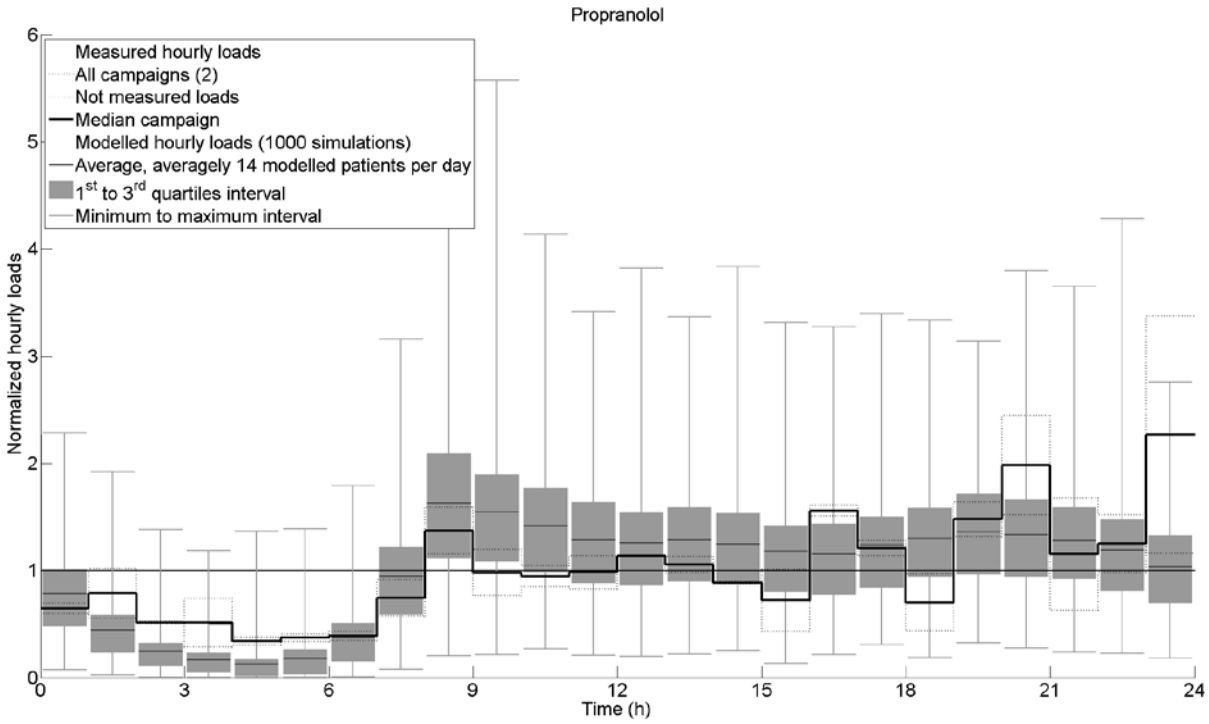

Figure 193: Comparison of the dynamics of the measured and modelled hourly loads of Propranolol in the urban catchment.

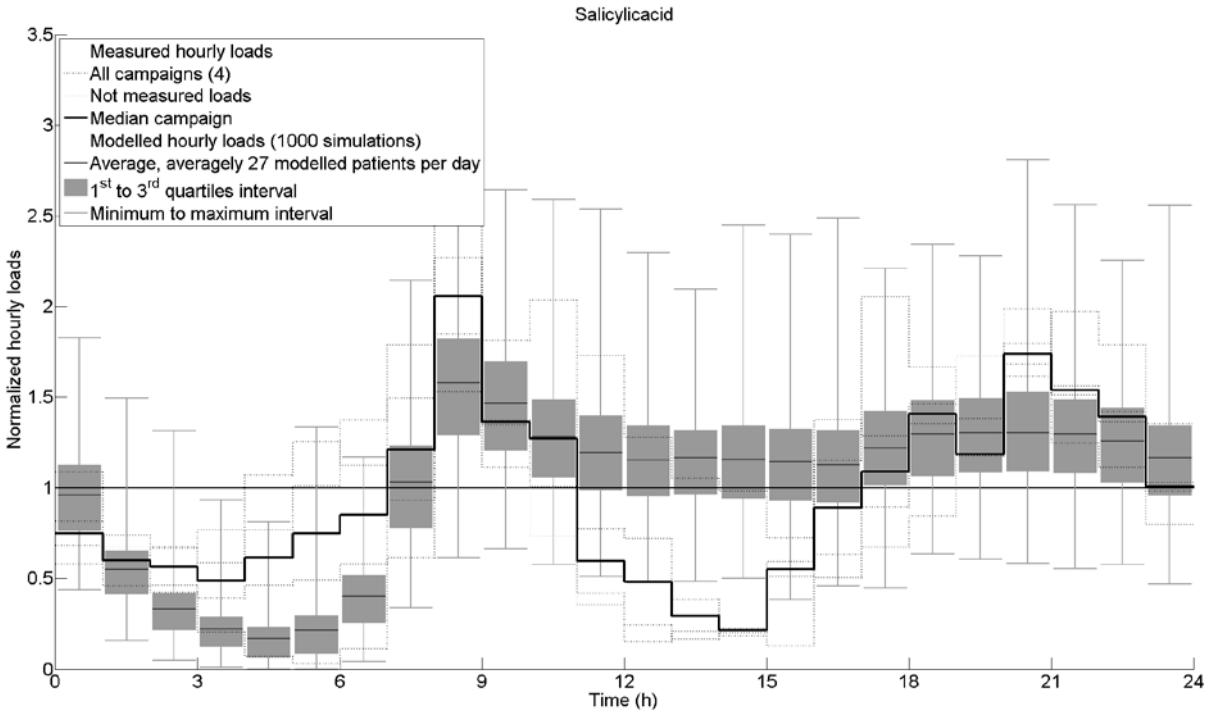

Figure 194: Comparison of the dynamics of the measured and modelled hourly loads of Salicylic acid in the urban catchment.

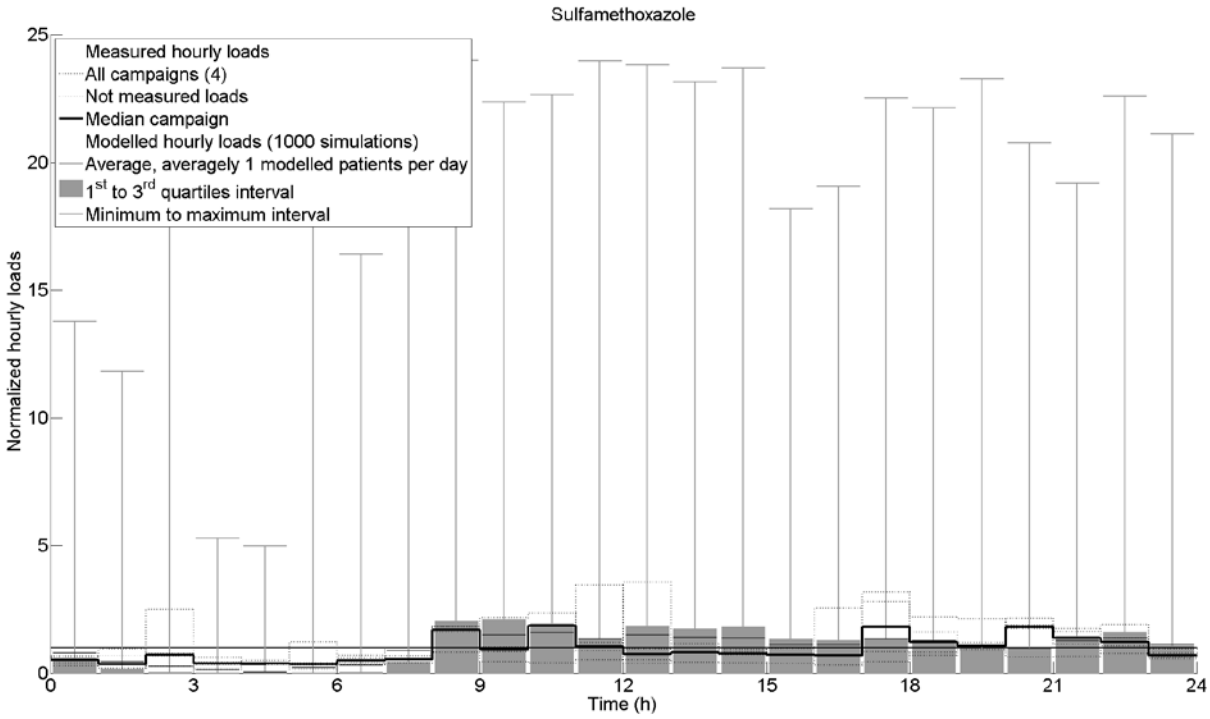

Figure 195: Comparison of the dynamics of the measured and modelled hourly loads of Sulfamethoxazole in the urban catchment.

APPENDIX 20: MODELLED HOURLY PHARMACEUTICALS LOADS OF THE CHAL HOSPITAL

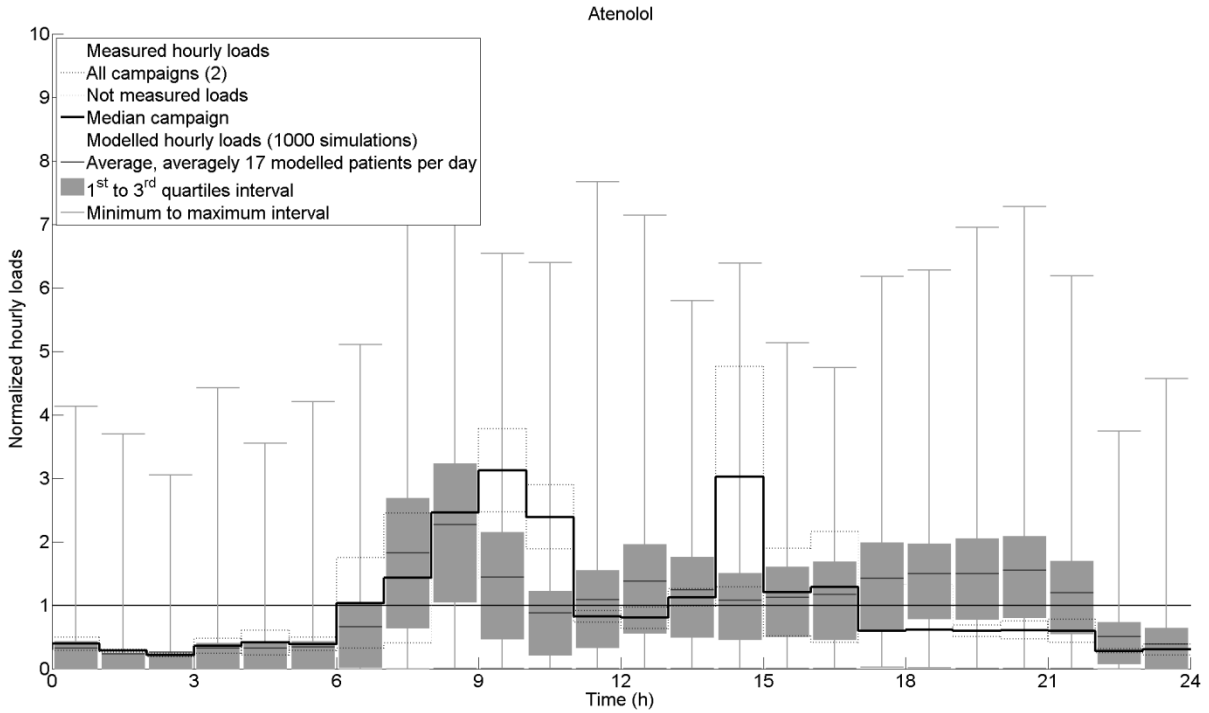

Figure 196: Comparison of the dynamics of the measured and modelled hourly loads of Atenolol in the CHAL hospital.

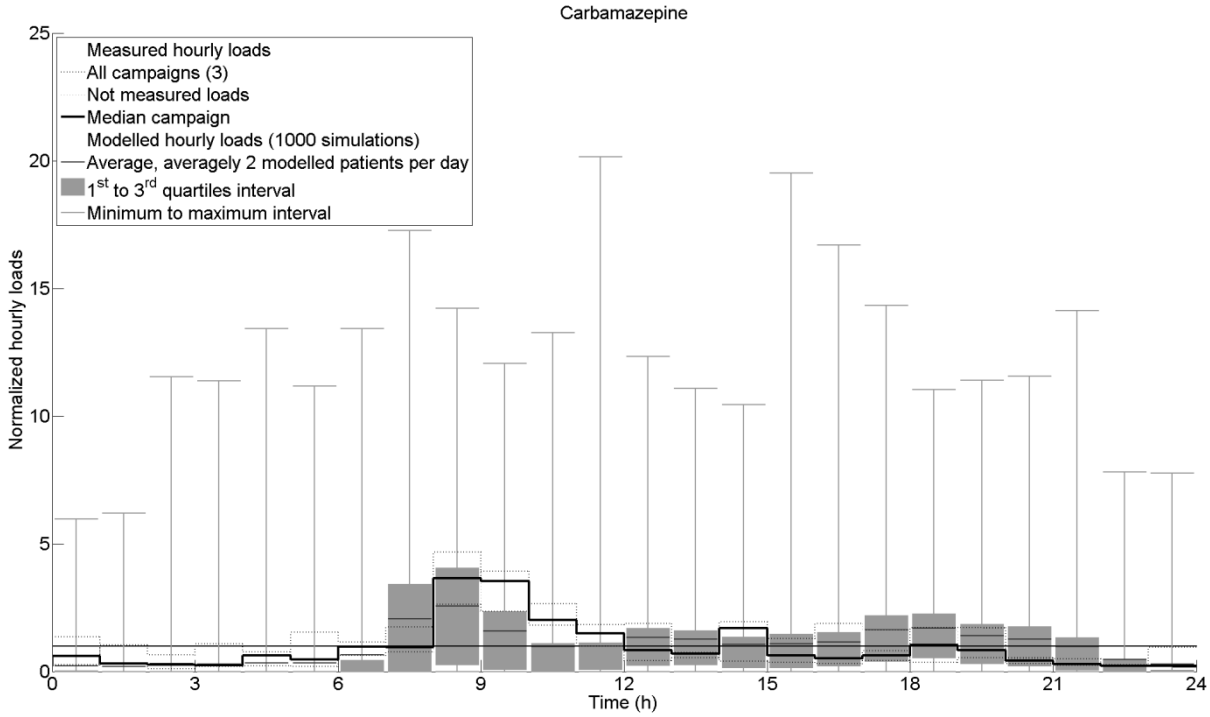

Figure 197: Comparison of the dynamics of the measured and modelled hourly loads of Carbamazepine in the CHAL hospital.

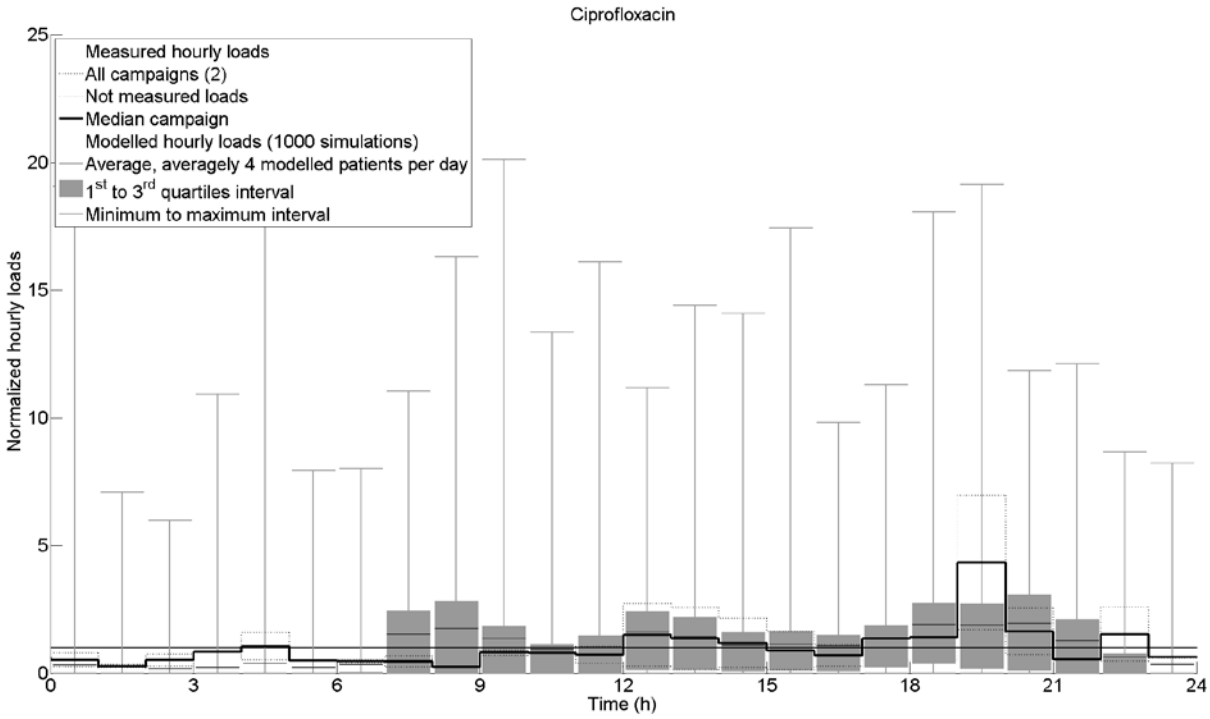

Figure 198: Comparison of the dynamics of the measured and modelled hourly loads of Ciprofloxacin in the CHAL hospital.

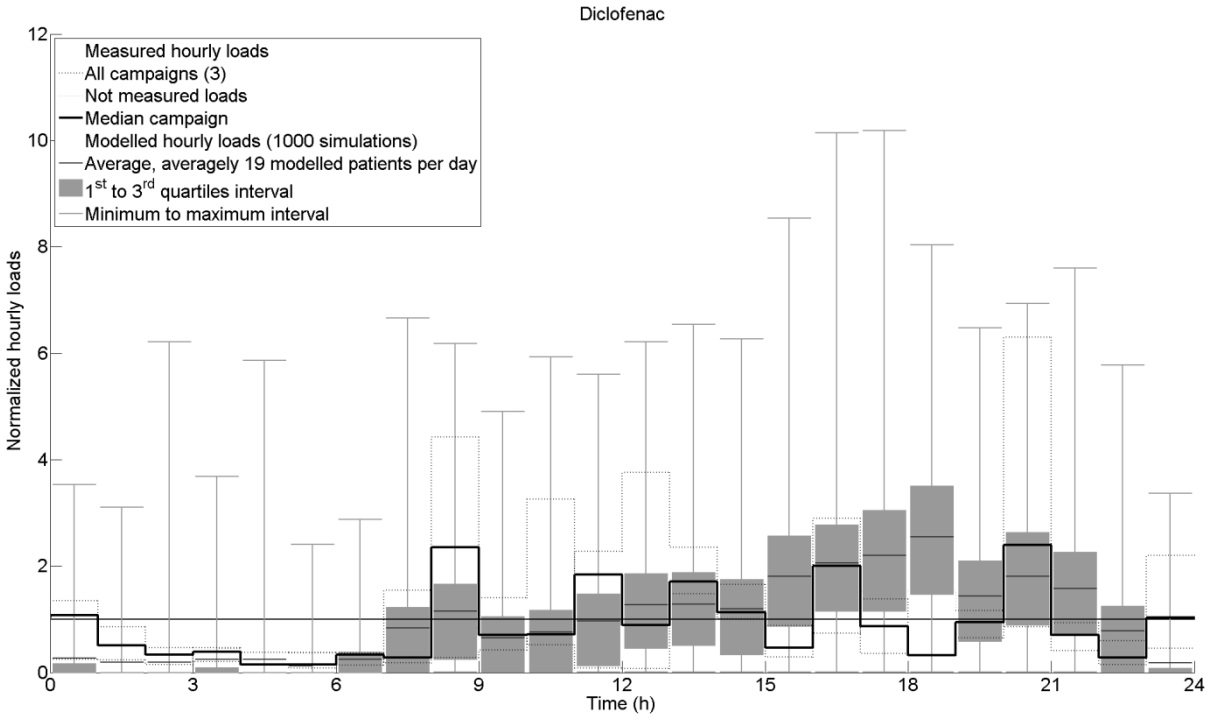

Figure 199: Comparison of the dynamics of the measured and modelled hourly loads of Diclofenac in the CHAL hospital.

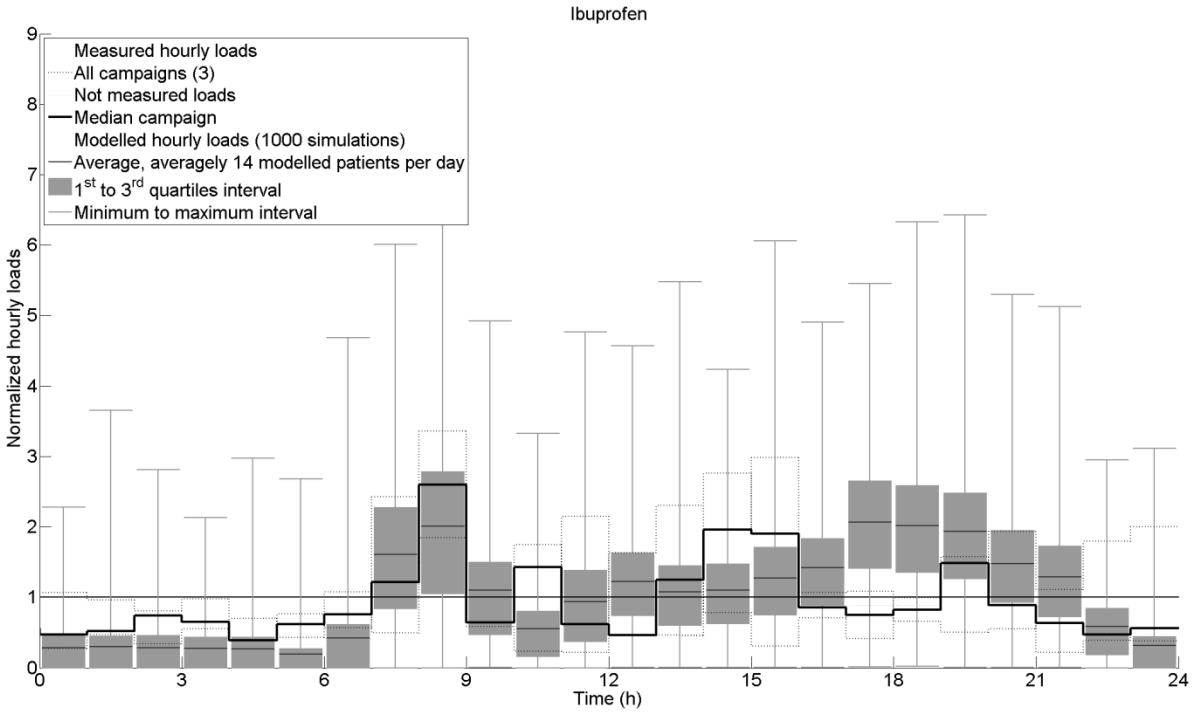

Figure 200: Comparison of the dynamics of the measured and modelled hourly loads of Ibuprofen in the CHAL hospital.

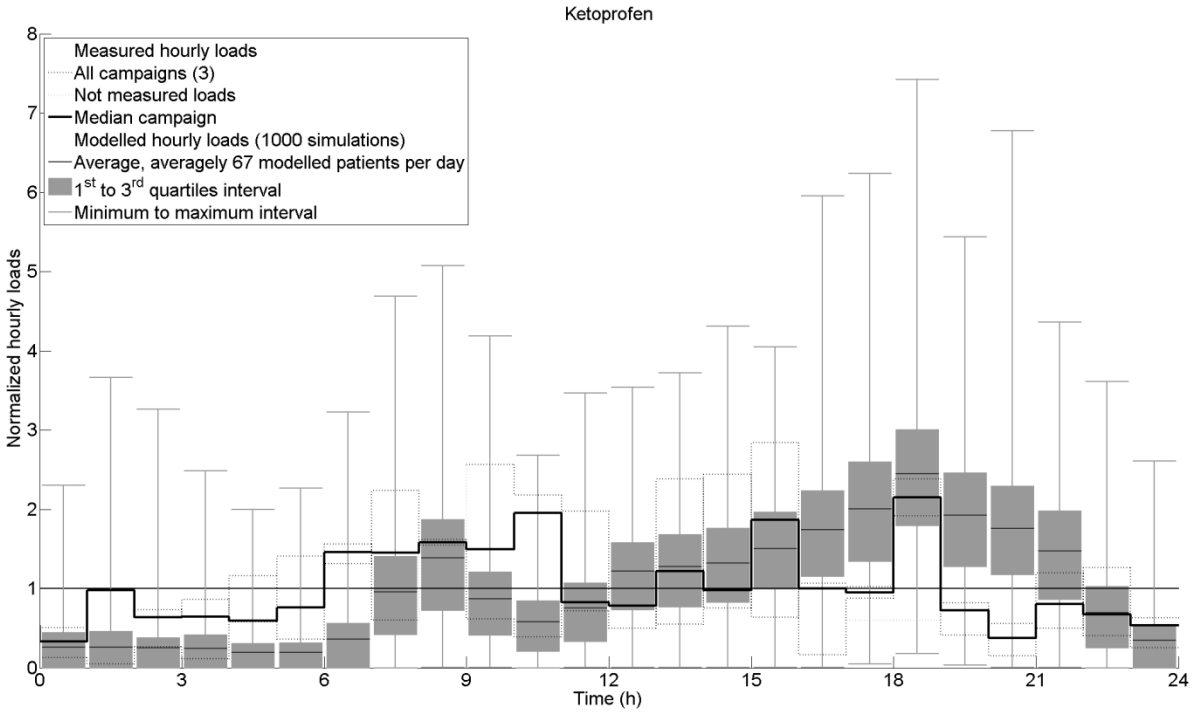

Figure 201: Comparison of the dynamics of the measured and modelled hourly loads of Ketoprofen in the CHAL hospital.

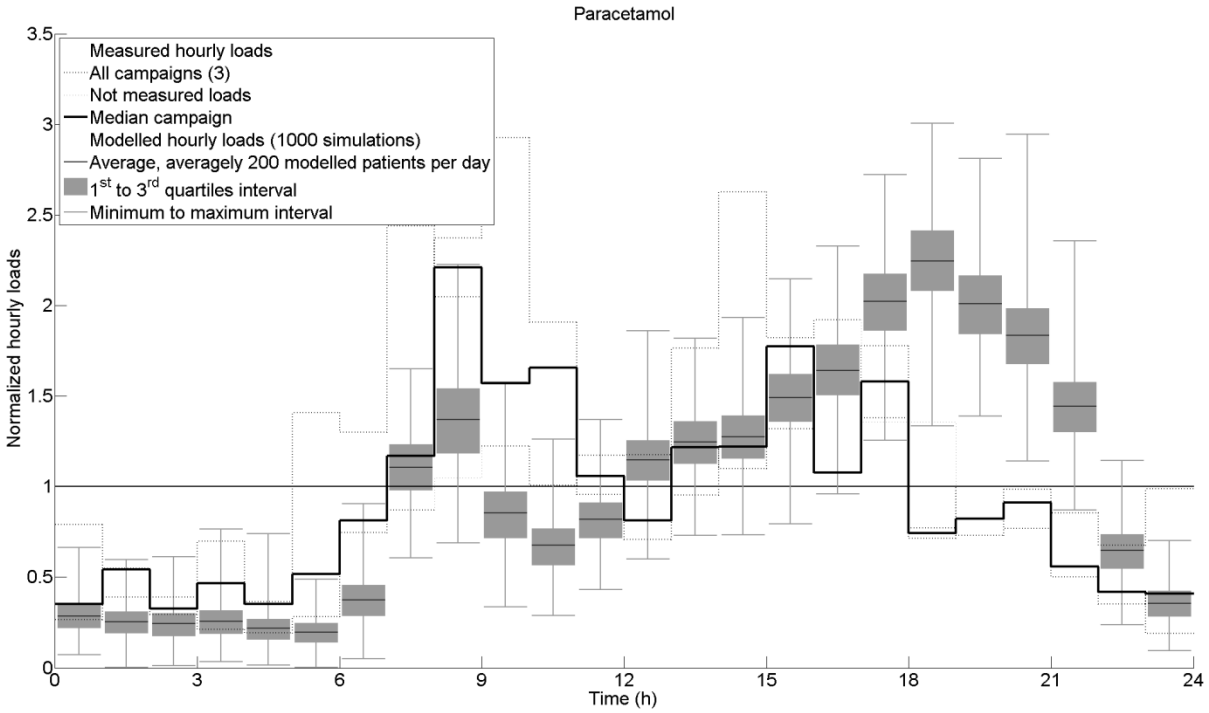

Figure 202: Comparison of the dynamics of the measured and modelled hourly loads of Paracetamol in the CHAL hospital.

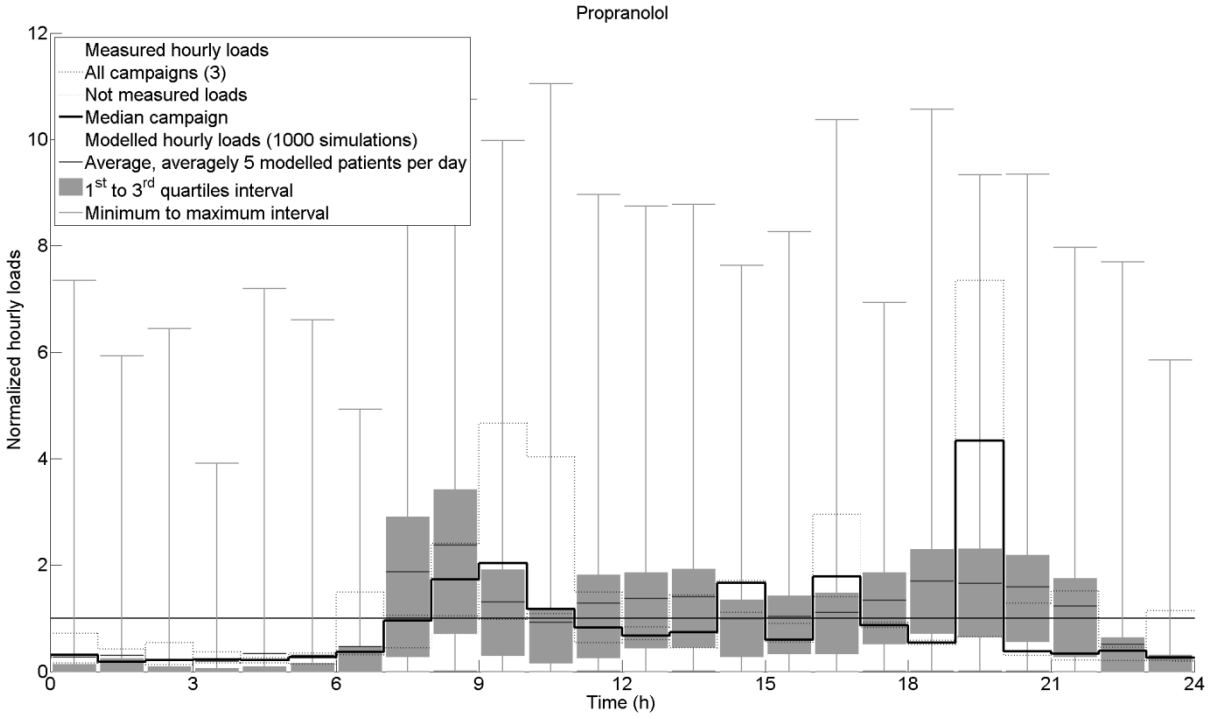

Figure 203: Comparison of the dynamics of the measured and modelled hourly loads of Propranolol in the CHAL hospital.

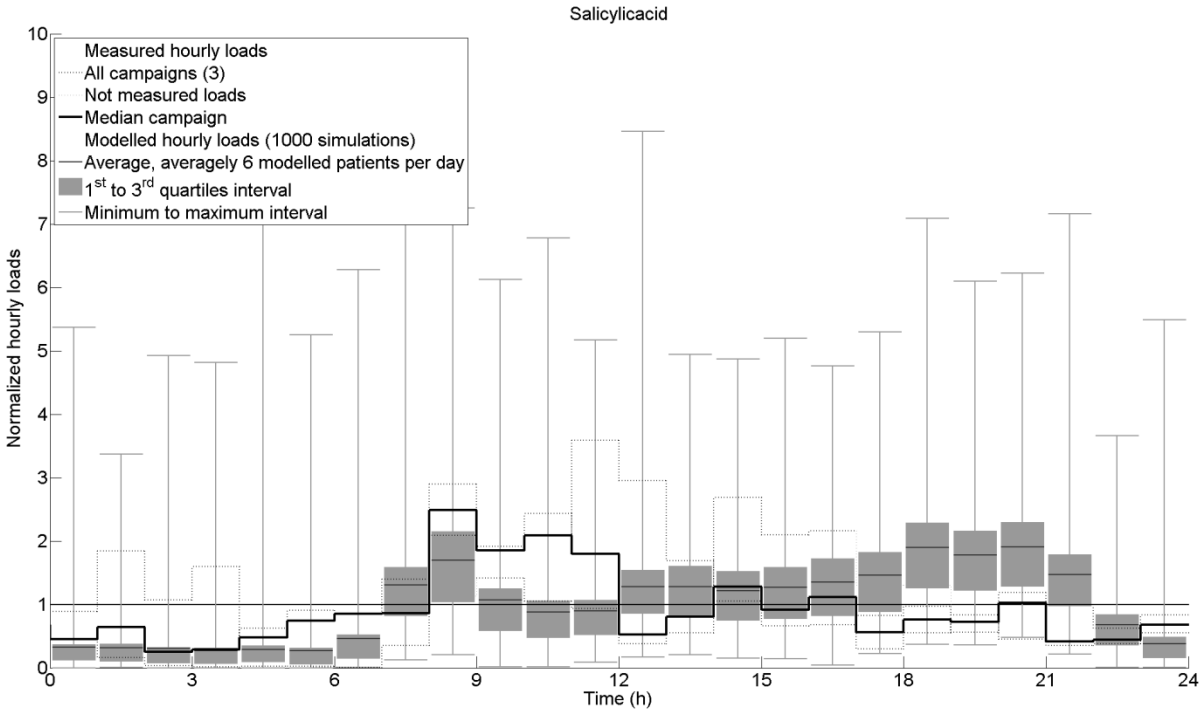

Figure 204: Comparison of the dynamics of the measured and modelled hourly loads of Salicylic acid in the CHAL hospital.

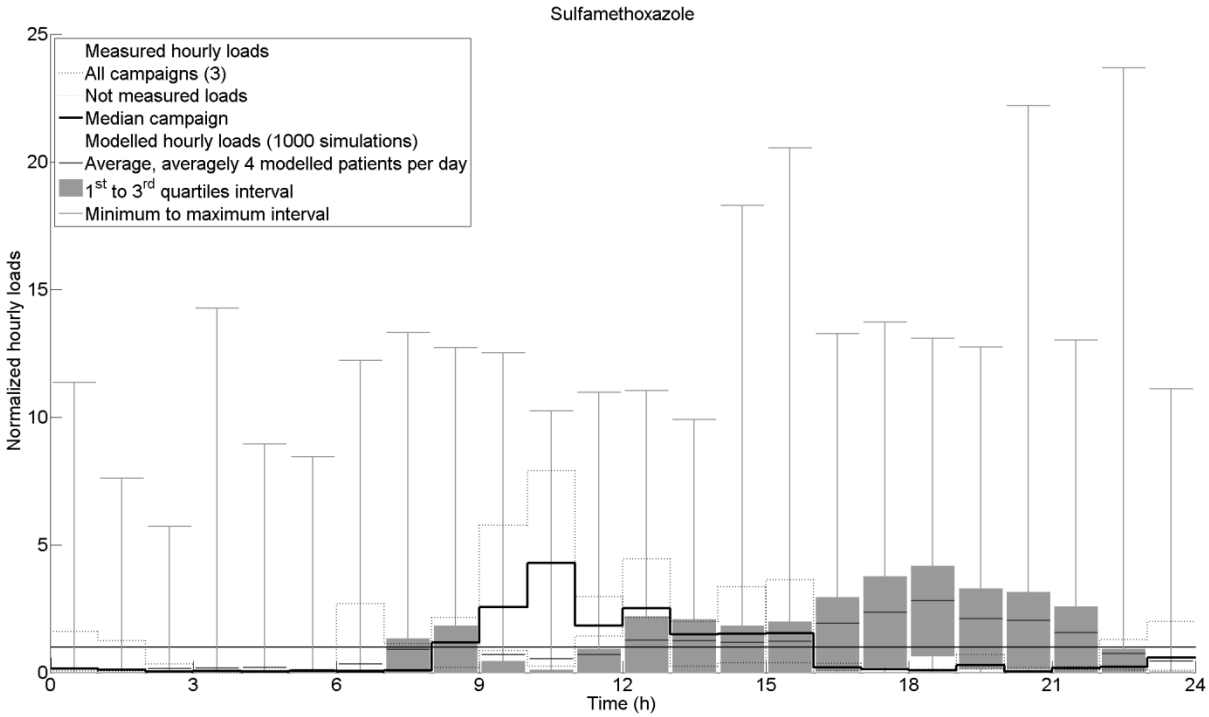

Figure 205: Comparison of the dynamics of the measured and modelled hourly loads of Sulfamethoxazole in the CHAL hospital.

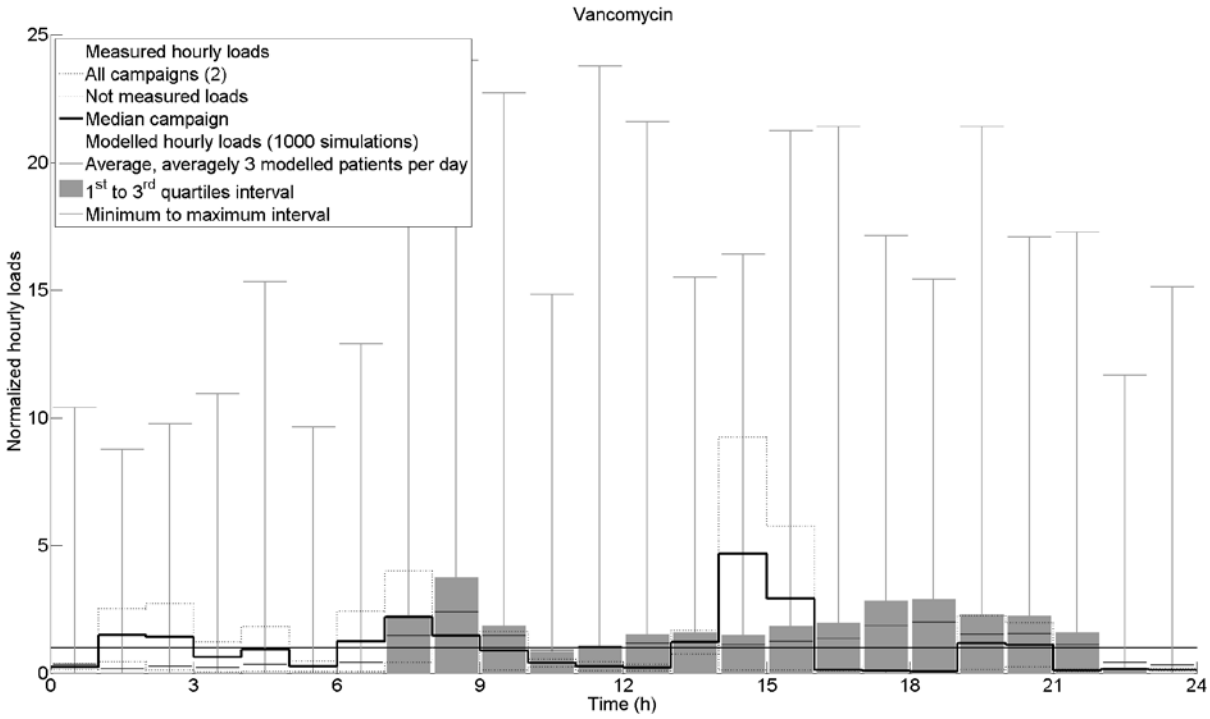

Figure 206: Comparison of the dynamics of the measured and modelled hourly loads of Vancomycin in the CHAL hospital.

APPENDIX 21: IMPLEMENTATION OF A CLASSIC PROPORTIONAL MODEL

In order to assess the performance of the new stochastic model, a classic 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 in the sewers, is absorbed by the blood system, is metabolized and is metabolized as glucuro and sulfo-conjugates. It uses all the different proportional coefficients of the metabolism process used for the new stochastic model. It corresponds to the average of the maximum and minimum theoretical excretion rate calculated in appendix 4.

For the urban catchment, the results are given in table 52.

Table 52: Results of the classic proportional model for the urban catchment.

Molecule	Pharmaceutical sales			Average theoretical excretion rate (%)	Modelled daily load (mg/day)
	Average daily sales (mg/day) (30 015 inhabitants)	Average daily sales per capita (mg/day/capita)	Average daily sales for the urban catchment (mg/day) (≈16 000 inhabitants)		
Atenolol	26 563	0.88	14 159	96	13 600
Aztreonam					
Carbamazepine	34 082	1.14	18 167	12.5	2 300
Ciprofloxacin					
Diclofenac	39 330	1.31	20 965	11	2 300
Econazole					
Ethinylestradiol					
Ibuprofen	510 363	17.00	272 057	25	68 000
Ketoprofen	30 468	1.02	16 241	88.5	14 400
Meropenem					
Paracetamol	4 345 642	144.78	2 316 517	87.5	2 027 000
Propranolol	12 166	0.41	6 485	21	1 400
Salicylic acid	458 302	15.27	244 305	25	61 100
Sulfamethoxazole	11 390	0.38	6 071	56	3 400
Vancomycin					

For the CHAL hospital, the results are given in table 53.

Table 53: Results of the classic proportional model for the CHAL hospital.

Molecule	Average daily distribution (mg/day)	Average theoretical excretion rate (%)	Modelled daily load (mg/day)
Atenolol	1 275	96	1 200
Aztreonam			
Carbamazepine	2 374	12.5	300
Ciprofloxacin	3 716	76	2 800
Diclofenac	1 818	11	200
Econazole	1 186		
Ethinylestradiol			
Ibuprofen	16 750	25	4 200
Ketoprofen	6 657	88.5	5 900
Meropenem	1 043		
Paracetamol	598 620	87.5	523 800
Propranolol	790	21	200
Salicylic acid	19 208	25	4 800
Sulfamethoxazole	8 600	56	4 800
Vancomycin	5 624		5 500

APPENDIX 22: LIST OF THE 47 MOLECULES FIRST SELECTED

Table 54: List of the 47 molecules first selected. *: molecules measurable in 2010 by the CNRS-SCA.

High priority	Low priority
Amiodarone	Amitriptyline
Atenolol*	Atracurium
Carbamazepine*	Fluorouracil
Ciprofloxacin*	Ifosfamide
Cyclophosphamide	Iobitridol
Desloratadine	Iohexol
Dextropropoxiphen	Iomeprol
Diclofenac*	Iopamidol
Econazole*	Iopromide
Ethinylestradiol*	Metoclopramide
Fluidione	Mitotane
Gadopentic acid	Tamoxifen
Gentamycin	Trimetazidine
Hexetidine	Trolamine
Hydrocortisone	
Ibuprofen*	
Ketoprofen*	
Lidocaïne	
Metformin	
Methylprednisolone	
Mifepristone	
Nicardipine	
Norfloxacin	
Norgstimate	
Pantaprozol	
Paracetamol*	
Prednisolone	
Propofol	
Propranolol*	
Ritonavir	
Salicylic acid*	
Sulfamethoxazole*	
Telithromycin	

RÉSUMÉ ÉTENDU

INTRODUCTION

La présence de résidus de médicaments (RdM) dans les eaux de surfaces a été détectée pour la première fois dans les années 70. Depuis, leur présence est avéré dans tous les compartiments du cycle de l'eau (rivières, lacs, eaux côtières, eaux souterraines, eaux potable, eaux usées…) et sur l'ensemble de la planète. Évaluer et gérer les risques associés à cette contamination est devenu un important champ d'études au sein des sciences appliquées à l'environnement.

Aucun risque n'a encore été démontré concernant la santé humaine notamment du fait des faibles concentrations mesurées dans les eaux potables. Cependant, il est encore nécessaire d'évaluer ce risque car l'exposition chronique à une combinaison de molécules peut induire des risques à long termes même à faible concentrations et en interaction avec les autres polluants. Concernant les risques pour l'environnement, quelques cas ont pu être mis en évidence (changement du comportement de poissons, chute démographique de vautours, toxicité pour des algues…). Les recherches actuelles se concentrent sur l'étude des effets chroniques à de faibles concentrations à l'aide de différents outils (études de bio accumulation et concentration, indicateurs infra-létaux).

Les sources et chemins de dispersion des médicaments dans l'environnement ont été identifiés, mais des discussions subsistent quant à leurs importances relatives. Néanmoins, il est communément admis que la source principale est la consommation de médicaments par l'être humain donnant lieu à leur excrétion dans les eaux usées qui seront ensuite acheminées vers et traitées par les stations de traitements des eaux usées (STEU) pour être finalement déversées dans les eaux de surfaces. Il en est de même pour les RdM vétérinaires dispersés par les animaux ou par les épandages agricoles. Un point de discussion particulier consiste à savoir si les concentrations de médicaments en entrée de STEU sont fortement liées aux consommations de médicaments en hôpital.

L'échantillonnage et la mesure des médicaments à de faibles concentrations est toujours coûteuse (temps et argent) et difficile. C'est pourquoi, seulement quelques études se sont intéressées à la variabilité du phénomène. Des variations annuelles, saisonnières, journalières et horaires ont été observées. Évaluer la variabilité du phénomène est indispensable. En particulier, l'étude des variations infra-journalières est nécessaire afin de gérer correctement les flux de médicaments et de proposer de nouvelles solutions (nouveaux traitements, contrôle à la source…). Dans le cas des réseaux d'assainissement unitaires, l'étude des variations infra-journalières est également nécessaire pour évaluer les rejets directs vers les eaux de surfaces au sein des déversoirs d'orages.

En partie pour compenser le manque de mesures, mais également pour mieux comprendre la présence de résidus de médicaments dans l'eau, des modèles de prédictions ont été proposés depuis les années 90. Presque tous se concentrent sur la source et le chemin de dispersion principal dans l'environnement ou une partie de celui-ci (*i.e.* consommation humaine, excrétions dans les réseaux d'assainissement, traitement et déversement par les STEU, dispersion dans l'environnement). Ne considérant que les premières étapes (consommation jusqu'à l'entrée en STEU), tous les modèles supposent les flux de RdM entrant en STEU sont proportionnels aux ventes de médicaments en pharmacies. Le coefficient de proportionnalité usuellement adopté correspond à la fraction de principe actif excrétée inchangée par le corps humain. La plupart du temps, les résultats de ces modèles sont difficiles à interpréter. Les quatre principaux problèmes étant :

- Imprécisions des données de ventes : il est difficile d'obtenir des données de ventes de médicaments. La plupart du temps, seules les consommations annuelles d'un pays sont disponibles, et elles ne

comptabilisent pas toujours les ventes de médicaments non remboursés. De ce fait, les variations spatiales et temporelles des ventes ne sont pas connues.

- Différence entre ventes et consommations : ventes et consommations ne concordent pas ni en terme de quantité ni en terme de dynamique. Certains médicaments ne sont pas consommés, ou sont consommé sur de longues périodes de temps. Cela implique que les variations journalières de ventes et de consommations ne sont pas nécessairement les mêmes. Concernant les variations infra-journalières, les données de ventes (même les plus précises) ne peuvent être associées à des schémas de consommations.
- Paramètres simples et mal définis : les paramètres utilisés dans les modèles ne reflètent pas la variabilité des phénomènes qu'ils représentent, tel que la fraction global d'excrétion de molécule mère par le corps humain qui varie grandement d'un individu à un autre et qui ne prends pas en compte le mode d'administration de la molécule.
- Population évolutive : les habitants d'un bassin versant modélisé ne sont pas nécessairement les seuls a excrété des médicaments dans le réseau d'assainissement. Des travailleurs ou visiteurs peuvent venir de l'extérieur. De plus, les habitants peuvent quitter le bassin. Au sein de bassins suffisamment grands, cela peut être négligé lorsqu'un équilibre existe entre les entrants et les sortants. Mais pour des petits bassins, les nombres d'entrants et de sortants peuvent différer significativement.

Le point commun de ces problèmes est l'importance d'obtenir des données détaillées sur les bassins versants modélisés. Mais, ces données ne sont pas toujours facilement accessibles.

Néanmoins, quelques études ont proposé des modèles plus élaboré :

- En utilisant des données de ventes précises (spatialement et temporellement) ;
- En décrivant des phénomènes plus complexes ;
- En utilisant des distributions statistiques pour les ventes de médicaments ou les paramètres des modèles afin de reproduire la nature stochastique de la dispersion des RdM ;
- En incorporant des projections démographiques pour étudier l'évolution à long terme de la contamination par les médicaments ;
- En modélisant l'emploi du temps des individus pour reproduire les variations infra-journalières des flux de RdM (une étude faite en parallèle de cette thèse).

Dans ce contexte, deux sites ont été étudiés durant cette thèse : 1) un semi-urbain de 16 000 habitants répartis sur 130 km² ; et 2) un hôpital généraliste de 450 lits (non intégré au site semi-urbain). Quinze molécules ont été présélectionnées pour leurs importants volumes de ventes et leurs potentiels écotoxique. Les objectifs de la thèse sont :

- Mesurer, pour les deux sites, les flux de RdM entrant en STEU, les comparer et évaluer leurs variabilités à différentes échelles de temps.
- Acquérir et analyser des données de ventes de médicaments détaillées pour les deux sites.
- Modéliser, pour les deux sites, les flux de RdM entrant en STEU au pas de temps horaire en considérant la nature stochastique du phénomène.

SITES D'ÉTUDE

Le travail de doctorat a été effectué dans la cadre des projets SIPIBEL, IRMISE Arve aval et SIPIBEL-RILACT. Ils traitent tous les trois de la même zone géographique : le bassin versant de la STEU de Bellecombe et son environnement. La STEU de Bellecombe est située en France près de la frontière franco-suisse (figure 207). Les eaux usées traitées sont déversées dans la rivière Arve.

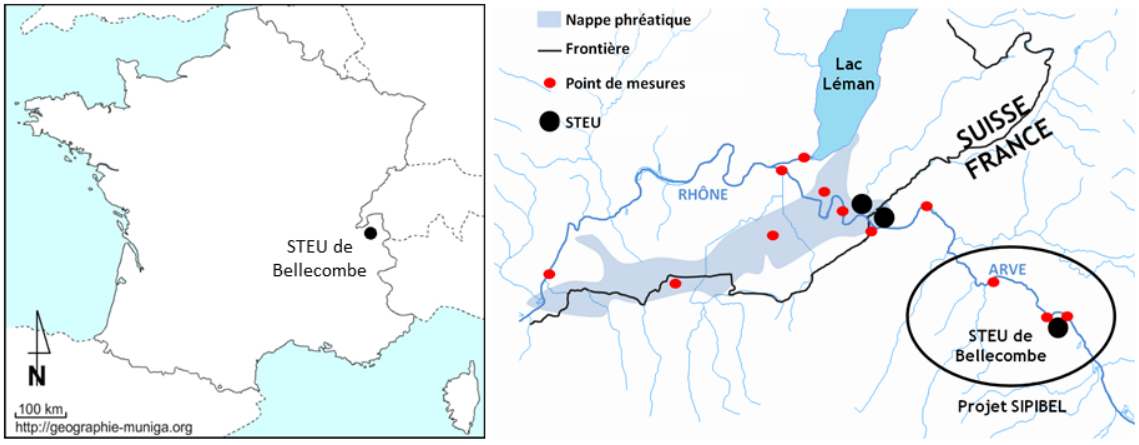

Figure 207: Situation géographique de la STEU de Bellecombe et des différents points de mesures des trois projets (gauche http://geographie-muniga.org, consulté en 2017, droite modifié GRAIE, 2016).

Programmé pour ouvrir en Février 2012, un nouvel hôpital (Centre Hospitalier Alpes Léman, CHAL) devait être raccordé à la STEU de Bellecombe. Toutefois, les autorités en charge de la gestion de l'eau ont décidé que les eaux usées de l'hôpital devrait être traitées séparément de celles du tissu urbanisé au sein d'une STEU dédié à cause des potentiels risques liés aux résidus de médicaments. En raison des coûts élevés, des risques et des difficultés à gérer une STEU au sein d'un hôpital, le CHAL et les autorités locales ont demandées aux autorités l'approbation de démarrer un programme de recherche afin de caractériser les usées de l'hôpital en comparaison aux eaux usées domestiques. L'étude devait démontrer si le mélange des eaux usées de l'hôpital et domestiques dans une seule STEU n'induisait pas de risques pour la rivière Arve et les installations de potabilisation en aval. La STEU de Bellecombe a donc été divisée en deux parties : une pour le traitement des eaux usées de l'hôpital et l'autre pour les eaux usées domestiques ; créant de ce fait deux STEU, deux entrées de STEU et deux sorties de STEU.

Dans ce contexte, un premier projet a débuté en 2010 : SIPIBEL (Site Pilote de Bellecombe). Son objectif principal était de caractériser les eaux usées urbaines et hospitalières dans la STEU de Bellecombe ainsi que les effets sur la qualité des eaux de l'Arve. De nombreux paramètres journaliers ont été quantifiés, dont les flux de RdM, aux deux entrées de la STEU et dans la rivière Arve à l'amont et à l'aval de la STEU.

En parallèle, pour étendre et compléter le cadre de SIPIBEL, un autre projet a débuté en 2012 : IRMISE Arve aval (Impacte des Rejets de Micropolluants Issus de Station d'Épuration dans la rivière Arve). Le but était d'explorer la dispersion des RdM à l'aval de la STEU. Des mesures supplémentaires ont été planifiées pour quantifier les flux de RdM dans l'eau de l'Arve et du Rhône, à la sortie d'autres STEU et dans la nappe phréatique du genevois (figure 207). De plus, trois campagnes de 7 jours consécutifs de mesures journalières ont été faites aux deux entrées de la STEU de Bellecombe pour explorer les variations journalières de flux de ces contaminants.

Un troisième projet a débuté en 2014 pour continuer les recherches entreprises : SIPIBEL-RILACT (Risques et Leviers d'Action relatifs aux micropolluants). De nouvelles mesures ont été planifiées pour explorer les variations horaires des flux de RdM aux deux entrées de la STEU de Bellecombe, et leurs éventuelles dégradations au sein des réseaux d'assainissements (mesures in-situ et en condition de laboratoire).

Les trois projets ont de nombreux autres objectifs. Des descriptions complètes peuvent être trouvées à www.sipibel.org (Lecomte, 2016).

Bassin versant urbain

Le bassin versant urbain comprend 30 000 habitants répartis sur 14 communes dont seulement 16 000 sont raccordés à la STEU de Bellecombe. 14 500 des 30 000 habitants sont actifs, mais les 14 communes ne contiennent que 7 000 postes (INSEE, 2012).

Des données de ventes de médicaments ont été achetées auprès de la société IMS-Health. Elles détaillent les ventes mensuelles de médicaments sur une période de 2,5 ans depuis janvier 2012 pour: 1) les six pharmacies sur le territoire de la STEU de Bellecombe ; et 2) l'ensemble des pharmacies de Haute-Savoie (793 000 habitants et 223 pharmacies).

D'après l'analyse des consommations d'eau potable, les eaux usées devraient être composé de 79,5 % d'eaux usées domestiques et de 20,5 % d'eaux usées issus d'activités économiques diverses. Le réseau d'assainissement s'étend sur 130 km² et inclue 230 km de conduite circulaire de diamètre supérieur à 0,5 m. 29 pompes de relèvements sont présentes. D'importants problèmes d'eaux parasitaires et d'infiltrations ont été signalés.

Hôpital CHAL

L'hôpital est un hôpital généraliste de 450 lits. Les distributions de médicaments par la pharmacie centrale de l'hôpital ont été collectées. Elles détaillent entre mars 2012 et octobre 2014 de : 1) 120 jours de distributions journalières correspondant aux jours de mesures et des quatre jours précédents ; 2) 138 semaines consécutives de distributions hebdomadaires ; et 3) de 32 mois consécutifs de distributions mensuelles.

L'hôpital est relié à la partie hospitalière de la STEU de Bellecombe par une conduite unique d'environ 500 m avec une pompe de relèvement en fin de parcours.

MESURES

Débits d'eaux usées en entrée de STEU

Pour chacune des deux entrées de la STEU de Bellecombe (entrée urbaine et hospitalière), le débit des eaux usées est mesuré au pas de temps de la minute par un canal Venturi couplé à une sonde ultrasonique (table 54).

Table 55: Débitmètres et échantillonneurs automatiques de la STEU de Bellecombe

		Canal Venturi	Sonde Ultrasonique	Echantillonneur
Entrée urbain de la STEU	Marque	Endress-Hauser	Endress-Hauser	Endress-Hauser
	Modèle	QV 308	FMU 861 / FDU 80	ASP Station A
Entrée hospitalière de la STEU	Marque	ISMA	Endress-Hauser	Endress-Hauser
	Modèle	Type 2	Prosonic FMU 90	ASP Station 2000

Deux années complètes (2012 et 2013) ont été enregistrées pour analyse. Les volumes journaliers et horaires sont extraits pour chaque campagne de mesure.

Concentration de résidus de médicaments

Quatre types de campagnes de mesures ont été effectués :

- "**24 h**": depuis Mars 2012, un échantillon moyen de 24 h tous les mois, toujours débutant un mardi à 8 h du matin avec analyse de la fraction dissoute seulement. 36 campagnes ont été effectuées pour le bassin urbain et 47 pour l'hôpital CHAL.
- "**7 x 24 h**": 7 échantillons consécutifs moyens de 24 h avec analyse de la fraction dissoute seulement. 3 campagnes ont été effectuées pour chaque site débutant les 25/06/2013, 18/09/2013 and 21/05/2014.
- "**24 x 1 h**": 24 échantillon consécutifs moyen de 1 h, toujours débutant un mardi à 8 h du matin avec analyse de la fraction dissoute seulement. Pour l'entrée urbaine de la STEU, 4 campagnes ont été effectuées (29/09/2015, 17/11/2015, 19/01/2016 and 15/03/2016) et 3 pour l'entrée hospitalière (27/10/2015, 17/11/2015 and 09/02/2016).
- "**24 h particulaire**": un échantillon moyen de 24 h, toujours débutant un mardi à 8 h du matin avec analyse de la fraction particulaire seulement. 8 campagnes ont été effectuées pour les deux sites entre 2013 et 2015.

Toutes les dates de campagnes sont un compromis entre régularité (une par mois pour les "24 h"), faisabilité technique, précipitations (d'importantes infiltrations d'eaux de pluie diluent les médicaments) et spécificité du calendrier (pas de période de vacances, pas en weekend, pas de jour fériés).

L'objectif des mesures était de quantifier les 15 molécules à usage de médicaments du projet parmi de nombreux autres paramètres (plus de 130 au total). Comme de très faibles concentrations étaient attendues (de quelques ng/L à quelques µg/L), d'importants efforts ont été fait pour minimiser les problèmes de contamination. C'est pourquoi l'ensemble de la procédure de mesure évolué jusqu'à l'été 2013. Des blancs de prélèvements ont été régulièrement effectués pour détecter des problèmes et corriger les données si possibles.

La procédure de mesure est décrite par Lecomte (2016). Elle est dérivée des recommandations technique française (Aquaref, Cemagref, 2011). Le dosage en médicaments des échantillons récoltés est accompli par l'Institut des Sciences Analytiques (Lecomte, 2016), l'un des partenaires du projet. Les incertitudes d'analyses et les limites de détection (LoD) et quantification (LoQ) pour les 15 molécules sont présentées dans la table 55. Un indice de qualité est attribué à chaque mesure : "Correcte", "Incertaine" ou "Incorrecte".

Table 56: Incertitudes d'analyses et limites de détection (LoD) et quantification (LoQ) pour les 15 molécules étudiées (Source: Institut des Sciences Analytiques). Les incertitudes d'analyses ne sont pas fournies pour l'Aztréonam, Éthinylestradiol and Méropénème.

Molécule	LoD (ng/L)	LoQ (ng/L)	Incertitudes analytiques à la concentration mesurée (%)
Aténolol	0.5	4.1	3
Aztréonam	8	50	-
Carbamazépine	0.2	0.6	4
Ciprofloxacine	3.5	35.3	27
Diclofénac	1	5	16
Éconazole	0.6	1.2	27
Éthinylestradiol	0.4	7.3	-
Ibuprofène	0.2	0.5	20
Kétoprofène	1	9.8	7
Méropénème	8	50	-
Paracétamol	1.1	12.2	30
Propranolol	0.2	0.6	5
Acide salicylique	0.7	13.3	35
Sulfaméthoxazole	1.2	5.9	25
Vancomycine	8	50	50

MODÈLE

Le but du modèle est de prédire les flux de RdM de deux jours consécutifs à l'entrée de la STEU au pas de temps de la minute. L'intention est de développer un modèle le plus générique possible, non spécifique aux sites étudiés et qui puisse facilement être compléter. Il est développé entièrement avec le logiciel Matlab®2012a.

Peu importe le bassin versant étudié, les flux de RdM à la sortie du bassin versant sont le résultat de l'interaction entre les sources des polluants et une structure de convergence qui concentre les polluants en sortie du bassin versant. Plus d'un type de source de polluants peut être présente. Elles doivent être identifiées et quantifiées. Le transport des polluants et leurs potentielles transformations au sein de la structure convergente doivent être décrit.

Pour les deux sites étudiés, l'unique source de RdM est la consommation puis l'excrétion par la population. Toutefois, il est possible de définir différents types de populations, notamment les habitants du bassin versant urbain, les personnes travaillants dans le bassin versant urbain et les patients alités de l'hôpital. Les entrées et sorties de ces populations sur les sites doivent être prisent en compte pour correctement modéliser les flux journaliers et horaires de rejets de RdM.

La plupart des phénomènes influençant la consommation et l'excrétion de principes actifs de médicaments au cours du temps ne sont pas facilement prédictible de manière déterministe. Il est donc nécessaire de proposer un modèle stochastique.

Au sein des réseaux d'assainissements, deux types de métabolites sont généralement reconnus pour se retransformer en molécule mère : les glucuro et sulfo-conjugués. Ils sont donc également modélisés en plus des flux de RdM.

Pour prédire le transport, le modèle doit également être capable de générer les flux d'eaux usées.

Au final, le model consiste en trois éléments fondamentaux qui peuvent être arrangés en structure de différentes complexité. Chaque élément est capable de générer ou transporter les débits d'eaux usées, les flux de principes actifs et leurs glucuro et sulfo-conjugués. Ces éléments sont :

- Source d'eaux usées et de RdM : L'ensemble des foyers du bassin versants urbains, ainsi que leurs consommations d'eaux sont prédit grâce à la modélisation des emplois du temps de chaque habitant. En fonction des statistiques de ventes ou distributions de médicaments, le nombre de patients de chaque journée tiré au hasard. La posologie, le métabolisme et l'utilisation des toilettes de chaque habitant est ensuite modélisé.
- Conduite : Chaque conduite est subdivisée en sous-conduite d'une longueur prédéterminée. Chaque subdivision de conduite est modélisée à l'aide du modèle de Muskingum (Mac Carthy, 1940).
- Station de pompage : Les flux sortants sont calculés en fonction du volume d'eaux usées stocké. Au-delà d'un certain volume stocké les pompe s'activent jusqu'à ce qu'un volume minimum soit atteint. Le mélange des polluants dans la station est supposé homogène.

Pour simplifier la description des structures mises en place pour les sites étudiés. Une structure générique constituée de 20 sources et 20 conduites est utilisée. Les diagrammes des structures utilisées pour le bassin versant urbain et l'hôpital sont respectivement présentés en figure 208 et figure 209.

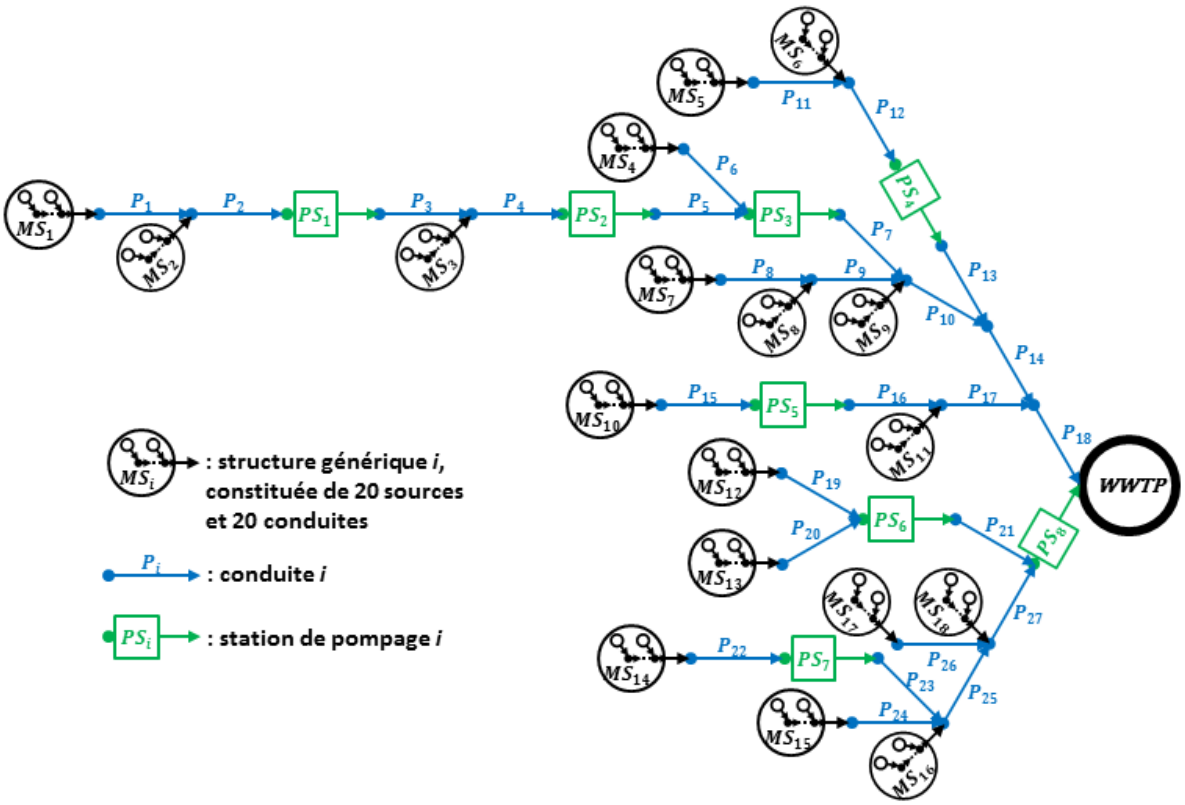

Figure 208: Structure du modèle du bassin versant urbain.

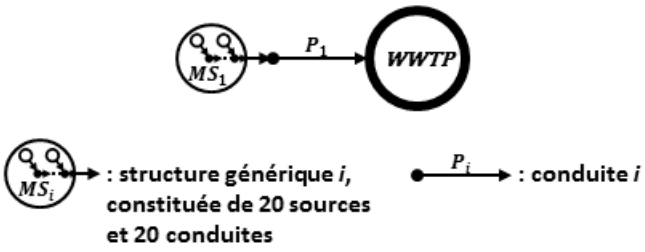

Figure 209: Structure du modèle de l'hôpital CHAL.

BASSIN VERSANT URBAIN

Ventes de médicaments

Les analyses révèlent d'une part que le taux de vente moyen des médicaments par habitant est différent entre les six pharmacies de Bellecombe et la Haute-Savoie (ratio moyen pondéré des taux de ventes de Bellecombe sur ceux de la Haute-Savoie égal à 0.61) et d'autre part que les ventes de la Haute-Savoie et des six pharmacies de Bellecombe ont les mêmes dynamiques mais que la variabilité des ventes mensuelles de Haute-Savoie est inférieure à celle de Bellecombe (effet lissant du nombre d'habitants).

En conséquence, il a été décidé d'utiliser les données de ventes mensuelles de Bellecombe pour leur variabilité supérieure mais de les affecter d'un coefficient correcteur pour atteindre les taux de ventes par habitants des 223 pharmacies de Haute-Savoie. Les taux de ventes de Haute-Savoie sont considéré plus fiables car il est plus difficile d'estimer le nombre d'habitants fournis en médicaments par les 6 pharmacies de Bellecombe que par les 223 de Haute-Savoie. Les ventes sont présentées en table 56.

La quantité de donnée ne permet pas d'analyse robuste des dynamiques annuelles ou des saisonnalités.

Flux journaliers mesurés

Les campagnes de mesures "24 h particulaire" ont montré que les molécules sont principalement présentes sous formes dissoutes (en moyenne à 90 %). Toutefois, Aztréonam, Ciprofloxacine, Méropénème et Vancomycine n'ont pas été testé ; et les résultats de l'Éconazole et l'Éthinylestradiol ne permettent pas de conclure.

Vingt campagnes de mesures "24 h" de qualité correcte sont analysées (table 56). Aztréonam, Ciprofloxacine, Éconazole, Éthinylestradiol, Méropénème et Vancomycine ne sont jamais mesurées mais parfois détectées. Pour les autres molécules, les flux journaliers moyen mesurés couvrent une gamme de valeurs importantes (figure 210). De plus, la dispersion des flux journaliers pour une même molécule est également importante (coefficient de variation toujours supérieur à 24 %). La dynamique des flux journaliers n'a pas été analysée du fait de la courte période de temps couverte par les mesures (Août 2013 à Octobre 2015). Toutefois, quelques-unes sont suspectées de présenter une dynamique saisonnière. Quant aux concentrations mesurées, elles se trouvent dans la gamme des valeurs décrites dans la littérature.

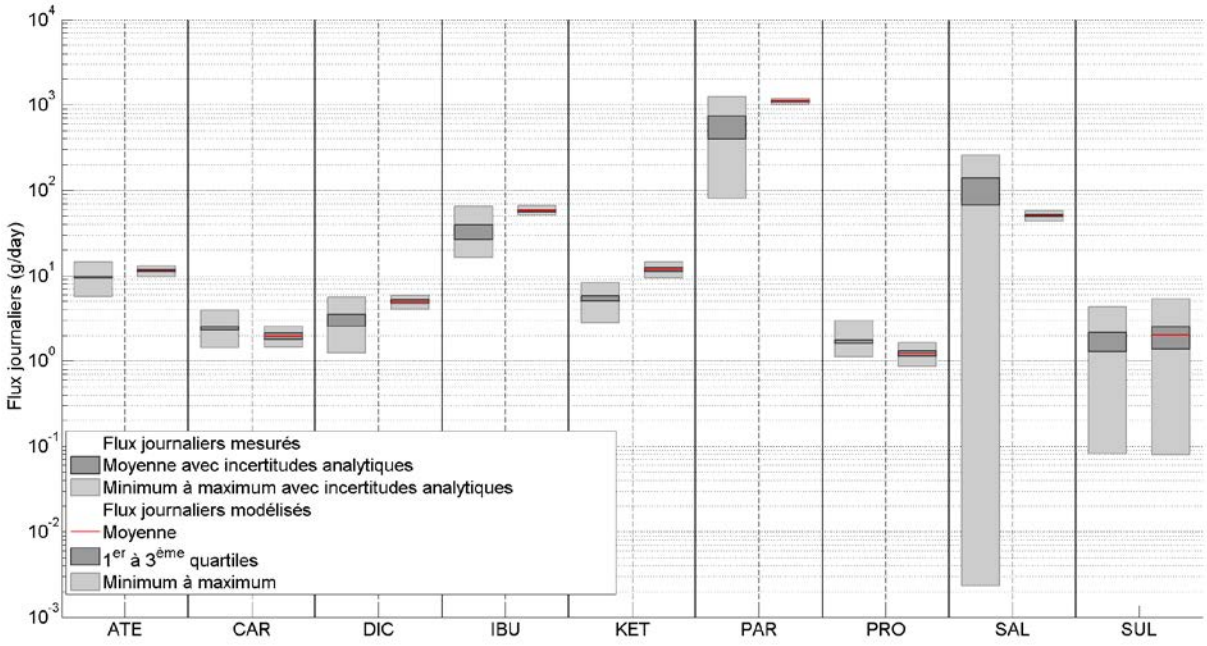

Figure 210: Flux journaliers mesurées et modélisés pour le bassin versant urbain.

Pour les molécules quantifiées, il n'est possible d'associer des masses de médicaments vendus que pour six campagnes (table 56). L'analyse montre qu'un simple lien de proportionnalité entre les flux mesurés à l'entrée de la STEU et les masses vendues sur la même période n'est pas satisfaisant (coefficient de détermination presque jamais supérieur à 0,26). Aussi, la variabilité des flux mesurés est plus importante que celle des ventes.

L'analyse des campagnes "7 x 24 h" n'est pas concluante du fait du nombre limité de données.

Flux horaires mesurés

Quatre campagnes "24 x 1 h" sont analysées. Aztréonam, Ciprofloxacine, Éconazole, Éthinylestradiol, Méropénème et Vancomycine ne sont jamais mesurées mais parfois détectées. Aténolol, Ibuprofène, Kétoprofène, Paracétamol, Propranolol et Acide Salicylique ont des dynamiques semblables d'une campagne à une autre, à l'inverse de la Carbamazépine, du Diclofénac et du Sulfaméthoxazole. Les dynamiques sont propres à chaque molécule et sont distinctes de la dynamique des débits d'eaux usées. Toutefois, les dynamiques de l'Aténolol, l'Ibuprofène, le Kétoprofène et le Paracétamol partage des similarités.

Flux journaliers modélisés

Le ratio flux moyen modélisé sur mesuré est utilisé. Les résultats sont considérés comme bon si le ratio flux moyen modélisé sur mesuré est compris entre 0,5 et 2 (*i.e.* lorsque le modèle sur ou sous-estime moins de deux fois le flux moyen mesuré). De plus, pour que le modèle soit jugé fiable, il doit produire de bon résultat pour chaque molécule. Les résultats sont présentés en figure 210 et table 56.

Les résultats du modèle sont les meilleurs lorsque sont pris en compte les flux de molécules mères et les flux de leurs glucuro-conjugués. Dans cette configuration, huit des neuf molécules modélisées ont des ratios satisfaisants. Les mauvaises performances du modèle pour le Kétoprofène peuvent être expliquées du fait des incertitudes le concernant (large gamme possible pour le taux d'excrétion de glucuro-conjugués et incertitudes sur le sort des formes non-orale de la molécule). Ainsi, il est raisonnable et réaliste de supposer que les glucuro-conjugués se dé-conjuguent rapidement et totalement au sein du réseau d'assainissement alors que les sulfo-conjugués ne le font pas.

Le modèle est donc capable, dans son état actuel, de prédire de manière fiable les flux journaliers de résidus de médicaments à l'entrée de la STEU pour le bassin versant urbain avec une précision raisonnable au regard des données disponibles et des incertitudes analytiques. La variabilité des flux journaliers reste néanmoins sous-estimée.

Un modèle proportionnel, basé sur le travail de Heberer and Feldmann (2005), est utilisé comme point de comparaison. L'erreur relative (Re) de chaque molécule est calculée et comparé (table 56).

Les erreurs relatives du nouveau modèle sont inférieures à celle du modèle classique pour cinq des neuf molécules. Aussi, les erreurs relatives moyenne, minimum et maximum sont toutes inférieures pour le nouveau modèle. Cela indique que le nouveau modèle donne de meilleurs résultats que le modèle classique, tout en donnant une information sur la variabilité des flux journaliers. Mise à part la nature stochastique du nouveau modèle, la principale différence impactant les flux journaliers est l'intégration de la dynamique des populations au cours d'une journée (personnes entrant ou sortant du bassin versant pour aller travailler par exemple).

Flux horaires modélisés

La comparaison des flux horaires est rendu compliquée par le faible nombre de mesures, rendant la détermination d'une dynamique moyenne des flux hasardeuse. Afin de contourner cette difficulté, un indicateur dérivé du coefficient de Nash-Sutcliffe (NSE) est proposé :

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

$$\boldsymbol{si}\ Q_1(\tilde{L}_{modelled}(t)) \geq \tilde{L}_{measured}(t)\ \boldsymbol{alors}\ \tilde{L}_{fuzzy}(t) = Q_1(\tilde{L}_{modelled}(t))$$
$$\boldsymbol{si}\ Q_3(\tilde{L}_{modelled}(t)) \leq \tilde{L}_{measured}(t)\ \boldsymbol{alors}\ \tilde{L}_{fuzzy}(t) = Q_3(\tilde{L}_{modelled}(t))$$
$$\boldsymbol{sinon}\ \tilde{L}_{fuzzy}(t) = \tilde{L}_{measured}(t)$$

Avec :
$\tilde{L}_{measured}(t)$: flux horaire mesuré normalisé au temps t
$\tilde{L}_{fuzzy}(t)$: flux horaire mesuré normalisé au temps t construit pour le calcul du NSE_{fuzzy}
$\overline{\tilde{L}_{measured}}$: flux horaire mesuré normalisé moyen
$Q_1(X)$, $Q_3(X)$: premier et troisième quartiles d'une liste de valeur X
$\tilde{L}_{modelled}(t)$: distribution des flux horaires modélisé normalisé au temps t

Les résultats du modèle pour une molécule sont considérés comme satisfaisants lorsque le NSE_{fuzzy} est supérieur à 0,5. Aussi, le modèle est considéré comme fiable s'il a des résultats satisfaisants pour toutes les molécules. Les résultats sont présentés en table 56.

Sept des neuf molécules modélisés ont un NSE_{fuzzy} supérieur ou proche de 0,5. Les résultats des deux molécules ayant des scores inférieurs à 0,5 peuvent s'expliquer du fait de la faible consommation de la Carbamazépine et de la présence de pics isolés des flux journaliers mesurés pour les deux molécules qui baisse dramatiquement le score. Des campagnes de mesures supplémentaires devraient permettre d'obtenir des scores non perturbé par la présence d'artefacts aléatoires.

Le modèle est donc capable, dans son état actuel, de prédire de manière fiable les flux horaires de RdM à l'entrée de la STEU pour le bassin versant urbain avec une précision raisonnable. Cependant, le modèle reste sensible à la présence d'évènement chaotiques et isolé dans lors des campagnes de mesures.

Table 57 : Résultats des mesures et de la modélisation pour le bassin versant urbain.

Molécule	Vente de médicaments		Flux journaliers mesurés			Corrélation linéaire	Modèle stochastique proposé			Comparaison avec le modèle classique Erreur relative	
	Masse moyenne mg/jour /habitant	Nombre moyen de DDD DDD/jour /10 000 habitants	Détection	Quantification	Flux moyen (écart-type) g/jour	Flux mesuré = α x masse vendue R^2	Flux moyen journalier g/jour	Ratio flux modélisé sur mesuré	NSE_{fuzzy} moyen des flux horaires normalisés modélisés avec, pour référence, les flux horaires normalisés mesurés	Modèle stochastique proposé %	Modèle proportionnel classique %
Aténolol	0,88	118	19/19	19/19	9,6 (2,3)	0,21	11,4 (0,5)	1,19	0,18	19	42
Aztréonam	0	0	0/20	0/20	< 0,03 (0,008)						
Carbamazépine	1,14	11	19/19	19/19	2,4 (0,6)	0,84	2,0 (0,2)	0,81	0,19	19	6
Ciprofloxacine	0,53	5	7/18	0/18	< 0,07 (0,07)						
Diclofénac	1,31	131	19/19	19/19	3,0 (0,8)	0,24	5 (0,3)	1,64	0,50	64	24
Éconazole	0,09	11	3/19	0/19	< 0,002 (0,001)						
Éthinylestradiol	0,001	540	0/20	0/20	< 0,002 (0)						
Ibuprofène	17	142	20/20	20/20	33,0 (8,4)	0,09	57 (2,4)	1,73	0,71	73	106
Kétoprofène	1,02	102	20/20	20/20	5,4 (1,5)	0,09	11,8 (0,9)	2,19	0,72	119	167
Méropénème	0	0	0/20	0/20	< 0,03 (0,008)						
Paracétamol	145	483	18/18	18/18	564,4 (192,8)	0,02	1 104 (27,7)	1,96	0,53	207	259
Propranolol	0,41	25	18/18	18/18	1,7 (0,5)	0,2	1,2 (0,1)	0,73	0,65	27	19
Acide salicylique	15	51	20/20	19/20	102,4 (56,1)	0,01	50,7 (2,3)	0,50	0,45	50	40
Sulfaméthoxazole	0,38	2	19/19	19/19	1,7 (0,9)	0,26	2,0 (1,0)	1,17	0,60	44	99
Vancomycine	0	0	1/20	0/20	< 0,04 (0,04)						

HÔPITAL CHAL

Distribution de médicaments

Les analyses révèlent que les distributions de médicaments par la pharmacie centrale de l'hôpital peuvent être impactées par des facteurs autres que la consommation véritable de médicaments par les patients alités, notamment la gestion des stocks de médicaments (retours à la pharmacie centrale, pic d'approvisionnements, réapprovisionnements par paquets…). Les distributions journalières sont les plus impactées, mais les distributions mensuelles sont trop lissées pour refléter la variabilité des consommations.

En conséquence, il a été décidé d'utiliser les distributions hebdomadaires après traitement de celles-ci (suppression des retours et des pics de réapprovisionnements, lissage par application d'une moyenne mobile de 3 semaines). Les distributions sont présentées en table 57.

La quantité de donnée ne permet pas d'analyse robuste des dynamiques annuelles ou des saisonnalités.

Flux journaliers mesurés

Les campagnes de mesures "24 h particulaire" ont montré que les molécules sont principalement présentes sous formes dissoutes (en moyenne à 97 %). Toutefois, Aztréonam, Ciprofloxacine, Méropénème et Vancomycine n'ont pas été testé ; et les résultats de l'Éconazole et l'Éthinylestradiol ne permettent pas de conclure.

Vingt-quatre campagnes de mesures "24 h" de qualité correcte sont analysées (table 57). Aztréonam, Éconazole, Éthinylestradiol et Méropénème ne sont jamais mesurées mais parfois détectées. Pour les autres molécules, les flux journaliers moyen mesurés couvrent une gamme de valeurs importantes (figure 211). De plus, la dispersion des flux journaliers pour une même molécule est également importante (coefficient de variation toujours supérieur à 21 %). La dynamique des flux journaliers n'a pas été analysée du fait de la courte période de temps couverte par les mesures (Août 2013 à Octobre 2015). Toutefois, quelques molécules sont suspectées d'avoir une dynamique saisonnière. Les concentrations mesurées se trouvent majoritairement dans la gamme des valeurs décrites dans la littérature.

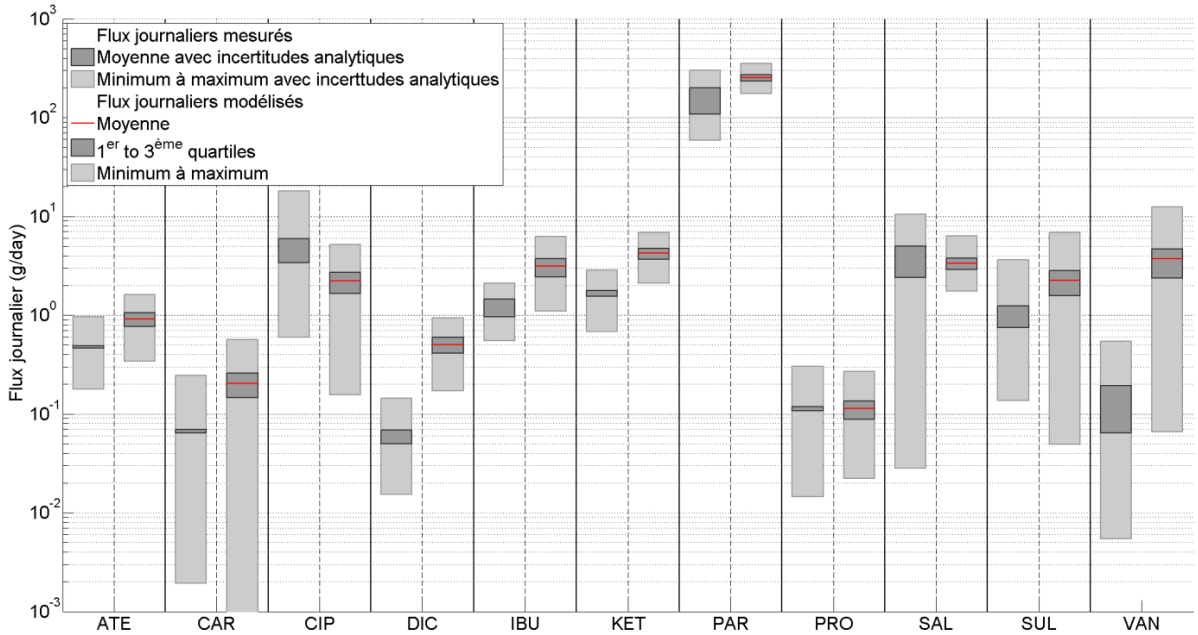

Figure 211: Flux journaliers mesurées et modélisés pour l'hôpital CHAL.

Pour les molécules quantifiées, il n'est possible d'associer des masses de médicaments distribués que pour douze à quatorze campagnes (table 57). L'analyse montre qu'un simple lien de proportionnalité entre les flux mesurés à l'entrée de la STEU et les masses vendues sur la même période n'est pas satisfaisant (coefficient de détermination jamais supérieur à 0,50). Aussi, la variabilité des flux mesurés est plus importante que celle des ventes.

L'analyse des campagnes "7 x 24 h" n'est pas concluante du fait du nombre limité de données.

Flux horaires mesurés

Trois campagnes "24 x 1 h" sont analysées. Aztréonam, Éconazole, Éthinylestradiol et Méropénème ne sont jamais mesurées mais parfois détectées. Aténolol, Carbamazépine et Paracétamol ont des dynamiques semblables d'une campagne à une autre, à l'inverse de la Ciprofloxacine, Diclofénac, l'Ibuprofène, du Kétoprofène, du Propranolol, l'Acide Salicylique et du Sulfaméthoxazole. Les dynamiques sont propres à chaque molécule et sont distinctes de la dynamique des débits d'eaux usées. Toutefois, les dynamiques de l'Aténolol et de la Carbamazépine partage des similarités.

Flux journaliers modélisés

La même méthodologie que pour le bassin versant urbain est appliqué à l'hôpital CHAL (figure 211 et table 57).

Considérant les flux de molécules mères et leurs glucuro-conjugués, seulement quatre des onze molécules modélisés ont des ratios satisfaisants. Le modèle n'est donc pas capable dans son état actuel de prédire de manière fiable les flux journaliers de RdM à l'entrée de la STEU pour l'hôpital. La plupart du temps, le modèle surestime les flux journaliers.

Le même modèle proportionnel utilisé pour le bassin versant urbain sert de point de comparaison. Les erreurs relatives du modèle classique et du nouveau sont présenté en table 57. Les erreurs relatives du nouveau modèle sont inférieures à celle du modèle classique pour neuf des onze molécules. Aussi, les erreurs relatives moyenne, minimum et maximum sont toutes inférieures pour le nouveau modèle. Cela indique que le nouveau modèle donne de meilleurs résultats que le modèle classique, tout en donnant une information sur la variabilité des flux journaliers.

Flux horaires modélisés

Comme pour le bassin versant urbain, les NSE_{fuzzy} sont utilisés (table 57).

Cinq des onze molécules modélisés ont un NSE_{fuzzy} supérieur à 0,5. Cependant le nombre limité de campagnes de mesures et le faible nombre théorique de patients dans l'hôpital font dramatiquement baisser les scores. Dans ces conditions, il n'est pas possible de conclure sur la fiabilité du modèle pour l'hôpital. Cependant, les résultats sont encourageants et devraient s'améliorer avec des campagnes de mesures supplémentaires.

Table 58 : Résultats des mesures et de la modélisation pour l'hôpital CHAL.

Molécule	Distribution de médicaments		Flux journaliers mesurés			Corrélation linéaire	Modèle stochastique proposé			Comparaison avec le modèle classique Erreur relative	
	Masse moyenne mg/jour /lit	Nombre moyen de DDD DDD/jour /1 000 lits	Détection	Quantification	Flux moyen (écart-type) g/jour	Flux mesuré = α x masse vendue R^2	Flux moyen journalier g/jour	Ratio flux modélisé sur mesuré	NSE_{fuzzy} moyen des flux horaires normalisés modélisés avec, pour référence, les flux horaires normalisés mesurés	Modèle stochastique proposé %	Modèle proportionnel classique %
Aténolol	2.7	36	21/21	21/21	0,5 (0,2)	0,3	0,9 (0,2)	1,91	0,62	91	157
Aztréonam			0/24	0/24	< 0,001 (0)						
Carbamazépine	4,8	4	22/22	22/22	0,07 (0,08)	0,08	0,2 (0,09)	3,06	0,55	206	343
Ciprofloxacine	8	9	23/23	23/23	4,6 (3,9)	0,07	2,2 (0,8)	0,48	0,59	52	39
Diclofénac	3,9	39	22/22	22/22	0,06 (0,03)	0,12	0,5 (0,1)	8,49	0,42	753	239
Éconazole	2,5	31	4/23	1/23	< 0,001 (0)						
Éthinylestradiol			0/24	0/24							
Ibuprofène	36,5	31	22/22	22/22	1,2 (0,3)	0,34	3,1 (0,9)	2,59	0,54	159	248
Kétoprofène	14,5	144	22/22	22/22	1,7 (0,5)	0,50	4,2 (0,8)	2,55	0,40	155	254
Méropénème	2	1	0/24	0/24	< 0,001 (0)						
Paracétamol	1 307	436	21/21	21/21	153,9 (33,0)	0,23	251,7 (27,3)	1,64	0,06	64	240
Propranolol	1,6	11	23/23	23/23	0,1 (0,08)	0,11	0,1 (0,04)	1,00	0,52	0	47
Acide salicylique	41,2	13	23/23	23/23	3,7 (2,0)	0,12	3,4 (0,7)	0,90	0,34	10	30
Sulfaméthoxazole	17,3	9	21/21	21/21	1,0 (0,8)	0,24	2,2 (1,0)	1,64	0,18	126	386
Vancomycine	11,3	7	22/22	22/22	0,1 (0,1)	0,49	3,7 (1,9)	29,1	0,18	2 820	4 184

CONCLUSIONS ET PERSPECTIVES

L'accomplissement des trois objectifs de la thèse est évalué ci-dessous :

- **Mesurer, pour les deux sites, les flux de médicaments entrant en STEU, les comparer et évaluer leurs variabilités à différentes échelles de temps.**

  Quatre types de campagnes de mesures ont été effectuées sur les deux sites. Les matériels et méthodes ont été définis avec soin pour éviter des biais. Toutes les campagnes se sont déroulées sur quelques années toujours le même jour de la semaine (mardi à mercredi) et pendant des périodes normales (hors vacances, hors jours fériés). Quelques molécules n'ont jamais ou presque jamais été quantifiées, rendant leur analyse difficile. Pour le bassin versant urbain, six molécules sont concernées : Aztréonam, Ciprofloxacine, Éconazole, Éthinylestradiol, Méropénème et Vancomycine. Pour l'hôpital CHAL, elles sont quatre : Aztréonam, Éconazole, Éthinylestradiol et Méropénème.

  Les campagnes "24 h particulaire" ont permis de comparer la distribution des flux de résidus de médicaments entre phase dissoute et particulaire. Sept campagnes ont été effectuées pour chaque site. Les résultats montrent que les molécules quantifiées sont principalement en phase dissoute (au moins 90 % de flux total). Cependant, ce résultat ne peut être étendu à l'ensemble des molécules à usage pharmaceutique car elles ne représentent pas une classe chimique uniforme.

  Les campagnes "24 h" ont mesuré les flux dissous journaliers. Respectivement, 20 et 24 campagnes ont été effectuées pour le site urbain et hospitalier sur une période de deux ans. La gamme des flux mesurés est importante pour les deux sites. Le flux journalier moyen varie de 1,7 à 564 g/jour pour le bassin versant urbain et de 0,06 à 154 g/jour pour l'hôpital CHAL. La variabilité des flux journaliers pour chaque molécule est importante. En effet, les coefficients de variations sont rarement inférieurs à 25 %. Aucune saisonnalité ni évolution annuelle n'a été identifiée par manque de données. Les concentrations mesurées sont soit similaires pour les deux sites, soit plus importantes pour le site hospitalier. Mais les flux sont toujours supérieurs pour le bassin versant urbain sauf pour deux molécules utilisées uniquement en hôpital. Cependant, il n'est pas nécessairement pertinent de comparer les deux sites de la sorte. Il serait intéressant de proposer un ratio pondéré considérant le nombre potentiel de personnes concernées, *i.e.* en divisant les flux urbains par le nombre de personnes raccordées à la STEU et en divisant les flux hospitaliers par le nombre de personnes susceptible d'être traitées dans cet hôpital (chiffre non disponible pour cette étude).

  Les campagnes "24 x 1 h" ont mesuré les dynamiques des flux au cours d'une journée. Respectivement, 4 et 3 campagnes ont été effectuées pour le site urbain et hospitalier. L'élément clé pour interpréter les résultats de ces campagnes est de considérer le nombre théorique de patients par jour pour chaque molécule (DDD/jour). En présence de nombreux patients, le hasard de leurs excrétions va se moyenner et donc les flux horaires mesurés à la STEU seront représentatifs de la dynamique moyenne. Inversement, avec peu de patients, les flux horaires mesurés seront fortement impactés par le hasard de la période de leurs excrétions et il sera donc difficile de connaitre la dynamique moyenne des flux avec un nombre restreint de campagnes. C'est le cas pour quelques molécules pour le bassin versant urbain (DDD/jour : Carbamazépine, 7 ; Sulfaméthoxazole, 1) et pour la plupart des molécules pour l'hôpital (DDD/jour : Ciprofloxacine, 4; Diclofénac, 17; Ibuprofène, 14; Propranolol, 5; Acide Salicylique, 6; Sulfaméthoxazole, 4; Vancomycine, 3). En conséquence, les dynamiques des flux horaires mesurés ne sont pas semblables d'une campagne à une autre pour ces molécules. Cependant, excepté pour quelques cas difficiles, les dynamiques des flux horaires mesurés pour les molécules consommées par de nombreux patients par jour se ressemblent d'une campagne à une autre. Les dynamiques moyennes des flux horaires mesurés ne sont pas nécessairement similaires d'une molécule à une autre, même si quelques molécules ont des dynamiques similaires. Cependant, aucune molécule ne partage sa dynamique avec la dynamique du débit d'eaux usées.

Les campagnes “7 x 24 h” avaient pour objectif d’identifier des dynamiques hebdomadaires. Trois campagnes ont été effectuées pour chaque site, mais la qualité des mesures est considérée comme “incertaine” à cause de problèmes techniques. Néanmoins, aucune dynamique n’a pu être mise en évidence.

- **Acquérir et analyser des données de ventes de médicaments détaillées pour les deux sites.**

  Les données de pharmacies sont collectées car il est supposé qu’elles sont liées aux consommations de médicaments.

  Pour le bassin versant urbain, les données de ventes ont été achetées à une société collectant les données de ventes en pharmacies. Les ventes mensuelles de 2,5 années de deux territoires ont été analysées. Le premier territoire comprend les six pharmacies présentes sur le bassin versant et qui fournissent, supposément, les 30 000 habitants du bassin versant (dont la moitié seulement est raccordée à la STEU). Le second territoire est bien plus grand et couvre l’ensemble de la Haute-Savoie (793 000 habitants). Les données des six pharmacies ont une variabilité plus importante que celle de la Haute-Savoie. Cependant, les données donnent des taux de ventes de médicaments différents (masse vendue par jour et par habitant) selon leur source. Comme le nombre d’habitants fourni en médicaments par les six pharmacies est bien plus incertain que pour la Haute-Savoie, il a été décidé de garder les données des six pharmacies pour leur variabilité mais de leur affecter un coefficient correcteur afin d’obtenir des taux de vente de médicaments similaires à la Haute-Savoie.

  Pour l’hôpital CHAL, les distributions de médicaments ont été directement fournies par la pharmacie centrale de l’hôpital. Trois échelles temporelles ont été analysées : jours, semaines et mois. Les analyses révèlent que les données sont affectées par la gestion des stocks et ne sont donc pas nécessairement représentatives de la véritable consommation des patients. Par exemple, les données indiquent que les médicaments peuvent revenir à la pharmacie centrale, ou que les médicaments peuvent être distribués par paquets (*i.e.* un nombre fixe à chaque fois ou un multiple de ce dernier), ou qu’aucun médicament n’est distribué durant les weekends. Les distributions journalières sont les plus impactées, mais elles sont potentiellement les plus proches de la véritable variabilité des consommations. Les distributions hebdomadaires sont choisies comme compromis et traitées pour estimer les distributions journalières probables (*i.e.* suppression des valeurs suspectes et lissage par application d’une moyenne mobile sur trois semaines).

  Les 15 molécules sont vendues sous la forme de 188 spécialités dans le bassin versant urbain, et de 56 spécialités dans l’hôpital. Pour chaque molécule, les cinq (respectivement trois) spécialités les plus vendues représentent plus de 90 % de la masse totale vendue dans le bassin versant urbain (respectivement dans l’hôpital). La plupart des spécialités consiste en des formes orales (tablettes, pilules…), mais pour certaines molécules les formes dermiques (crèmes, gel…) sont également importantes. Les formes intraveineuses ne sont présentes que pour l’hôpital et sont parfois l’unique forme disponible. La gamme des ventes ou distributions est importante. Les masses moyennes vendues ou distribuées en un jour vont de 0,04 à 4 346 g/jour pour le bassin versant urbain et de 0,7 à 590 g/jour pour l’hôpital. Considérant la DDD de chaque molécule, le nombre théorique moyen de patients par jour varie de 6 à 1 620 pour le bassin versant urbain et de 0,4 à 200 pour l’hôpital.

  Afin d’explorer le lien entre ventes ou distributions et flux mesurés à la STEU, les ventes ou distributions sont associées aux flux journaliers mesurés. Les données n’ont pas permis d’établir une corrélation linéaire satisfaisante et la variabilité des flux mesurés est systématiquement plus importante que celles des venets ou distributions.

  Les données de ventes sont difficiles à obtenir, à analyser et leur habilité à représenter précisément les consommations et donc les flux dans les eaux usées est discutable.

- **Modéliser, pour les deux sites, les flux de résidus de médicaments entrant en STEU au pas de temps horaire en considérant la nature stochastique du phénomène.**

Un modèle au pas de temps de la minute a été proposé et testé pour les deux sites. La plupart des phénomènes sont modélisés avec une approche stochastique. Seulement une partie des 15 molécules étudiées est modélisée car certaines molécules ne sont jamais, ou presque, quantifiées dans les flux journaliers ou horaires pour les deux sites.

Pour le bassin versant urbain, seulement neuf molécules sont modélisées :

Flux journaliers

Les résultats indiquent que les flux de glucuro-conjugués doivent être ajoutés au flux de molécule mère. Sans eux, le modèle est moins performant. De plus, l'ajout de sulfo-conjugués conduit à des surestimations. **Ainsi, au regard des présents résultats, il est raisonnable et réaliste de supposer que les sulfo-conjugués ne se retransforment pas en molécule mère dans les réseaux d'assainissement tandis que les glucuro-conjugués le sont de manière rapide et totale.**

Considérant les flux de molécules mère et de glucuro-conjugués seulement, les ratios flux moyen journalier modélisés sur mesurés varient de 0,5 à 2 pour huit des neuf molécules modélisées (moyenne de 1,32). Une molécule est surestimée : le Ketoprofène avec un ratio de 2,19. Cependant, ces paramètres métaboliques ne sont pas connus avec précisions. Les ratios des coefficients de variation modélisés sur mesurés varient de 0,07 à 0,83 (moyenne de 0,28). Cela indique que la variabilité des flux journaliers est sous-estimée par le modèle.

Comparé à un modèle proportionnel classique de la littérature, le nouveau modèle stochastique produit de meilleurs résultats pour six des neuf molécules. L'erreur relative moyenne passe de 82 % pour le modèle proportionnel classique à 48 % pour le nouveau modèle stochastique.

En conclusion, le modèle est capable de reproduire fidèlement les flux journalier avec suffisamment de précision pour un bassin versant urbain, mais leur variabilité reste sous-estimée. Le modèle améliore la performance moyenne du modèle classique d'un tiers.

Flux horaires

Les NSE_{fuzzy} moyens (variation du NSE) pour chaque molécule varient de 0,18 à 0,72 (moyenne de 0,50). Ils sont supérieurs ou proche de 0,50 pour sept des neuf molécules modélisées. Les performances limitées pour les deux molécules ayant des NSE_{fuzzy} inférieurs à 0,5 peuvent être partiellement expliquées par la sensibilité des dynamiques de flux aux faibles taux de consommation de certaines molécules et à des pics de mesures suspects.

Les variations entre les différentes répétitions stochastiques du modèle sont importantes (coefficient de variations moyen de chaque heure variant de 19 à 51 % selon la molécule). Cependant, la comparaison des variabilités des flux horaires modélisés et mesurés n'est pas possible par manque de mesures.

Aucune comparaison avec d'autres modèles n'est possible (un seul autre modèle mais sans critère objectif).

En conclusion, le modèle est capable de reproduire fidèlement les flux horaires avec suffisamment de précision pour un bassin versant urbain.

Pour l'hôpital CHAL, onze molécules ont été modélisées :

Flux journaliers

Seulement quatre des onze molécules ont des ratios flux journaliers moyen modélisés sur mesurés variant de 0,5 à 2. Six des sept autres molécules ont des ratios supérieurs à 2. Cela indique que le modèle surestime globalement les flux journaliers (ratio médian de 2,26). Aussi, la variabilité des flux journaliers modélisés est en moyenne la moitié de celle des flux journaliers mesurés. La gamme des flux journaliers mesurés intercepte celle des flux journaliers mesurés pour 10 molécules. Ces résultats non satisfaisants peuvent être

le résultat de nombreux facteurs. Cela confirme la spécificité d'un hôpital par rapport à un bassin versant urbain.

Comparé à un modèle proportionnel classique de la littérature, le nouveau modèle stochastique produit de meilleurs résultats pour neuf des onze molécules. L'erreur relative moyenne passe de 560 % pour le modèle proportionnel classique à 400 % pour le nouveau modèle stochastique.

En conclusion, le modèle n'est pas capable de reproduire fidèlement les flux journaliers avec suffisamment de précision pour un hôpital, mais ces résultats restent meilleurs que ceux d'un modèle proportionnel classique.

Flux horaires

Les NSE_{fuzzy} moyens pour chaque molécule varient de 0,06 à 0,62 (moyenne de 0,40). Ils sont supérieurs à 0,50 pour cinq des onze molécules modélisées. Comme pour le bassin versant urbain, les performances limitées du modèle peuvent être partiellement expliquées par la sensibilité des dynamiques de flux aux faibles taux de consommation (neuf molécules avec moins de 17 DDD distribuées par jour).

Les variations entre les différentes répétitions stochastiques du modèle sont importantes (coefficient de variations moyen de chaque heure variant de 27 à 73 % selon la molécule). Cependant, la comparaison des variabilités des flux horaires modélisés et mesurés n'est pas possible par manque de mesures.

Aucune comparaison avec d'autres modèles n'est possible.

Le manque de mesures combiné à de faibles taux de consommation de médicaments au sein de l'hôpital empêche de conclure définitivement sur l'application du modèle à un hôpital. Cependant, les résultats sont encourageants et la plupart des résultats non satisfaisants devraient être améliorés par de nouvelles mesures.

Concernant les résidus de médicaments étudiés, les résultats du modèle sont globalement satisfaisants. Le modèle produit fidèlement des résultats satisfaisants dans des conditions normales pour les flux journaliers et horaires. Cependant, il sous-estime toujours la variabilité des flux journaliers. Il produit de meilleurs résultats que le modèle proportionnel classique. Dans son état actuel, le modèle peut être utilisé avec confiance pour un bassin versant urbain de taille suffisante. L'utilisation du modèle pour les hôpitaux est délicate à cause de leur spécificité inhérente et de leur faible taux de consommation de médicaments. Le nouveau modèle stochastique fournit des informations supplémentaires (variabilité des flux et flux horaires) par rapport au modèle proportionnel classique. Cependant, il requiert d'avantage de données et sa mise en place est plus difficile.

De plus, le modèle est aussi capable de prédire les débits d'eaux usées pour un bassin versant urbain avec une grande précision concernant aussi bien les volumes journaliers que la dynamique. Après calibration, le modèle a été vérifié à l'aide de 43 périodes d'un jour au pas de temps de la minute. Le NSE moyen est égal à 0,89 et le minimum est de 0,60.

Dans ce contexte, les travaux ultérieurs devraient se concentrer sur :

- D'avantage de mesures de flux horaires de RdM,
- L'étude de la consommation domestique des médicaments,
- D'avantage de connaissances accessibles sur le métabolisme humain des médicaments,
- L'étude de la dynamique de l'utilisation des toilettes,
- L'étude du sort des RdM et de leurs métabolites et produits de dégradation au sein des réseaux d'assainissements,
- L'amélioration du nouveau modèle stochastique à l'aide des points précédents,
- L'établissement d'un modèle détaillé pour l'hôpital en le subdivisant en plusieurs entités notamment,
- L'intégration du modèle dans un cadre plus large intégrant une STEU et un milieu récepteur,
- L'analyse des incertitudes de mesures concernant les flux de RdM,
- L'élargissement pertinent de la liste des médicaments, métabolites ou produits de dégradation à modéliser,

La simplification du modèle pour une utilisation plus simple et rapide.

FOLIO ADMINISTRATIF

FOLIO ADMINISTRATIF

THESE DE L'UNIVERSITE DE LYON OPEREE AU SEIN DE L'INSA LYON

NOM : POUZOL DATE de SOUTENANCE : 20/02/2018

Prénoms : Tanguy, Vincent, Calixte

TITRE : MONITORING AND MODELLING OF PHARMACEUTICALS IN WASTEWATER: DAILY AND HOURLY LOADS IN BOTH HOSPITAL AND URBAN WASTEWATER

NATURE : Doctorat Numéro d'ordre : 2018LYSEI009

Ecole doctorale : MEGA DE LYON (MECANIQUE, ENERGETIQUE, GENIE CIVIL, ACOUSTIQUE) - EDA162

Spécialité : Génie Civil

RESUME :

Daily and hourly loads of 15 pharmaceutical molecules at the inlet of a wastewater treatment plant have been measured over 3 years and modelled for both an urban catchment of 16 000 inhabitants and a hospital of 450 beds. Some molecules are never or rarely quantified. Daily loads range from 0.6 to 564 g/day depending of the molecule and the 24 h measurement campaign. Seasonal or weekly patterns are not identified. Pharmaceuticals hourly loads dynamics are distinctive from one another and from wastewater flow. The measured hourly loads are severely impacted by the random behaviour of the patients when the daily mass consumed is low. Thus, the average dynamics is difficult to identify. The main hypothesis to model pharmaceuticals loads in wastewater is that they result from the following steps: pharmaceuticals sales or distributions, human consumption, metabolism and excretion. Pharmaceuticals sales for the urban catchment and distribution for the hospital have been collected at different space and timescales (respectively 1, 6 and 223 pharmacies and daily, weekly and monthly). Larger scales are more reliable for magnitude but the variability of the smaller ones is closer to the variability observed in the measurements. The quantities of pharmaceuticals sold or distributed range from 0.4 to 1 600 theoretical patients per day. Associating measured daily loads with sales or distributions, no linear correlation is found. A minute time step stochastic model is proposed and applied to both sites. It produces reliable and accurate results for both daily and hourly loads. However, results are difficult to interpret when only a few patients are consuming a pharmaceutical. Also, the model does not reproduce the inherent specificity of the hospital. In addition, the model is also able to predict the domestic wastewater flow of an urban catchment with great accuracy for both daily volumes and dynamics.

MOTS-CLÉS: Stochastic modelling, time-use data, metabolism, posology, pharmaceuticals dynamics

Laboratoire (s) de recherche : Laboratoire DEEP (Déchets Eaux Environnement Pollutions)

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Composition du jury :

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