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Manuscript Draft

Manuscript Number: STOTEN-D-16-01615R1

Title: Predicted and measured concentrations of pharmaceuticals in hospital effluents. Examination of the strengths and weaknesses of the two approaches through the analysis of a case study.

Article Type: Research Paper

Keywords: hospital effluents, measured concentrations, pharmaceuticals, predicted concentrations, sensitivity analysis, uncertainty analysis

Corresponding Author: Prof. Paola Verlicchi, Ph.D.

Corresponding Author's Institution: University of Ferrara

First Author: Paola Verlicchi, Ph.D.

Order of Authors: Paola Verlicchi, Ph.D.; Elena Zambello

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Ferrara, April 23rd 2016

Dear Prof. Damia Barceló
Editor in Chief
*Science of the Total Environment*,

referring to the revised paper:

**Predicted and measured concentrations of pharmaceuticals in hospital effluents. Examination of the strengths and weaknesses of the two approaches through the analysis of a case study.**

by **Paola Verlicchi and Elena Zambello**

in submitting it to Your international Journal, I would like to make the following remarks:

- the work described in this paper has not been previously published and it is not under consideration for publication elsewhere,

- the *Corresponding Author* is PAOLA VERLICCHI

- Her address is:

Department of Engineering
University of Ferrara
Via Saragat 1
I-44122 Ferrara
Italy
Tel +39.(0)532.974938
Fax +39.(0)532.974870
mail paola.verlicchi@unife.it

The revision accounted for all the suggestions and comments by the reviewers.

Unique features of the study

The paper examines strengths and weaknesses in predicting and measuring concentrations of pharmaceuticals in hospital effluent by the analysis of a case study related to 38 compounds. It discusses the main factors leading to uncertainties in the values obtained by the two approaches (an uncertainty analysis was carried out for measured concentrations and a sensitivity analysis for predicted ones). It provides suggestions to reduce uncertainties in direct measurements - sampling mode resulted the most critical factor - and in predicted concentrations – with regard to excretion factor, consumption data and wastewater volume.

This is the first study facing these issues for hospital effluent, for a wide spectrum of compounds belonging to different therapeutic classes. I think it could be useful in planning sampling protocols in experimental investigations on hospital wastewater as well as in selecting the values of parameters in case of models predicting concentrations in hospital effluent.

Finally, the request in the Author's guide (submitted manuscripts have to cover at least two spheres) is satisfied as the topic of this paper deals with anthroposphere (effluents from hospital care structures) and hydrosphere (water environment, occurrence of micropollutants and potential risks due to their presence).

Sincerely Yours

Paola Verlicchi

## Replies to reviewers

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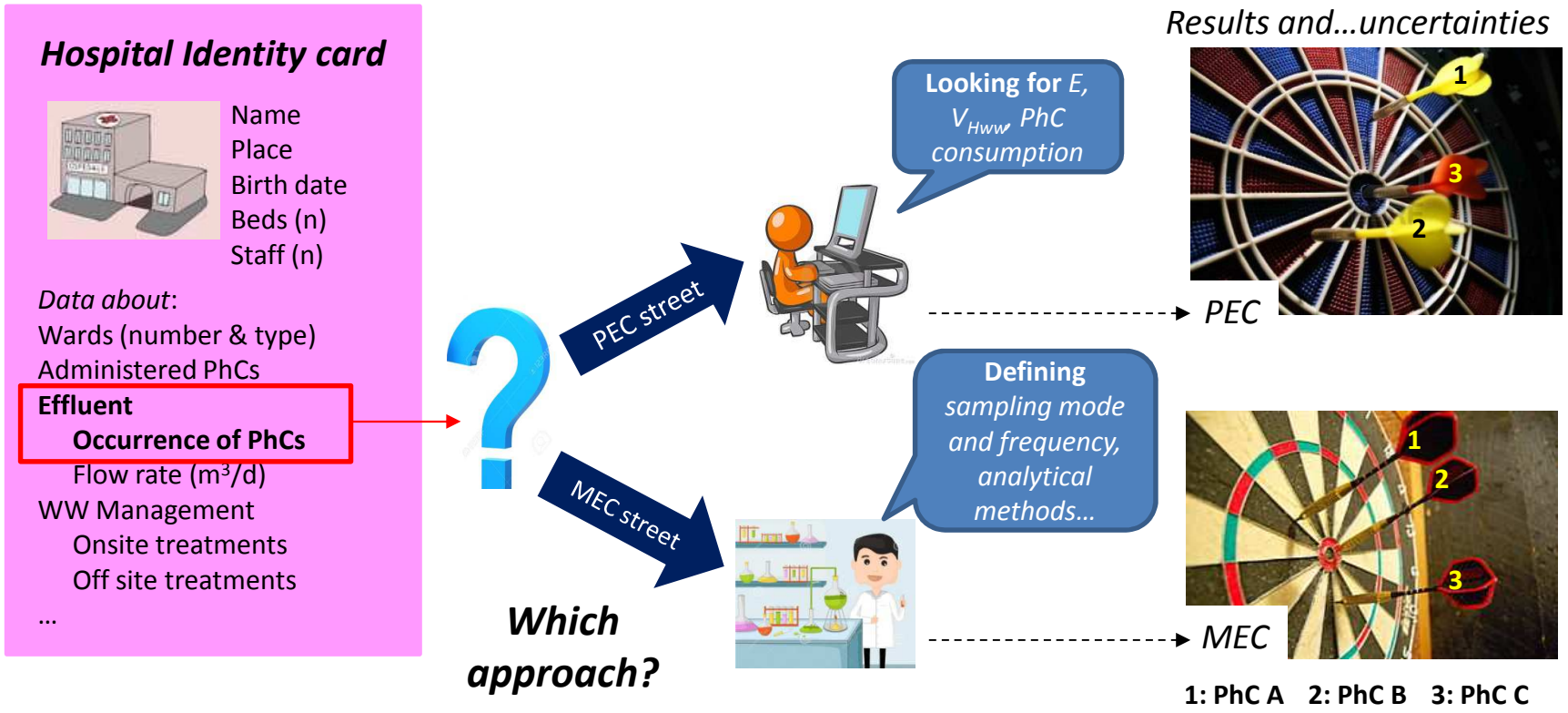

**Highlights**

Characterization of hospital effluent in terms of concentrations of 38 pharmaceuticals

Predicted and measured concentrations analyzed

A good agreement was found for 4 (summer) and 5 (winter) compounds

Sampling mode greatly influences measured concentrations

Excretion factor and wastewater flow rate mostly influence predicted concentrations.

# Predicted and measured concentrations of pharmaceuticals in hospital effluents. Examination of the strengths and weaknesses of the two approaches through the analysis of a case study.

Paola Verlicchi[1,2,*], Elena Zambello[1]

[1]Department of Engineering University of Ferrara, Via Saragat 1, I-44122 Ferrara Italy
[2]Terra&Acqua Technopole, University of Ferrara, Via Borsari, 46, I-44121 Ferrara, Italy
* Corresponding Author: paola.verlicchi@unife.it

**Abstract**

This study deals with the chemical characterization of hospital effluents in terms of the predicted and measured concentrations of 38 pharmaceuticals belonging to 11 different therapeutic classes. The paper outlines the strengths and weaknesses of the two approaches through an analysis of a case study referring to a large hospital. It highlights the observed (and expected) ranges of variability for the parameters of the adopted model, presents the results of an uncertainty analysis of direct measurements (due to sampling mode and frequency and chemical analysis) and a sensitivity analysis of predicted concentrations (based on the annual consumption of pharmaceuticals, their excretion rate and annual wastewater volume generated by the hospital). Measured concentrations refer to two sampling campaigns carried out in summer and winter in order to investigate seasonal variability of the selected compounds. Predicted concentrations are compared to measured ones in the three scenarios: summer, winter and the whole year.

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## 1 Introduction

Knowledge of which kind of pollutants occur in a hospital effluent and their concentration levels is necessary for scientists, practitioners, administrators and decision-makers in order to evaluate their potential impact on the environment. In the last fifteen years, investigations and studies have addressed different issues of this multi-faceted topic, among them the chemical characterization of hospital effluents in terms of detection of a *selection* of pharmaceuticals (PhCs) (Verlicchi et al., 2012; Santos et al., 2013), detergents and disinfectants (Boillot et al., 2008; McArdell et al., 2011), contrast media (Weissbrodt et al.,

2009; Mendoza et al., 2015); estimation of the contribution of a hospital to the influent PhC load of a municipal wastewater treatment plant (WWTP) (Heberer and Feldmann 2005; Thomas et al., 2007; Langford and Thomas, 2009; Ort et al., 2010a, Beier et al., 2011; Herrmann et al., 2015); analysis of the most appropriate hospital effluent management (Pauwels and Verstraete, 2006; Verlicchi et al., 2015, Schuster et al., 2008); removal efficacy of conventional and advanced treatments with regard to selected PhCs (Gautam et al., 2007; Pills report, 2012), ecotoxicity (Perrodin et al., 2015; Frédéric et al., 2014); environmental risk evaluation posed by PhC in hospital effluent (Escher et al., 2011; Mendoza et al., 2015); antibiotic resistance assessment (Kummerer and Henninger, 2003; Stalder et al.,2014); framework for proposing proper management and treatment (Emmanuel et al., 2005; Al Aukidy et al., 2014), prioritization of compounds to monitor (Jean t al., 2012, Helwig et al., 2013; Daouk et al., 2015).

The image emerging from available literature data is a snapshot whose resolution is evolving, due to the development of sophisticated analytical methods that are (and will be) improving new insights in the clouds of suspect compounds, the so called *known-unknowns,* as well as non-target compounds called *unknown-unknowns,* (Daughton, 2014).

Up to now, only a few studies have provided models for predicting PhC concentrations in hospital effluents and quite often they have referred to particular situations - a military hospital in Heberer and Feldmann (2005) and Mullot et al. (2010), a psychiatric hospital in Herrmann et al. (2015) and Escher et al. (2011), a regional general hospital in Escher et al. (2011), an intensive care unit in de Sousa et al. (2009) - or specific compounds, such as dypirone (metamizole) in Heberer and Feldmann (2005) or therapeutic classes, such as antibiotics in Kummerer and Henninger (2003) and de Sousa et al (2009).

As pollutant content in hospital effluents is strictly correlated to the activities occurring within the structure, its chemical characterization is site-specific. In an effort to fill the *identity card* of the effluent of a health care structure, two options arise - planning an experimental campaign leading to the so-called *measured environmental concentrations* (MECs) of the compounds of interest, and/or adopting a model based on the pharmaceuticals dispensed within the structure, resulting in the so-called *predicted environmental concentrations* (PECs).

Both approaches present strengths and weaknesses and advantages and drawbacks, not only with regard to the accuracy and reliability of the obtained concentrations, but also in terms of the difficulties in obtaining authorizations for water sampling, difficulties in sampling and analysis, the (long) timescale for obtaining “input” data (consumption data), specific competences for the adoption of the predictive models, and costs for chemical analysis.

This study presents and compares the results of the application of these two approaches to the effluent of a large hospital with regard to a selection of common PhCs and it discusses the strengths and weaknesses of MEC (already presented and discussed in Verlicchi et al., 2012) and PEC. It then compares their reliability and accuracy on the basis of an uncertainty (for MECs) and a sensitivity (for PECs) analysis. Finally, it

provides suggestions and guidelines to help in defining choices for both approaches in order to improve the accuracy of the obtained results whilst taking into consideration the nature of the PhCs and their observed or expected consumption pattern.

# 2 Materials and Methods

## *2.1 Investigated hospital*

The selected hospital is a large-size health care structure (900 beds, 2,000 personnel), including a wide spectrum of health services and more than 50 wards. It offers a comprehensive set of the medical services typical of a modern regional hospital such as general medicine, surgery, orthopedics, psychiatry, neurology, trauma, oncology, radiology, hemodialysis, obstetrics, gynecology and neonatology, intensive care units, infectious diseases, and casualty unit. The average annual flow rate (corresponding to water consumption) provided by the internal technical staff is 220,095 $m^3$/year corresponding to an average daily flow rate of 603 $m^3$/d, and a specific bed consumption equal to 670 L/ (bed d).

## *2.2 Selected compounds.*

The pharmaceuticals included in this study were based on these criteria: high prescription rates or volumes, availability of reliable analytical methods and occurrence and ubiquity in the water environment. There were 38 selected compounds belonging to 11 different therapeutic classes, as reported in Table 1.

**Table 1.**

## *2.3 Measured environmental concentrations (MECs)*

Measured environmental concentrations were those already presented and discussed in a previous study as well as sample preparation, standards and analytical methods (Verlicchi et al., 2012). Briefly, they refer to two experimental campaigns carried out in summer 2009 (end of August-beginning of September) and winter 2010 (March) at the raw effluent of a large hospital in the Po Valley (see section 2.1). 24-h time proportional water samples were taken in four dry days over each of the two periods. Samples were analyzed in one run, in order to reduce analysis uncertainty, according to Ort et al. (2010a).

### 2.3.1 Uncertainty analysis

The uncertainty associated with the measured PhC concentrations was calculated from the individual uncertainties in sampling mode and frequency($U_{sampling}$) and chemical analysis ($U_{analysis}$):

$$U_{total} = \sqrt{U_{Sampling}^2 + U_{Analysis}^2} \qquad \text{(eq. 1)}$$

105 The uncertainty in sampling mode and frequency was estimated according to the studies by Ort et al.
106 (2010b,c), considering the number of pulses in the hospital sewage network containing the PhCs of interest
107 (based on their provided figures of consumption within the hospital (Table 2), corresponding daily defined
108 dose, DDD, (see Table SD-3 in Supplementary Data), assuming that there are 5 toilet flushes per patient per
109 day) and the adopted sampling mode and frequency (time proportional sampling, $\Delta$t of 60 min, Verlicchi et
110 al., 2012).
111 The uncertainty of the chemical analysis was estimated from the relative recoveries (three spiked samples),
112 intra-day instrumental precision (six injections of standard at 50 ng/mL every 4 h) and other uncertainty
113 factors (i.e. 2%, according to Kovalova et al., 2012). The mixture of chemical standards was prepared just
114 before the analysis, so the error associated with the stability of the solution could be considered negligible.
115 Details of the uncertainty analysis are provided in the Supplementary data section.
116

117 ## *2.4 Predicted environmental concentrations (PEC)*

118 ### 2.4.1 Model adopted for the estimation of PEC

119 PECs were evaluated on the basis of pharmaceutical consumptions within the selected health care
120 structure during a whole year. Data were provided by the internal Pharmaceutical Service and refer to
121 2011, but due to similarity with the consumption of the two previous years, they could also be considered
122 for 2010 and 2009. This office manages the hospital drug warehouse and provides wards, medical units,
123 surgeries and laboratories with the (periodic) requested quantities and types of medicaments. All these
124 requests are recorded in a database in terms of specific code, brand name, medicament description, form
125 (tablets, suppositories, tubes, vials, bottles, sachets) and dispensed quantity (number of tablets, vials,
126 tubes, bottles, or sachets). Data were provided in an electronic format (an electronic sheet) as a list of the
127 38 selected active pharmaceutical ingredients administered during the whole year, the different drug
128 preparations containing them, the corresponding number of units (bottle, tablets, suppositories, infusions,
129 ampoules, sachets..) and the quantity (mg) of active ingredient in each unit of each drug preparation.
130 PECs were assessed assuming a constant administration along the whole year for each of them, by applying
131 eq. 2:
132

133 $$PEC_{HWW,i} = \frac{M_i E_i}{Q} \qquad \text{(eq. 2)}$$

134

135 where $M_i$ is the annual quantity of selected PhC *i* administered within the hospital, $E_i$ is the assumed
136 excretion factor of the unchanged compound *i* and *Q* is the annual volume of wastewater. By adopting this
137 equation, it is assumed that the annual amount is completely administered and excreted on-site and that
138 no waste is produced.

$M_i$ was evaluated as the sum of all amounts $m_i$ (g) of the same PhC (in terms of the active principle ingredient) *i* administered by the *n* drug preparations (tablets, vials for injection...) containing it, according to eq. 3:

$$M_i = \sum_{i=1}^{n} m_i \qquad \text{(eq. 3)}$$

$m_i$ was obtained from the units consumed for each drug preparation $U_i$ and the amount of active ingredient contained in each unit, $m_{Ui}$ . (Eq. 3)

$$m_i = U_i m_{U_i} \qquad \text{(eq. 4)}$$

Dispensed amounts considered for this study are reported in Table 2, together with the corresponding weight percentage with respect to the sum of the amounts referring to the selected 38 compounds.

**Table 2**

### 2.4.2 Excretion factor

Once a pharmaceutical has been administered, it is partially absorbed and partially excreted as an unchanged compound (parent compound), or as its metabolites, depending on the reactions involved in the metabolism process and the individual characteristics of the person who assumed it, (namely human health conditions, age, gender, diet, body weight, ethnicity), to the mode of use (pharmaceutical administered doses), mode of application (oral, rectal, dermal, parental), time of assumption, and interference with other administered drugs (Daughton and Ruhoy, 2009; Monteiro and Boxall, 2010).
The excretion factor corresponds to the sum of the fraction of the compound excreted in urine and faeces in unchanged active molecules and the fraction of parent molecules existing as a glucoronide conjugate (Jean et al., 2012; Besse et al., 2008). The metabolites are not considered, even though many of them still remain active.
The excretion factors of active pharmaceutical ingredients are sparse in literature and for most of them different values have been provided (Jjemba et al., 2006). Table SD-1 in Supplementary data reports the available values found in literature, with the corresponding reference. According to Lai et al.(2011), for each compound of interest, an excretion factor equal to the average value calculated as (max+min)/2 was assumed on the basis of the collected figures. Table 2 compiles the average values and the observed range of variability (based on literature data from Table SD-1).

### 2.4.3 Wastewater flow rate

The value of flow rate assumed for hospital effluents is evaluated on the basis of water consumption on an annual basis. It is often assumed equal to (potable) water consumption (Daouk et al., 2015; Escher et al., 2011), and sometimes to 80-85 % of this amount (Metcalf and Eddy, 1991, Wangsaatmaja, 1997). In this study the annual hospital flow rate was estimated on the basis of a water balance regarding the health care structure, that considers the following input and output flows:

- annual water consumption provided by the Hospital Medical Direction (equal to 220 095 $m^3$/year) ($Q_{cons}$);
- influent flow due to water bags used in surgery rooms ($Q_{bags}$). This was evaluated assuming that a volume of 10 L is used in each operation, 20 operations occur for 5 days a week and for 52 weeks per year: $Q_{bags}$ = 10 x20 x5x 52 = 52 000 L/year = 52 $m^3$/year;
- influent flow due to the effluent produced by different users within the hospital ($Q_{users}$): inpatients ( evaluated assuming that each bed is always occupied, thus 900 inpatients are always present in the structure and for each one the contribution is equal to 2 L/d), outpatients ( evaluated assuming that 900 people are present for 12 hours each day, and for each of them the contribution is 1 L/d ), visitors and staff (it was assumed that they amount to one third of the whole personnel - that is 2000/3 persons – for each day. Each contributes for 2 L/d): ($Q_{users}$ =900x2 x 365 + 900 x 1 x 365 + 2000/3 x2 x 365)/1000 = 1,472 $m^3$/year;
- water losses ($Q_{losses}$)due to water distribution system failure (aged system)= 30 % of the water consumed, equal to roughly 62 815 $m^3$/year. This value was chosen as recommended by the local Water Management Body and is equal to the percentage water loss value, found for (internal) water distribution and sewer system of similar characteristics (in terms of materials, age, maintenance frequency), in the same geographical area.

Hospital flow rate was assessed by eq. 5:

$$Q = Q_{cons} + Q_{bags} + Q_{users} - Q_{losses} \quad \text{(eq. 5)}$$

and amounts to Q = 220 095 + 52+1,472 -62,815 = 158 804 $m^3$/year corresponding to a daily flow rate equal to 435 $m^3$/d.

A refinement of the flow rate evaluation was carried out on the basis of the reported fluctuations in two medium size hospitals (Figures SD-1 and SD-2) for the months in which water sampling occurred. A refinement of the new values of PEC was also presented and discussed in section 4.3.1.

### 2.4.4 Sensitivity analysis

A sensitivity analysis has been developed in order to quantify the influence of the expected variation of each of the three parameters included in the adopted model (eq. 2) on the PEC value - excretion factor $E_i$, pharmaceutical consumption $M_i$, and wastewater flow rate $Q$. For each factor, a specific variability range was defined, according to published data or specific considerations. In particular:

- as for excretion rate $E_i$, the variability ranges were those reported in Table 2 for the selected compounds, defined on the basis of all the collected literature data compiled in Table SD-1;
- regarding the parameter $M_i$, that is the annual quantity of administered PhC *i*, variation was defined for each compound based on literature data and specific considerations referring to long-, medium- and short-term administration, types of disease, and seasonality.
- Finally, the variability range for the hospital flow rate *Q* was defined on the basis of two considerations. The first is related to the observed variation in water consumption over the year in two Italian medium size hospitals (400-450 beds), leading to a variation from -41 % to +71 % compared to the average monthly value (De Luigi, 2009; Galletti, 2011; Verlicchi et al., 2013, see Figures SD-1 and SD-2 in the Supplementary data for details). The daily flow rate is assumed to be constant each day of a month. The second consideration is that water consumption in hospitals may change from weekdays to the weekend, as some activities (diagnostic , laboratories) stop on Saturdays and Sundays and in some cases, (in)patients may go home for the weekend and have to come back at the beginning of the following week. We estimated that this variation could amount to +10 % (weekdays) and -10 % (weekends) compared to the average daily flow rate, based on Weissbrodt et al.(2009). As a result, the hospital flow rate may vary between -51 % and +81 %. We decided not to consider variation during a day, as PEC values are compared to MECs related to 24-h composite water samples.

We assume that each parameter may change at a time within its defined range, while the others assume the constant value reported in Table 2. By applying eq. 2, a new value of PEC is obtained for each compound *i* and varying the parameter *j* within its range. The corresponding percentage variation ΔPEC is evaluated according to eq. 6 (for the compound *i* and for the new values of the parameter *j*). In equation 6, $PEC_0$ corresponds to the value found in the first step of the analysis.

$$\Delta PEC|_{i,j} = \frac{PEC_{new,i,j} - PEC_{0,i}}{PEC_{0,i}} \times 100 \qquad i = \text{compound } 1, 2, \ldots 38,\ j = \text{parameter } E_i, Q, M \qquad \text{(eq. 6)}$$

# 3 Results

## *3.1 Measured environmental concentrations*

Table 3 reports the range of concentration and the average value for the selected compounds measured in the hospital effluent in the two experimental investigations (*n*= 4 in each period) and with reference to all the collected data (year, *n*= 8).

**Table 3**

An analysis of the occurrence of the selected compounds and a comparison of the detected concentrations in the two periods are reported and discussed in Verlicchi et al. (2012). It is worth noting here that tamoxifen was monitored in both periods but it was never found at a concentration higher than its limit of detection (lod). This could be due to the fact that cytostatics are compounds that are mostly administered to outpatients and could be largely excreted elsewhere, as remarked by Weissbrodt et al. (2009). In the two sampling periods, other compounds belonging to different therapeutic classes were found below their limit of detection: chloramphenicol, timolol, diazepam and paroxetine in summer and chlortetracycline, doxycycline and lisinopril in winter.

### *3.2 Analysis of dispensed amount of pharmaceuticals*

A first analysis of the data provided by the Internal Pharmaceutical Service regarding the selected 38 PhCs (= active pharmaceutical ingredients, API) is reported in Table 4 in terms of the number of dispensed products (that is number of different medicaments containing a specific active pharmaceutical ingredient, belonging to the same therapeutic class), administered amount of each therapeutic class and corresponding weight percentage to the total dispensed amount.

It emerges that, based on this selection, 96 different products were dispensed within the health care structure, of which 31 were antibiotics, and 19 analgesics and anti-inflammatories. The total administered amount was 171 kg on an annual basis, mostly due to analgesics and anti-inflammatories (roughly 114 kg, corresponding to 66.9 % in weight) and antibiotics (roughly 36 kg, 21 % in weight), followed by diuretics (6.79 kg/year, 4%) and receptor antagonists (5.3 kg, 3.10 %). Analgesics-anti-inflammatories and antibiotics contributed more than 88 % in weight compared to all of the selected compounds. As a PhC may be dispensed in different forms, the excretion factor may vary, as remarked in section 2.4.2 and in Table SD-1.

**Table 4**

A look inside each therapeutic class leads to the details of Table 2, reporting the dispensed amount for each active ingredient and its percentage weight with respect to the total dispensed amount. The ranking of the most administered compounds shows at the top: acetaminophen (59 %), ciprofloxacin (12 %), ibuprofen (4 %), furosemide (3.97 %) and metronidazole (3.53 %).

### *3.3 Comparison between predicted and measured concentrations*

The comparison is carried out by considering the ratio PEC/MEC for each compound in three different scenarios: the whole year, summer, and winter, depending on the assumed value for MEC - the average value evaluated on the basis of all the collected data ($PEC/MEC_{av}$), the mean of the collected data in

summer (PEC/$MEC_{av,\ summer}$) and in winter (PEC/$MEC_{av,\ winter}$). The aim is to analyse the seasonal variability expected for PhC consumption patterns in hospitals (Daouk et al., 2016; Verlicchi et al., 2014).

Of the accuracy evaluation criteria proposed in literature, we attempted to apply those defined by Ort et al. (2009) and already applied in Daouk et al. (2016) and Verlicchi et al., (2014). According to these criteria:

- if $0.5 \leq PEC/MEC \leq 2$, then PEC is acceptable,
- if $PEC/MEC < 0.5$, then PEC is unacceptably low;
- if $PEC/MEC > 2$, then PEC is unacceptably high.

It is important to remark that we do not consider *a priori* that MECs are more accurate and reliable than PECs, and the criteria were applied to evaluate how different the results of the two approaches are.

Figure 1 refers to the average measured concentrations (based on data collected for the whole year) and predicted ones - the ratio $PEC/MEC_{av}$ is reported in descending order, from the highest to the lowest.

It emerges that PEC is only acceptable for 7 PhCs, for 21 compounds PEC is unacceptably high and for the remaining 10 it is unacceptably low. The 7 compounds for which PEC and $MEC_{av}$ are quite similar are: diazepam, codeine, hydrochlorothiazide, enalapril, atenolol, clarithromycin and norfloxacin. Similar analyses are carried out for the two distinct experimental periods - Figure 2 for summertime and Figure 3 for winter.

**Figure 1**

Referring to the hot season, only four compounds exhibited comparable values of PEC and $MEC_{av,summer}$: atenolol, lorazepam, atorvastatin and fluoxetine; 30 compounds exhibited a ratio $PEC/MEC_{av,summer} > 2$ and the remaining 4 compounds a ratio < 0.5. In winter, PEC and $MEC_{av,winter}$ were similar for five compounds: sulfadiazine, codeine, hydrochlorothiazide, enalapril and atenolol; 22 PhCs had a $PEC > 2\ MEC_{av,winter}$ and 11 had a $PEC < 0.5\ MEC_{av,winter}$.

Among compounds exhibiting a ratio higher than 1 there are compounds that were found below their corresponding limit of detection (lod) in summer, winter or both seasons (see section 3.1). For them the ratio would be “infinity”. We decided to maintain these PhCs in this analysis (and graphs) to remark that the case PEC > 0 and MEC < lod occurred. In Figures 1-3, their corresponding rectangles are white and an arrow on the top remarks that the ratio is “out of scale”.

It is worth noting that predicted and measured concentrations were only comparable in the three scenarios (year, summer and winter) for atenolol; in the distinct periods, the group of compounds for which PEC and MEC are comparable varies, including compounds characterized by different consumption patterns, as will be discussed below.

The comparison concludes with Figure 4 reporting the observed range of measured concentrations (min-max) during the two experimental campaigns (red rectangles) and the predicted ones (triangles) evaluated according to eq. 2.

**Figure 2**.

**Figure 3**.

**Figure 4**.

It emerges that:

- for 22 out of 38 compounds PEC > $MEC_{max}$
- for 8 out of 38 compounds PEC < $MEC_{min}$
- for 8 out of 38 compounds $MEC_{min}$ < PEC < $MEC_{max}$

PEC is between the observed range of variability of MEC for APIs of different classes: codeine, clarithromycin, norfloxacin, enalapril, hydrochlorothiazide, lisinopril, atenolol, sotalol and lorazepam (for them, the MEC range rectangle is green in Fig. 4).

**Table 5**.

An in-depth analysis of Table 5 highlights that for 20 compounds PECs are *always* higher than twice the observed average MECs. This is the case for 9 antibiotics (chlortetracycline, doxycycline, chloramphenicol, metronidazole, erythromycin, trimethoprim, azithromycin, ciprofloxacin and sulfamethoxazole), 4 analgesics/anti-inflammatories (acetaminophen, ketoprofen, diclofenac, ibuprofen), 2 beta blockers (propranolol and metoprolol), 1 beta agonist (salbutamol), 1 receptor antagonist (ranitidine), 1 psychiatric drug (carbamazepine), 1 diuretic (furosemide) and 1 antineoplastic (tamoxifen).
It is quite difficult to explain these remarked differences between measured and predicted values and this recurring behavior for so many different kinds of active ingredients.
As reported in section 2.4.1, consumption data refer to the year 2011, whereas measured concentrations are related to water samples taken in Summer 2009 and Winter 2010. The discrepancies found in comparing PECs and MECs could also be due to the fact that the two reference periods are different. But as

the Internal Pharmaceutical Service stated that PhC consumption was quite similar in the years 2009, 2010 and 2011 and they did not find consistent variations for the selected compounds, it is reasonable to think that this contribution keeps quite small.

# 4 Discussion

## *4.1 Comparison with previous studies*

Mullot et al. (2010) compare the measured and predicted concentrations for ciprofloxacin in a military French hospital for 14 days and PECs were always lower than MEC. The assumed value of excretion factor was 0.6, quite similar to the value assumed in this study (0.58). The ratio PEC/MEC varied between 0 and 0.82 and less than 0.5 was found for 10 days.

Daouk et al. (2016) evaluated the predicted concentrations of 17 substances (8 molecules in common with the current study) in the effluent of a Swiss hospital using the same model employed in this study (eq. 1). They assumed the wastewater volume equal to water consumption on an annual basis, and excretion rates equal to the mean values in urine and feces as unchanged drugs, according to two databases (www.uptodate.com and www.compendium.ch), resulting in different values than those reported in Table 2. They found 0.5< PEC/MEC<2 for 5 out of 15 (namely, with respect to the common PhCs, ibuprofen, metronidazole, sulfamethoxazole and ciprofloxacin), PEC/MEC > 2 for 7 compounds (in particular acetaminophen, codeine and carbamazepine), PEC/MEC < 0.5 for the remaining 5 substances (diclofenac the only compound in common with this study).

## *4.2 Seasonal variability of consumptions*

It is well known that PhC occurrence in hospital effluents is subject to fluctuations depending on the nature of the compound (in terms of specific pharmacokinetic, transformation in metabolites within the human body and other transformation products once in the sewerage), the individual taking the drug (through excreted amounts mainly via urine, feces), the dispensed quantity, and way and time (determining the expected release in the sewerage). Observed ranges of concentration for the 38 compounds in the two periods are reported in Figure SD-4, showing that the two ranges only partially overlap for a few compounds. This is the case for codeine, ketoprofen, sulfamethoxazole, metoprolol, carbamazepine and ranitidine - 6 pharmaceuticals belonging to 4 different therapeutic classes!

Seasonal variability occurred for some compounds, as expected and remarked by recent studies (Diwan et al. 2013, Verlicchi et al., 2013; Herrmann et al. 2016) In particular, this occurred for the antibiotics ciprofloxacin, clarithromycin, norfloxacin, ofloxacin and trimethoprim. Their differences could be due to disease outbreaks occurring generally in winter/at the beginning of spring, leading to an increment in the inpatients in health care structures requiring administration of specific antibiotics (Daouk et al., 2016; De

Luigi, 2009; Verlicchi et al., 2008, see also Table SD-2). Measured concentrations could reflect this different consumption, while predicted ones may not (this is the case of clarithromycin, which is largely overestimated in summer and underestimated in winter, see Figures 2 and 3).

Coutu et al. (2013) found that fluctuations exist but are less evident with respect to those found in urban wastewater. In the case of urban wastewater, differences in seasonal cycles for antibiotics are related to the types of infections for which they are prescribed - antibiotics presenting a pronounced seasonality in consumption are generally used for airway infections (bronchitis and pneumonia) and for throat, nose and ear infections (pharyngitis, sinusitis and earache), whereas antibiotics used for non-seasonal diseases such as infections of the skin, bones, joints, and stomach present quite smooth discrepancies from the average annual consumption. On the contrary, in hospitals, antibiotics are administered to treat different diseases and infections than in the community and seasonal variations are quite evident for some specific compounds, including azithromycin, metronidazole, norfloxacin, ofloxacin and clindamycine. For these drugs, the ratio between the peak monthly consumption and the average monthly consumption ranges between 0.2 and 5, resulting in a percentage variation between -80 % and + 400 %). Ciprofloxacin is often one of the most frequently administered antibiotics and its occurrence dispersion in hospital effluents is extremely low.

Diclofenac and ibuprofen exhibited higher consumption levels in winter, resulting in higher concentrations (Figure SD-4) whereas their corresponding PECs were always overestimated.

The deviations from the evaluated average consumption should be less evident for beta blockers, diuretics, and anti-hypertensives, which are generally administered over long periods (sometimes for the whole life). Despite this consideration, sotalol and enalapril exhibited differences in observed concentrations in summer and winter (Figure SD-4) - sotalol was overestimated in summer and underestimated in winter, while enalapril was overestimated in summer (Figures 2 and 3).

Among the psychiatric drugs, differences in consumption were found for diazepam, lorazepam and fluoxetine but not for carbamazepine, probably due to the fact that it is prescribed not only as a psychiatric drug, but also as a pain killer (for instance in the case of trigeminal inflammation).

These considerations highlight that a prediction based on annual consumption may lead to a consistent overestimation for groups of compounds (analgesics/anti-inflammatories, antibiotics, and antineoplastics often administered to out-patients) that are often considered the most representative and critical for hospital effluents (Santos et al., 2013; Le Corre et al., 2012; Al Aukidy et al., 2014).

Measured concentrations can provide a snapshot of a defined period and, according to recent studies (Ort et al., 2010c, Kovalova et al., 2012, Weissbrodt et al., 2009), it is fundamental to plan and define the appropriate sampling mode and frequency leading to the collection and analysis of *representative* samples. This concept will be addressed in the uncertainty analysis.

## *4.3 Potential factors affecting predicted concentrations*

### 4.3.1 Water flow rate

The adopted model (eq. 2) includes the *annual wastewater volume* produced within the hospital, and it considers that in each day the same flow rate is released into the sewage system. As remarked above, predicted concentrations are quite often based on water consumption. In this study we carried out a water balance to the health care structure, including expected *inlet contributions* (water bags used in surgery rooms, human effluents produced by different users within the hospital) as well as *outlet streams* (losses in the distribution system). The water balance is carried out on an annual basis and, as a consequence, it assumes that every day water consumption and wastewater production follow the same corresponding flow rate patterns. This may lead to discrepancies with respect to the *real* wastewater flow rate generated during a specific day in a different period of the year or week (week days and weekend).

Water consumption profiles observed in medium size hospitals in a *type-day* are presented and discussed in Verlicchi et al. (2013). To better focus on this issue, an analysis of the observed variations of flow rates *vs.* month and *vs.* day hour are reported in Figures SD-1, SD-2, SD-3 in Supplementary data. Analysis of flow rate variation during the year will lead to the definition of an expected range of flow rate variability on an annual basis, for a general hospital, required by the sensitivity analysis.

It is worth noting daily variations of the flow rate - it is evident that (24-h) composite *flow* proportional water samples will be preferred, as the analysis will weigh both variation in occurrence and in flow and will be more representative of the real conditions (this will result in a lower uncertainty, as discussed by Lai et al. (2011)).

A refinement of PEC evaluation was carried out assuming a “revised” value for flow rate on the basis of Figures SD-1 and SD-2. With regard to the summer campaign (water samples were taken at the end of August-beginning of September 2009), the percentage variation of the flow rate with respect to the average one was assumed equal to +10 % accounting for the variations observed in the hospital of Figure SD-1 in August and September (whose summer fluctuations were considered more similar to those expected for the investigated hospital). Referring to the winter campaign (water samples were taken in March 2010) a percentage variation of -30 % with respect to the average value was assumed (an average of both trends). The graphs with the refined evaluation of PhC predicted and measured concentrations in the two seasons are reported in Supplementary Data (Figures SD-5 and SD-6). It emerges that in both seasons a good accuracy was found for 7 compounds (against 4 substances in summer and 5 substances in winter according to the previous comparison).

### 4.3.2 Pharmaceutical Consumption Data

We assumed that amounts of PhCs delivered to the different wards and medical units by the internal pharmacy corresponds to quantities *effectively* and *evenly* administered over the year. This hypothesis,

445 generally made (Besse et al., 2008; Carlsson et al., 2006) could not perfectly reflect the real consumption
446 pattern, especially for PhCs used in acute treatments, such as antibiotics that can lead to consistent
447 variations with regard to the average consumption on a yearly basis (Verlicchi et al., 2013; Daouk et al.,
448 2016).
449 As consumptions are site-specific, it is unadvisable to downscale consumption for the studied case from
450 national hospital consumption data or to use data referring to health care structures located elsewhere, or
451 even in another country (Schuster et al., 2008).
452 In general, it could be quite hard to obtain PhC consumption data. They are more often and easily available
453 in terms of *sales* data (Coutu et al., 2013; Verlicchi et al., 2014), generally on an annual and sometimes
454 regional basis (comprising different health care structures). Moreover it could be difficult to directly obtain
455 the consumption *amount* (kg/year) of the active ingredients of interest. Hospital internal services could
456 provide a list of extremely detailed information regarding each type of medication containing the active
457 ingredient of interest, the corresponding form, the content of the active ingredient in each item, the
458 number of items delivered to the different wards, and alternatively the unit doses (defined daily doses).
459 These data have to be carefully processed to convert the overall unit doses into grams of active ingredient,
460 while considering their dosages (Coutu et al., 2016; Jean et al., 2012).
461 It is worth noting that consumption data provided by hospital pharmacies may be affected by several biases
462 (Jean et al., 2012; Helwing et al., 2013). In fact they do not consider that:

463 • within the hospital, drugs may be administered to outpatients or leaving patients;
464 • drug packages may not be completely consumed (and only occasionally packages may be returned
465 to the hospital pharmacy in the case of discharged or deceased patients);
466 • in-patients may not assume the prescribed medicine (different patient compliance degrees may be
467 expected for the different therapeutic classes and in relation to the medicine form: tablet, pill,
468 etc.),
469 • during their stay in hospital, in-patients might continue their treatment and assume drugs
470 previously prescribed by general practitioners and which were not dispensed by the hospital (for
471 instance diuretics, lipid regulators, beta-blockers);
472 • in specialized hospitals (i.e. psychiatric facilities), a percentage of patients go home during the
473 weekend;
474 • activities within radiology departments are quite intense during weekdays and much “quieter” at
475 weekends;
476 • outpatient units and wards are in operation only during weekdays;
477 • where laundry is an internal service, it is in operation during the week and on Saturday morning,
478 not on Sundays. This could lead to higher concentrations of PhCs as laundry water consumption
479 was estimated to be around 33 % of the whole hospital consumption (Kern et al., 2013).

Moreover, any adopted PEC model does not consider a potential degradation/sorption of the released active compound into the sewage from the release point to the sampling one, nor transformation from parent compounds and/or viceversa, which will influence occurrence of the compound itself.

PEC models hardly focus on short-term fluctuations as they generally require *annual* consumption data. Antibiotic consumption patterns in hospitals may present fluctuations over the year, depending on the specific drug.

Monthly consumption data were only available for a few compounds. Table SD-2 reports the percentage variations for carbamazepine and antibiotics in two Italian medium-size hospitals compared to the corresponding average monthly dispensed amount (De Luigi, 2009; Verlicchi et al., 2008). Although the two structures are similar in size and type of ward and diagnosis activity, consumption patterns of the investigated groups of compounds are different - carbamazepine varied between -45 % and + 98 % in one hospital and -75 % and +128 % in the other. Antibiotics were found to vary between -20 % and +17 % in one hospital and -26 % and + 36 % in the other.

An analysis of consumption data is useful to search for the most administered drugs, which are compounds whose detection frequency is expected to be high (Daouk et al., 2016).

### 4.3.3 Excretion factor

This parameter is quite difficult to evaluate as it depends on many factors, as already remarked in Verlicchi et al. (2014). Table SD-1 in Supplementary Data reports the values proposed by different studies and they refer to excretion of the parent compound and not to its metabolites. Most of the selected PhCs show a wide variability range, since values may refer only to excretion by urine, or by feces or to both (Lienert et al., 2007b).

The excretion factor may vary from 0.1 to 1 and, in some cases, it could also be > 1 due to generation of the parent compound from its metabolites (Besse et al., 2008). This is the case of hydrochlorothiazide for which an excretion factor ranging from 0,24 to 1,20 is reported (see Tables 2 and SD-1).It is necessary to look for the most accurate excretion values that would allow more realistic predicted concentrations.

If the value is not available or not reliable enough for a specific compound, Lienert et al. (2007a) suggest adopting the “default values” reported in Table 6.

Other authors (among them Le Corre et al., 2012) suggest adopting a more conservative approach - they prefer to suppose that no metabolism occurs within the human body and that the total amount of a given substance is excreted unchanged. This assumption should partly counterbalance parameters that are not considered in drug consumption, including non-compliance and improper disposal of unused medications. On the contrary, any value of excretion factor assumed will lead to an uncertainty (overestimation or underestimation) that will be analyzed in the sensitivity analysis of the proposed model.

514 It may also happen that unused, left-over, unwanted and expired medications are directly poured down the
515 sink or flushed down toilets instead of returning them to the hospital pharmacy department and then to an
516 authorized supplier or reverse distributor. From the point of view of *good practices,* these practices are not
517 permitted and should be avoided, as they lead to a further release of persistent contaminants (as
518 unchanged compounds) into the water cycle via the sewage network and after, into the environment
519 (Mankes and Silver, 2013). From the point of view of uncertainties in predicted concentrations, these
520 practices represent an unquantifiable source of medicine in the hospital sewage network.
521
522 **Table 6.**
523

524 ### *4.4 Potential factors affecting measured concentrations*

525 As already discussed in Verlicchi et al. (2014), direct measurement of PhCs in hospital effluent may be
526 affected by the sampling mode and frequency, matrix effect, instrumental and human errors, and analytical
527 method limitations. Their influence will be quantified in the uncertainty analysis that follows.

528 ## 5 Uncertainty analysis

529 ### *5.1 Uncertainties in measured concentrations*

530 The results of the uncertainty analysis carried out for MEC of the group of PhCs are reported in Table 7 in
531 terms of $U_{total}$ ($U_{sampling}$, $U_{analysis}$) and in Supplementary Data in greater detail (Table SD-3). It emerges that
532 uncertainty due to the sampling mode and frequency mainly contributes to the total uncertainty for all the
533 selected compounds ($U_{sampling}$ ranges are between 25 % and over 100 %). $U_{analysis}$ varies between 4 and 16 %.
534 Compounds with a total uncertainty less than 40 % are 14: 1 beta-agonist (salbutamol**)**, 4 analgesics and
535 antinflammatories (all of those investigated with the exception of ibuprofen and indomethacine),1
536 antibiotic (ciprofloxacin), 2 beta-blockers (metoprolol and atenolol), 2 anti-hypertensives
537 (hydrochlorothiazide and enalapril), 1 diuretic (furosemide), 1 lipid regulator (atorvastatin), and 2
538 psychiatric drugs (lorazepam and diazepam).
539 The parameter that contributes the most to total uncertainty for MEC is sampling mode. If a flow
540 proportional one was adopted, sampling uncertainty would be at most 25-30 % for pharmaceuticals with
541 more than 50 pulses per day. For those with around only 10 pulses per day, the sampling uncertainty would
542 be around 75 % (See table SD-3 for the pulses for each compound).
543

544 ### *5.2 Sensitivity analyses of the predictive model*

545 Results of the sensitivity analysis are reported in Table 7, in terms of the minimum and maximum
546 percentage variation of the "new" PEC value with respect to $PEC_0$ (resulting by assuming the average

547 excretion factor for each compound, a constant consumption of each selected PhC during the year and a
548 constant wastewater volume through the year).
549 Regarding variations in PhC consumption, different assumptions were made:
550 - as for antibiotics, a percentage variation ranging from -36 % to + 30 % was assumed, based on
551 investigations of medium size hospitals, reported and discussed by Galletti (2011), De Luigi (2009)
552 and Verlicchi et al. (2008) (see Table SD-2);
553 - referring to carbamazepine, the consumption pattern presented for two medium size hospitals
554 (Verlicchi et al., 2008; De Luigi, 2009) was considered. It shows a consistent variation over the
555 months. In particular, the percentage variation with respect to the average value varied from -75 %
556 to +128 % (see Table SD-2 in Supplementary Data for further details);
557 - as for analgesics/antinflammatories, consumption profiles are not yet available. It is reasonable to
558 assume that levels do not vary gradually over the year as they are administered as pain killers,
559 antipyretics or antinflammatories. This assumption is supported by the evidence that in a hospital
560 patients require analgesics/antinflammatories every day for different (unhealthy) reasons, resulting
561 in modest monthly (also daily) variation of their consumption with respect to the average. In this
562 study it was assumed that the variability range is between -20% and + 20 %;
563 - A different approach was followed for all the remaining compounds belonging to the other classes.
564 As no consumption pattern is available for each of them and they are administered to patients for
565 specific diseases, it is quite difficult to suggest specific ranges). For these compounds, we prudently
566 assume an uncertainty of (50 %, +50), which is the same value proposed by Le Corre et al., (2012)
567 and considered “conservative”.
568
569 Based on data reported on Table 7, it emerges that *E* and wastewater volume greatly influence PEC values
570 for most compounds. Only for ofloxacin, glibenclamide, tamoxifen, salbutamol, atenolol and sotalol, does
571 the excretion factor not represent the most influencing factor, as expected uncertainties in administered
572 amount and wastewater flow rate are consistently higher. Unfortunately, consumption patterns are scarce
573 and available only for some antibiotics and carbamazepine. This underlines the need for further
574 investigations to improve knowledge of consumption trends in hospitals over the year and to better
575 evaluate the influence of PhC consumption on PEC uncertainty.
576 It is important to underline that water consumption increases during summer time (Fig. SD-1 and SD-2) and
577 a lower demand generally occurs in winter. In this season a higher consumption of antibiotics was found
578 (and expected), resulting in higher antibiotic concentrations in the hospital effluent with respect to the
579 predicted ones based on average PhC and average water consumption.
580 **Tab. 7**
581

In order to reduce uncertainties in PEC approach, great attention should be paid to the *most appropriate* adopted values of excretion factors, according to the evolution of new formulations as well as types of medicaments mostly used within the structure of interest, PhC consumption amounts (it would be recommended to use monthly consumption data), and wastewater flow rate.

## 6 Conclusions and perspectives

Knowledge of PhC concentrations in hospital effluents is essential for identifying proper management and treatment of the wastewater produced and also for carrying out an environmental risk assessment due to PhC residues in order to preserve the receiving environment.

This study outlines and compares the concentrations of 38 compounds belonging to 11 different therapeutic classes, resulting from direct measurements of the effluent of a large hospital and from a prediction model based on the documented annual consumptions within the structure.

It emerges that predicted concentrations are generally higher than measured ones, and for only a few compounds they are quite similar. It is not possible to establish which approach is more reliable and accurate for all the compounds since both options are affected by uncertainties, depending on the specific compounds and expected temporal variability. The uncertainty and sensitivity analysis carried out pointed out that PECs are generally mainly affected by the parameters of wastewater volume (from -45 to +104% for each compound) and excretion factor (different ranges, from -99 % to +99 %))and MECs by sampling mode (> 100 %).

Thus, measured or predicted concentration values should be carefully *handled* during subsequent analysis by scientists, practitioners and administrators.

It is quite difficult to suggest which strategy to adopt for a more accurate characterization of a hospital effluent. It is well known that a wide spectrum of compounds is used within a hospital. It would be quite hard to provide a snapshot including the occurrence of *all* the compounds. Both prediction or measurement would take too long, as well as being unsustainable efforts.

The starting step would be to define the prioritization criteria (Helwig et al., 2013; Daouk et al., 2015; Jean et al., 2012) for selecting a list of compounds for specific health-care structures. For instance, psychiatric and geriatric hospitals are likely to use a quite different range of drugs than general hospitals. For some of them, investigations have already highlighted the collection of greater concern (Helwig et al., 2013; Herrmann et al., 2015; Mendoza et al., 2015; Yuan et al., 2013).

Thus, a hybrid approach could be the best solution, as it combines the adoption of a model to (roughly) predict concentrations of selected PhCs based on their annual consumption, wastewater volume and average excretion factors and of specific sampling campaigns covering the (expected) most critical periods during the year. Moreover, the use of PECs should be used with some confidence for substances where no analytical method is available to experimentally determine concentrations or where the limit of

quantification is not low enough , as remarked by Ort et al. (2010b). This strategy should lead to a refinement of hospital effluent chemical characterization and would lead to a more accurate identity card of the health care structure, reflecting its singularity.

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# Predicted and measured concentrations of pharmaceuticals in hospital effluents. Examination of the strengths and weaknesses of the two approaches through the analysis of a case study.

Paola Verlicchi[1,2,*], Elena Zambello[1]

[1]Department of Engineering University of Ferrara, Via Saragat 1, I-44122 Ferrara Italy
[2]Terra&Acqua Technopole, University of Ferrara, Via Borsari, 46, I-44121 Ferrara, Italy
* Corresponding Author: paola.verlicchi@unife.it

**Abstract**

This study deals with the chemical characterization of hospital effluents in terms of the predicted and measured concentrations of 38 pharmaceuticals belonging to 11 different therapeutic classes. The paper outlines the strengths and weaknesses of the two approaches through an analysis of a case study referring to a large hospital. It highlights the observed (and expected) ranges of variability for the parameters of the adopted model, presents the results of an uncertainty analysis of direct measurements (due to sampling mode and frequency and chemical analysis) and a sensitivity analysis of predicted concentrations (based on the annual consumption of pharmaceuticals, their excretion rate and annual wastewater volume generated by the hospital). Measured concentrations refer to two sampling campaigns carried out in summer and winter in order to investigate seasonal variability of the selected compounds. Predicted concentrations are compared to measured ones in the three scenarios: summer, winter and the whole year.
It was found that predicted and measured concentrations are in agreement for a limited number of compounds (namely atenolol, atorvastatin and hydrochlorothiazide), and for most compounds the adoption of the model leads to a large overestimation in all three periods. Uncertainties in predictions are mainly due to the wastewater volume and excretion factor, whereas for measured concentrations, uncertainties are mainly due to sampling mode.

**Keywords**: hospital effluents, measured concentrations, pharmaceuticals, predicted concentrations, sensitivity analysis, uncertainty analysis

## 1 Introduction

Knowledge of which kind of pollutants occur in a hospital effluent and their concentration levels is necessary for scientists, practitioners, administrators and decision-makers in order to evaluate their potential impact on the environment. In the last fifteen years, investigations and studies have addressed different issues of this multi-faceted topic, among them the chemical characterization of hospital effluents in terms of detection of a *selection* of pharmaceuticals (PhCs) (Verlicchi et al., 2012; Santos et al., 2013), detergents and disinfectants (Boillot et al., 2008; McArdell et al., 2011), contrast media (Weissbrodt et al.,

2009; Mendoza et al., 2015); estimation of the contribution of a hospital to the influent PhC load of a municipal wastewater treatment plant (WWTP) (Heberer and Feldmann 2005; Thomas et al., 2007; Langford and Thomas, 2009; Ort et al., 2010a, Beier et al., 2011; Herrmann et al., 2015); analysis of the most appropriate hospital effluent management (Pauwels and Verstraete, 2006; Verlicchi et al., 2015, Schuster et al., 2008); removal efficacy of conventional and advanced treatments with regard to selected PhCs (Gautam et al., 2007; Pills report, 2012), ecotoxicity (Perrodin et al., 2015; Frédéric et al., 2014); environmental risk evaluation posed by PhC in hospital effluent (Escher et al., 2011; Mendoza et al., 2015); antibiotic resistance assessment (Kummerer and Henninger, 2003; Stalder et al.,2014); framework for proposing proper management and treatment (Emmanuel et al., 2005; Al Aukidy et al., 2014), prioritization of compounds to monitor (Jean t al., 2012, Helwig et al., 2013; Daouk et al., 2015).

The image emerging from available literature data is a snapshot whose resolution is evolving, due to the development of sophisticated analytical methods that are (and will be) improving new insights in the clouds of suspect compounds, the so called *known-unknowns,* as well as non-target compounds called *unknown-unknowns,* (Daughton, 2014).

Up to now, only a few studies have provided models for predicting PhC concentrations in hospital effluents and quite often they have referred to particular situations - a military hospital in Heberer and Feldmann (2005) and Mullot et al. (2010), a psychiatric hospital in Herrmann et al. (2015) and Escher et al. (2011), a regional general hospital in Escher et al. (2011), an intensive care unit in de Sousa et al. (2009) - or specific compounds, such as dypirone (metamizole) in Heberer and Feldmann (2005) or therapeutic classes, such as antibiotics in Kummerer and Henninger (2003) and de Sousa et al (2009).

As pollutant content in hospital effluents is strictly correlated to the activities occurring within the structure, its chemical characterization is site-specific. In an effort to fill the *identity card* of the effluent of a health care structure, two options arise - planning an experimental campaign leading to the so-called *measured environmental concentrations* (MECs) of the compounds of interest, and/or adopting a model based on the pharmaceuticals dispensed within the structure, resulting in the so-called *predicted environmental concentrations* (PECs).

Both approaches present strengths and weaknesses and advantages and drawbacks, not only with regard to the accuracy and reliability of the obtained concentrations, but also in terms of the difficulties in obtaining authorizations for water sampling, difficulties in sampling and analysis, the (long) timescale for obtaining “input” data (consumption data), specific competences for the adoption of the predictive models, and costs for chemical analysis.

This study presents and compares the results of the application of these two approaches to the effluent of a large hospital with regard to a selection of common PhCs and it discusses the strengths and weaknesses of MEC (already presented and discussed in Verlicchi et al., 2012) and PEC. It then compares their reliability and accuracy on the basis of an uncertainty (for MECs) and a sensitivity (for PECs) analysis. Finally, it

provides suggestions and guidelines to help in defining choices for both approaches in order to improve the accuracy of the obtained results whilst taking into consideration the nature of the PhCs and their observed or expected consumption pattern.

## 2 Materials and Methods

### *2.1 Investigated hospital*

The selected hospital is a large-size health care structure (900 beds, 2,000 personnel), including a wide spectrum of health services and more than 50 wards. It offers a comprehensive set of the medical services typical of a modern regional hospital such as general medicine, surgery, orthopedics, psychiatry, neurology, trauma, oncology, radiology, hemodialysis, obstetrics, gynecology and neonatology, intensive care units, infectious diseases, and casualty unit. The average annual flow rate (corresponding to water consumption) provided by the internal technical staff is 220,095 $m^3$/year corresponding to an average daily flow rate of 603 $m^3$/d, and a specific bed consumption equal to 670 L/ (bed d).

### *2.2 Selected compounds.*

The pharmaceuticals included in this study were based on these criteria: high prescription rates or volumes, availability of reliable analytical methods and occurrence and ubiquity in the water environment. There were 38 selected compounds belonging to 11 different therapeutic classes, as reported in Table 1.

**Table 1.**

### *2.3 Measured environmental concentrations (MECs)*

Measured environmental concentrations were those already presented and discussed in a previous study as well as sample preparation, standards and analytical methods (Verlicchi et al., 2012). Briefly, they refer to two experimental campaigns carried out in summer 2009 (end of August-beginning of September) and winter 2010 (March) at the raw effluent of a large hospital in the Po Valley (see section 2.1). 24-h time proportional water samples were taken in four dry days over each of the two periods. Samples were analyzed in one run, in order to reduce analysis uncertainty, according to Ort et al. (2010a).

#### 2.3.1 Uncertainty analysis

The uncertainty associated with the measured PhC concentrations was calculated from the individual uncertainties in sampling mode and frequency($U_{sampling}$) and chemical analysis ($U_{analysis}$):

$$U_{total} = \sqrt{U_{Sampling}^2 + U_{Analysis}^2} \qquad \text{(eq. 1)}$$

The uncertainty in sampling mode and frequency was estimated according to the studies by Ort et al. (2010b,c), considering the number of pulses in the hospital sewage network containing the PhCs of interest (based on their provided figures of consumption within the hospital (Table 2), corresponding daily defined dose, DDD, (see Table SD-3 in Supplementary Data), assuming that there are 5 toilet flushes per patient per day) and the adopted sampling mode and frequency (time proportional sampling, $\Delta$t of 60 min, Verlicchi et al., 2012).

The uncertainty of the chemical analysis was estimated from the relative recoveries (three spiked samples), intra-day instrumental precision (six injections of standard at 50 ng/mL every 4 h) and other uncertainty factors (i.e. 2%, according to Kovalova et al., 2012). The mixture of chemical standards was prepared just before the analysis, so the error associated with the stability of the solution could be considered negligible. Details of the uncertainty analysis are provided in the Supplementary data section.

## *2.4 Predicted environmental concentrations (PEC)*

### 2.4.1 Model adopted for the estimation of PEC

PECs were evaluated on the basis of pharmaceutical consumptions within the selected health care structure during a whole year. Data were provided by the internal Pharmaceutical Service and refer to 2011, but due to similarity with the consumption of the two previous years, they could also be considered for 2010 and 2009. This office manages the hospital drug warehouse and provides wards, medical units, surgeries and laboratories with the (periodic) requested quantities and types of medicaments. All these requests are recorded in a database in terms of specific code, brand name, medicament description, form (tablets, suppositories, tubes, vials, bottles, sachets) and dispensed quantity (number of tablets, vials, tubes, bottles, or sachets). Data were provided in an electronic format (an electronic sheet) as a list of the 38 selected active pharmaceutical ingredients administered during the whole year, the different drug preparations containing them, the corresponding number of units (bottle, tablets, suppositories, infusions, ampoules, sachets..) and the quantity (mg) of active ingredient in each unit of each drug preparation. PECs were assessed assuming a constant administration along the whole year for each of them, by applying eq. 2:

$$PEC_{HWW,i} = \frac{M_i E_i}{Q} \qquad \text{(eq. 2)}$$

where $M_i$ is the annual quantity of selected PhC *i* administered within the hospital, $E_i$ is the assumed excretion factor of the unchanged compound *i* and *Q* is the annual volume of wastewater. By adopting this equation, it is assumed that the annual amount is completely administered and excreted on-site and that no waste is produced.

$M_i$ was evaluated as the sum of all amounts $m_i$ (g) of the same PhC (in terms of the active principle ingredient) *i* administered by the *n* drug preparations (tablets, vials for injection...) containing it, according to eq. 3:

$$M_i = \sum_{i=1}^{n} m_i \qquad \text{(eq. 3)}$$

$m_i$ was obtained from the units consumed for each drug preparation $U_i$ and the amount of active ingredient contained in each unit, $m_{Ui}$ . (Eq. 3)

$$m_i = U_i m_{U_i} \qquad \text{(eq. 4)}$$

Dispensed amounts considered for this study are reported in Table 2, together with the corresponding weight percentage with respect to the sum of the amounts referring to the selected 38 compounds.

**Table 2**

### 2.4.2 Excretion factor

Once a pharmaceutical has been administered, it is partially absorbed and partially excreted as an unchanged compound (parent compound), or as its metabolites, depending on the reactions involved in the metabolism process and the individual characteristics of the person who assumed it, (namely human health conditions, age, gender, diet, body weight, ethnicity), to the mode of use (pharmaceutical administered doses), mode of application (oral, rectal, dermal, parental), time of assumption, and interference with other administered drugs (Daughton and Ruhoy, 2009; Monteiro and Boxall, 2010).
The excretion factor corresponds to the sum of the fraction of the compound excreted in urine and faeces in unchanged active molecules and the fraction of parent molecules existing as a glucoronide conjugate (Jean et al., 2012; Besse et al., 2008). The metabolites are not considered, even though many of them still remain active.
The excretion factors of active pharmaceutical ingredients are sparse in literature and for most of them different values have been provided (Jjemba et al., 2006). Table SD-1 in Supplementary data reports the available values found in literature, with the corresponding reference. According to Lai et al.(2011), for each compound of interest, an excretion factor equal to the average value calculated as (max+min)/2 was assumed on the basis of the collected figures. Table 2 compiles the average values and the observed range of variability (based on literature data from Table SD-1).

### 2.4.3 Wastewater flow rate

The value of flow rate assumed for hospital effluents is evaluated on the basis of water consumption on an annual basis. It is often assumed equal to (potable) water consumption (Daouk et al., 2015; Escher et al., 2011), and sometimes to 80-85 % of this amount (Metcalf and Eddy, 1991, Wangsaatmaja, 1997). In this study the annual hospital flow rate was estimated on the basis of a water balance regarding the health care structure, that considers the following input and output flows:

- annual water consumption provided by the Hospital Medical Direction (equal to 220 095 $m^3$/year) ($Q_{cons}$);
- influent flow due to water bags used in surgery rooms ($Q_{bags}$). This was evaluated assuming that a volume of 10 L is used in each operation, 20 operations occur for 5 days a week and for 52 weeks per year: $Q_{bags}$ = 10 x20 x5x 52 = 52 000 L/year = 52 $m^3$/year;
- influent flow due to the effluent produced by different users within the hospital ($Q_{users}$): inpatients ( evaluated assuming that each bed is always occupied, thus 900 inpatients are always present in the structure and for each one the contribution is equal to 2 L/d), outpatients ( evaluated assuming that 900 people are present for 12 hours each day, and for each of them the contribution is 1 L/d ), visitors and staff (it was assumed that they amount to one third of the whole personnel - that is 2000/3 persons – for each day. Each contributes for 2 L/d): ($Q_{users}$ =900x2 x 365 + 900 x 1 x 365 + 2000/3 x2 x 365)/1000 = 1,472 $m^3$/year;
- water losses ($Q_{losses}$)due to water distribution system failure (aged system)= 30 % of the water consumed, equal to roughly 62 815 $m^3$/year. This value was chosen as recommended by the local Water Management Body and is equal to the percentage water loss value, found for (internal) water distribution and sewer system of similar characteristics (in terms of materials, age, maintenance frequency), in the same geographical area.

Hospital flow rate was assessed by eq. 5:

$$Q = Q_{cons} + Q_{bags} + Q_{users} - Q_{losses} \quad \text{(eq. 5)}$$

and amounts to Q = 220 095 + 52+1,472 -62,815 = 158 804 $m^3$/year corresponding to a daily flow rate equal to 435 $m^3$/d.

A refinement of the flow rate evaluation was carried out on the basis of the reported fluctuations in two medium size hospitals (Figures SD-1 and SD-2) for the months in which water sampling occurred. A refinement of the new values of PEC was also presented and discussed in section 4.3.1.

### 2.4.4 Sensitivity analysis

A sensitivity analysis has been developed in order to quantify the influence of the expected variation of each of the three parameters included in the adopted model (eq. 2) on the PEC value - excretion factor $E_i$, pharmaceutical consumption $M_i$, and wastewater flow rate $Q$. For each factor, a specific variability range was defined, according to published data or specific considerations. In particular:

- as for excretion rate $E_i$, the variability ranges were those reported in Table 2 for the selected compounds, defined on the basis of all the collected literature data compiled in Table SD-1;
- regarding the parameter $M_i$, that is the annual quantity of administered PhC *i*, variation was defined for each compound based on literature data and specific considerations referring to long-, medium- and short-term administration, types of disease, and seasonality.
- Finally, the variability range for the hospital flow rate *Q* was defined on the basis of two considerations. The first is related to the observed variation in water consumption over the year in two Italian medium size hospitals (400-450 beds), leading to a variation from -41 % to +71 % compared to the average monthly value (De Luigi, 2009; Galletti, 2011; Verlicchi et al., 2013, see Figures SD-1 and SD-2 in the Supplementary data for details). The daily flow rate is assumed to be constant each day of a month. The second consideration is that water consumption in hospitals may change from weekdays to the weekend, as some activities (diagnostic , laboratories) stop on Saturdays and Sundays and in some cases, (in)patients may go home for the weekend and have to come back at the beginning of the following week. We estimated that this variation could amount to +10 % (weekdays) and -10 % (weekends) compared to the average daily flow rate, based on Weissbrodt et al.(2009). As a result, the hospital flow rate may vary between -51 % and +81 %. We decided not to consider variation during a day, as PEC values are compared to MECs related to 24-h composite water samples.

We assume that each parameter may change at a time within its defined range, while the others assume the constant value reported in Table 2. By applying eq. 2, a new value of PEC is obtained for each compound *i* and varying the parameter *j* within its range. The corresponding percentage variation $\Delta$PEC is evaluated according to eq. 6 (for the compound *i* and for the new values of the parameter *j*). In equation 6, $PEC_0$ corresponds to the value found in the first step of the analysis.

$$\Delta PEC|_{i,j} = \frac{PEC_{new,i,j} - PEC_{0,i}}{PEC_{0,i}} \times 100 \qquad i = \text{compound } 1, 2, \ldots 38, j = \text{parameter } E_i, Q, M) \qquad \text{(eq. 6)}$$

# 3 Results

## *3.1 Measured environmental concentrations*

Table 3 reports the range of concentration and the average value for the selected compounds measured in the hospital effluent in the two experimental investigations (*n*= 4 in each period) and with reference to all the collected data (year, *n*= 8).

**Table 3**

An analysis of the occurrence of the selected compounds and a comparison of the detected concentrations in the two periods are reported and discussed in Verlicchi et al. (2012). It is worth noting here that tamoxifen was monitored in both periods but it was never found at a concentration higher than its limit of detection (lod). This could be due to the fact that cytostatics are compounds that are mostly administered to outpatients and could be largely excreted elsewhere, as remarked by Weissbrodt et al. (2009). In the two sampling periods, other compounds belonging to different therapeutic classes were found below their limit of detection: chloramphenicol, timolol, diazepam and paroxetine in summer and chlortetracycline, doxycycline and lisinopril in winter.

### *3.2 Analysis of dispensed amount of pharmaceuticals*

A first analysis of the data provided by the Internal Pharmaceutical Service regarding the selected 38 PhCs (= active pharmaceutical ingredients, API) is reported in Table 4 in terms of the number of dispensed products (that is number of different medicaments containing a specific active pharmaceutical ingredient, belonging to the same therapeutic class), administered amount of each therapeutic class and corresponding weight percentage to the total dispensed amount.

It emerges that, based on this selection, 96 different products were dispensed within the health care structure, of which 31 were antibiotics, and 19 analgesics and anti-inflammatories. The total administered amount was 171 kg on an annual basis, mostly due to analgesics and anti-inflammatories (roughly 114 kg, corresponding to 66.9 % in weight) and antibiotics (roughly 36 kg, 21 % in weight), followed by diuretics (6.79 kg/year, 4%) and receptor antagonists (5.3 kg, 3.10 %). Analgesics-anti-inflammatories and antibiotics contributed more than 88 % in weight compared to all of the selected compounds. As a PhC may be dispensed in different forms, the excretion factor may vary, as remarked in section 2.4.2 and in Table SD-1.

**Table 4**

A look inside each therapeutic class leads to the details of Table 2, reporting the dispensed amount for each active ingredient and its percentage weight with respect to the total dispensed amount. The ranking of the most administered compounds shows at the top: acetaminophen (59 %), ciprofloxacin (12 %), ibuprofen (4 %), furosemide (3.97 %) and metronidazole (3.53 %).

### *3.3 Comparison between predicted and measured concentrations*

The comparison is carried out by considering the ratio PEC/MEC for each compound in three different scenarios: the whole year, summer, and winter, depending on the assumed value for MEC - the average value evaluated on the basis of all the collected data ($PEC/MEC_{av}$), the mean of the collected data in

summer ($PEC/MEC_{av,\ summer}$) and in winter ($PEC/MEC_{av,\ winter}$). The aim is to analyse the seasonal variability expected for PhC consumption patterns in hospitals (Daouk et al., 2016; Verlicchi et al., 2014).

Of the accuracy evaluation criteria proposed in literature, we attempted to apply those defined by Ort et al. (2009) and already applied in Daouk et al. (2016) and Verlicchi et al., (2014). According to these criteria:

- if $0.5 \leq PEC/MEC \leq 2$, then PEC is acceptable,
- if $PEC/MEC < 0.5$, then PEC is unacceptably low;
- if $PEC/MEC > 2$, then PEC is unacceptably high.

It is important to remark that we do not consider *a priori* that MECs are more accurate and reliable than PECs, and the criteria were applied to evaluate how different the results of the two approaches are.

Figure 1 refers to the average measured concentrations (based on data collected for the whole year) and predicted ones - the ratio $PEC/MEC_{av}$ is reported in descending order, from the highest to the lowest.

It emerges that PEC is only acceptable for 7 PhCs, for 21 compounds PEC is unacceptably high and for the remaining 10 it is unacceptably low. The 7 compounds for which PEC and $MEC_{av}$ are quite similar are: diazepam, codeine, hydrochlorothiazide, enalapril, atenolol, clarithromycin and norfloxacin. Similar analyses are carried out for the two distinct experimental periods - Figure 2 for summertime and Figure 3 for winter.

**Figure 1**

Referring to the hot season, only four compounds exhibited comparable values of PEC and $MEC_{av,summer}$: atenolol, lorazepam, atorvastatin and fluoxetine; 30 compounds exhibited a ratio $PEC/MEC_{av,summer} > 2$ and the remaining 4 compounds a ratio < 0.5. In winter, PEC and $MEC_{av,winter}$ were similar for five compounds: sulfadiazine, codeine, hydrochlorothiazide, enalapril and atenolol; 22 PhCs had a $PEC > 2\ MEC_{av,winter}$ and 11 had a $PEC < 0.5\ MEC_{av,winter}$.

Among compounds exhibiting a ratio higher than 1 there are compounds that were found below their corresponding limit of detection (lod) in summer, winter or both seasons (see section 3.1). For them the ratio would be “infinity”. We decided to maintain these PhCs in this analysis (and graphs) to remark that the case PEC > 0 and MEC < lod occurred. In Figures 1-3, their corresponding rectangles are white and an arrow on the top remarks that the ratio is “out of scale”.

It is worth noting that predicted and measured concentrations were only comparable in the three scenarios (year, summer and winter) for atenolol; in the distinct periods, the group of compounds for which PEC and MEC are comparable varies, including compounds characterized by different consumption patterns, as will be discussed below.

The comparison concludes with Figure 4 reporting the observed range of measured concentrations (min-max) during the two experimental campaigns (red rectangles) and the predicted ones (triangles) evaluated according to eq. 2.

**Figure 2**.

**Figure 3**.

**Figure 4**.

It emerges that:

- for 22 out of 38 compounds PEC > $MEC_{max}$
- for 8 out of 38 compounds PEC < $MEC_{min}$
- for 8 out of 38 compounds $MEC_{min}$ < PEC < $MEC_{max}$

PEC is between the observed range of variability of MEC for APIs of different classes: codeine, clarithromycin, norfloxacin, enalapril, hydrochlorothiazide, lisinopril, atenolol, sotalol and lorazepam (for them, the MEC range rectangle is green in Fig. 4).

**Table 5**.

An in-depth analysis of Table 5 highlights that for 20 compounds PECs are *always* higher than twice the observed average MECs. This is the case for 9 antibiotics (chlortetracycline, doxycycline, chloramphenicol, metronidazole, erythromycin, trimethoprim, azithromycin, ciprofloxacin and sulfamethoxazole), 4 analgesics/anti-inflammatories (acetaminophen, ketoprofen, diclofenac, ibuprofen), 2 beta blockers (propranolol and metoprolol), 1 beta agonist (salbutamol), 1 receptor antagonist (ranitidine), 1 psychiatric drug (carbamazepine), 1 diuretic (furosemide) and 1 antineoplastic (tamoxifen).
It is quite difficult to explain these remarked differences between measured and predicted values and this recurring behavior for so many different kinds of active ingredients.
As reported in section 2.4.1, consumption data refer to the year 2011, whereas measured concentrations are related to water samples taken in Summer 2009 and Winter 2010. The discrepancies found in comparing PECs and MECs could also be due to the fact that the two reference periods are different. But as

the Internal Pharmaceutical Service stated that PhC consumption was quite similar in the years 2009, 2010 and 2011 and they did not find consistent variations for the selected compounds, it is reasonable to think that this contribution keeps quite small.

# 4 Discussion

## *4.1 Comparison with previous studies*

Mullot et al. (2010) compare the measured and predicted concentrations for ciprofloxacin in a military French hospital for 14 days and PECs were always lower than MEC. The assumed value of excretion factor was 0.6, quite similar to the value assumed in this study (0.58). The ratio PEC/MEC varied between 0 and 0.82 and less than 0.5 was found for 10 days.

Daouk et al. (2016) evaluated the predicted concentrations of 17 substances (8 molecules in common with the current study) in the effluent of a Swiss hospital using the same model employed in this study (eq. 1). They assumed the wastewater volume equal to water consumption on an annual basis, and excretion rates equal to the mean values in urine and feces as unchanged drugs, according to two databases (www.uptodate.com and www.compendium.ch), resulting in different values than those reported in Table 2. They found 0.5< PEC/MEC<2 for 5 out of 15 (namely, with respect to the common PhCs, ibuprofen, metronidazole, sulfamethoxazole and ciprofloxacin), PEC/MEC > 2 for 7 compounds (in particular acetaminophen, codeine and carbamazepine), PEC/MEC < 0.5 for the remaining 5 substances (diclofenac the only compound in common with this study).

## *4.2 Seasonal variability of consumptions*

It is well known that PhC occurrence in hospital effluents is subject to fluctuations depending on the nature of the compound (in terms of specific pharmacokinetic, transformation in metabolites within the human body and other transformation products once in the sewerage), the individual taking the drug (through excreted amounts mainly via urine, feces), the dispensed quantity, and way and time (determining the expected release in the sewerage). Observed ranges of concentration for the 38 compounds in the two periods are reported in Figure SD-4, showing that the two ranges only partially overlap for a few compounds. This is the case for codeine, ketoprofen, sulfamethoxazole, metoprolol, carbamazepine and ranitidine - 6 pharmaceuticals belonging to 4 different therapeutic classes!

Seasonal variability occurred for some compounds, as expected and remarked by recent studies (Diwan et al. 2013, Verlicchi et al., 2013; Herrmann et al. 2016) In particular, this occurred for the antibiotics ciprofloxacin, clarithromycin, norfloxacin, ofloxacin and trimethoprim. Their differences could be due to disease outbreaks occurring generally in winter/at the beginning of spring, leading to an increment in the inpatients in health care structures requiring administration of specific antibiotics (Daouk et al., 2016; De

Luigi, 2009; Verlicchi et al., 2008, see also Table SD-2). Measured concentrations could reflect this different consumption, while predicted ones may not (this is the case of clarithromycin, which is largely overestimated in summer and underestimated in winter, see Figures 2 and 3).

Coutu et al. (2013) found that fluctuations exist but are less evident with respect to those found in urban wastewater. In the case of urban wastewater, differences in seasonal cycles for antibiotics are related to the types of infections for which they are prescribed - antibiotics presenting a pronounced seasonality in consumption are generally used for airway infections (bronchitis and pneumonia) and for throat, nose and ear infections (pharyngitis, sinusitis and earache), whereas antibiotics used for non-seasonal diseases such as infections of the skin, bones, joints, and stomach present quite smooth discrepancies from the average annual consumption. On the contrary, in hospitals, antibiotics are administered to treat different diseases and infections than in the community and seasonal variations are quite evident for some specific compounds, including azithromycin, metronidazole, norfloxacin, ofloxacin and clindamycine. For these drugs, the ratio between the peak monthly consumption and the average monthly consumption ranges between 0.2 and 5, resulting in a percentage variation between -80 % and + 400 %). Ciprofloxacin is often one of the most frequently administered antibiotics and its occurrence dispersion in hospital effluents is extremely low.

Diclofenac and ibuprofen exhibited higher consumption levels in winter, resulting in higher concentrations (Figure SD-4) whereas their corresponding PECs were always overestimated.

The deviations from the evaluated average consumption should be less evident for beta blockers, diuretics, and anti-hypertensives, which are generally administered over long periods (sometimes for the whole life). Despite this consideration, sotalol and enalapril exhibited differences in observed concentrations in summer and winter (Figure SD-4) - sotalol was overestimated in summer and underestimated in winter, while enalapril was overestimated in summer (Figures 2 and 3).

Among the psychiatric drugs, differences in consumption were found for diazepam, lorazepam and fluoxetine but not for carbamazepine, probably due to the fact that it is prescribed not only as a psychiatric drug, but also as a pain killer (for instance in the case of trigeminal inflammation).

These considerations highlight that a prediction based on annual consumption may lead to a consistent overestimation for groups of compounds (analgesics/anti-inflammatories, antibiotics, and antineoplastics often administered to out-patients) that are often considered the most representative and critical for hospital effluents (Santos et al., 2013; Le Corre et al., 2012; Al Aukidy et al., 2014).

Measured concentrations can provide a snapshot of a defined period and, according to recent studies (Ort et al., 2010c, Kovalova et al., 2012, Weissbrodt et al., 2009), it is fundamental to plan and define the appropriate sampling mode and frequency leading to the collection and analysis of *representative* samples. This concept will be addressed in the uncertainty analysis.

### *4.3 Potential factors affecting predicted concentrations*

#### 4.3.1 Water flow rate

The adopted model (eq. 2) includes the *annual wastewater volume* produced within the hospital, and it considers that in each day the same flow rate is released into the sewage system. As remarked above, predicted concentrations are quite often based on water consumption. In this study we carried out a water balance to the health care structure, including expected *inlet contributions* (water bags used in surgery rooms, human effluents produced by different users within the hospital) as well as *outlet streams* (losses in the distribution system). The water balance is carried out on an annual basis and, as a consequence, it assumes that every day water consumption and wastewater production follow the same corresponding flow rate patterns. This may lead to discrepancies with respect to the *real* wastewater flow rate generated during a specific day in a different period of the year or week (week days and weekend).

Water consumption profiles observed in medium size hospitals in a *type-day* are presented and discussed in Verlicchi et al. (2013). To better focus on this issue, an analysis of the observed variations of flow rates *vs.* month and *vs.* day hour are reported in Figures SD-1, SD-2, SD-3 in Supplementary data. Analysis of flow rate variation during the year will lead to the definition of an expected range of flow rate variability on an annual basis, for a general hospital, required by the sensitivity analysis.

It is worth noting daily variations of the flow rate - it is evident that (24-h) composite *flow* proportional water samples will be preferred, as the analysis will weigh both variation in occurrence and in flow and will be more representative of the real conditions (this will result in a lower uncertainty, as discussed by Lai et al. (2011)).

A refinement of PEC evaluation was carried out assuming a "revised" value for flow rate on the basis of Figures SD-1 and SD-2. With regard to the summer campaign (water samples were taken at the end of August-beginning of September 2009), the percentage variation of the flow rate with respect to the average one was assumed equal to +10 % accounting for the variations observed in the hospital of Figure SD-1 in August and September (whose summer fluctuations were considered more similar to those expected for the investigated hospital). Referring to the winter campaign (water samples were taken in March 2010) a percentage variation of -30 % with respect to the average value was assumed (an average of both trends). The graphs with the refined evaluation of PhC predicted and measured concentrations in the two seasons are reported in Supplementary Data (Figures SD-5 and SD-6). It emerges that in both seasons a good accuracy was found for 7 compounds (against 4 substances in summer and 5 substances in winter according to the previous comparison).

#### 4.3.2 Pharmaceutical Consumption Data

We assumed that amounts of PhCs delivered to the different wards and medical units by the internal pharmacy corresponds to quantities *effectively* and *evenly* administered over the year. This hypothesis,

generally made (Besse et al., 2008; Carlsson et al., 2006) could not perfectly reflect the real consumption pattern, especially for PhCs used in acute treatments, such as antibiotics that can lead to consistent variations with regard to the average consumption on a yearly basis (Verlicchi et al., 2013; Daouk et al., 2016).

As consumptions are site-specific, it is unadvisable to downscale consumption for the studied case from national hospital consumption data or to use data referring to health care structures located elsewhere, or even in another country (Schuster et al., 2008).

In general, it could be quite hard to obtain PhC consumption data. They are more often and easily available in terms of *sales* data (Coutu et al., 2013; Verlicchi et al., 2014), generally on an annual and sometimes regional basis (comprising different health care structures). Moreover it could be difficult to directly obtain the consumption *amount* (kg/year) of the active ingredients of interest. Hospital internal services could provide a list of extremely detailed information regarding each type of medication containing the active ingredient of interest, the corresponding form, the content of the active ingredient in each item, the number of items delivered to the different wards, and alternatively the unit doses (defined daily doses). These data have to be carefully processed to convert the overall unit doses into grams of active ingredient, while considering their dosages (Coutu et al., 2016; Jean et al., 2012).

It is worth noting that consumption data provided by hospital pharmacies may be affected by several biases (Jean et al., 2012; Helwing et al., 2013). In fact they do not consider that:

- within the hospital, drugs may be administered to outpatients or leaving patients;
- drug packages may not be completely consumed (and only occasionally packages may be returned to the hospital pharmacy in the case of discharged or deceased patients);
- in-patients may not assume the prescribed medicine (different patient compliance degrees may be expected for the different therapeutic classes and in relation to the medicine form: tablet, pill, etc.),
- during their stay in hospital, in-patients might continue their treatment and assume drugs previously prescribed by general practitioners and which were not dispensed by the hospital (for instance diuretics, lipid regulators, beta-blockers);
- in specialized hospitals (i.e. psychiatric facilities), a percentage of patients go home during the weekend;
- activities within radiology departments are quite intense during weekdays and much “quieter” at weekends;
- outpatient units and wards are in operation only during weekdays;
- where laundry is an internal service, it is in operation during the week and on Saturday morning, not on Sundays. This could lead to higher concentrations of PhCs as laundry water consumption was estimated to be around 33 % of the whole hospital consumption (Kern et al., 2013).

Moreover, any adopted PEC model does not consider a potential degradation/sorption of the released active compound into the sewage from the release point to the sampling one, nor transformation from parent compounds and/or viceversa, which will influence occurrence of the compound itself.
PEC models hardly focus on short-term fluctuations as they generally require *annual* consumption data. Antibiotic consumption patterns in hospitals may present fluctuations over the year, depending on the specific drug.
Monthly consumption data were only available for a few compounds. Table SD-2 reports the percentage variations for carbamazepine and antibiotics in two Italian medium-size hospitals compared to the corresponding average monthly dispensed amount (De Luigi, 2009; Verlicchi et al., 2008). Although the two structures are similar in size and type of ward and diagnosis activity, consumption patterns of the investigated groups of compounds are different - carbamazepine varied between -45 % and + 98 % in one hospital and -75 % and +128 % in the other. Antibiotics were found to vary between -20 % and +17 % in one hospital and -26 % and + 36 % in the other.
An analysis of consumption data is useful to search for the most administered drugs, which are compounds whose detection frequency is expected to be high (Daouk et al., 2016).

### 4.3.3 Excretion factor

This parameter is quite difficult to evaluate as it depends on many factors, as already remarked in Verlicchi et al. (2014). Table SD-1 in Supplementary Data reports the values proposed by different studies and they refer to excretion of the parent compound and not to its metabolites. Most of the selected PhCs show a wide variability range, since values may refer only to excretion by urine, or by feces or to both (Lienert et al., 2007b).
The excretion factor may vary from 0.1 to 1 and, in some cases, it could also be > 1 due to generation of the parent compound from its metabolites (Besse et al., 2008). This is the case of hydrochlorothiazide for which an excretion factor ranging from 0,24 to 1,20 is reported (see Tables 2 and SD-1).It is necessary to look for the most accurate excretion values that would allow more realistic predicted concentrations.
If the value is not available or not reliable enough for a specific compound, Lienert et al. (2007a) suggest adopting the “default values” reported in Table 6.
Other authors (among them Le Corre et al., 2012) suggest adopting a more conservative approach - they prefer to suppose that no metabolism occurs within the human body and that the total amount of a given substance is excreted unchanged. This assumption should partly counterbalance parameters that are not considered in drug consumption, including non-compliance and improper disposal of unused medications. On the contrary, any value of excretion factor assumed will lead to an uncertainty (overestimation or underestimation) that will be analyzed in the sensitivity analysis of the proposed model.

It may also happen that unused, left-over, unwanted and expired medications are directly poured down the sink or flushed down toilets instead of returning them to the hospital pharmacy department and then to an authorized supplier or reverse distributor. From the point of view of *good practices,* these practices are not permitted and should be avoided, as they lead to a further release of persistent contaminants (as unchanged compounds) into the water cycle via the sewage network and after, into the environment (Mankes and Silver, 2013). From the point of view of uncertainties in predicted concentrations, these practices represent an unquantifiable source of medicine in the hospital sewage network.

**Table 6.**

### *4.4 Potential factors affecting measured concentrations*

As already discussed in Verlicchi et al. (2014), direct measurement of PhCs in hospital effluent may be affected by the sampling mode and frequency, matrix effect, instrumental and human errors, and analytical method limitations. Their influence will be quantified in the uncertainty analysis that follows.

## 5 Uncertainty analysis

### *5.1 Uncertainties in measured concentrations*

The results of the uncertainty analysis carried out for MEC of the group of PhCs are reported in Table 7 in terms of $U_{total}$ ($U_{sampling}$, $U_{analysis}$) and in Supplementary Data in greater detail (Table SD-3). It emerges that uncertainty due to the sampling mode and frequency mainly contributes to the total uncertainty for all the selected compounds ($U_{sampling}$ ranges are between 25 % and over 100 %). $U_{analysis}$ varies between 4 and 16 %. Compounds with a total uncertainty less than 40 % are 14: 1 beta-agonist (salbutamol**)**, 4 analgesics and antinflammatories (all of those investigated with the exception of ibuprofen and indomethacine),1 antibiotic (ciprofloxacin), 2 beta-blockers (metoprolol and atenolol), 2 anti-hypertensives (hydrochlorothiazide and enalapril), 1 diuretic (furosemide), 1 lipid regulator (atorvastatin), and 2 psychiatric drugs (lorazepam and diazepam).

The parameter that contributes the most to total uncertainty for MEC is sampling mode. If a flow proportional one was adopted, sampling uncertainty would be at most 25-30 % for pharmaceuticals with more than 50 pulses per day. For those with around only 10 pulses per day, the sampling uncertainty would be around 75 % (See table SD-3 for the pulses for each compound).

### *5.2 Sensitivity analyses of the predictive model*

Results of the sensitivity analysis are reported in Table 7, in terms of the minimum and maximum percentage variation of the "new" PEC value with respect to $PEC_0$ (resulting by assuming the average

excretion factor for each compound, a constant consumption of each selected PhC during the year and a constant wastewater volume through the year).

Regarding variations in PhC consumption, different assumptions were made:

- as for antibiotics, a percentage variation ranging from -36 % to + 30 % was assumed, based on investigations of medium size hospitals, reported and discussed by Galletti (2011), De Luigi (2009) and Verlicchi et al. (2008) (see Table SD-2);
- referring to carbamazepine, the consumption pattern presented for two medium size hospitals (Verlicchi et al., 2008; De Luigi, 2009) was considered. It shows a consistent variation over the months. In particular, the percentage variation with respect to the average value varied from -75 % to +128 % (see Table SD-2 in Supplementary Data for further details);
- as for analgesics/antinflammatories, consumption profiles are not yet available. It is reasonable to assume that levels do not vary gradually over the year as they are administered as pain killers, antipyretics or antinflammatories. This assumption is supported by the evidence that in a hospital patients require analgesics/antinflammatories every day for different (unhealthy) reasons, resulting in modest monthly (also daily) variation of their consumption with respect to the average. In this study it was assumed that the variability range is between -20% and + 20 %;
- A different approach was followed for all the remaining compounds belonging to the other classes. As no consumption pattern is available for each of them and they are administered to patients for specific diseases, it is quite difficult to suggest specific ranges). For these compounds, we prudently assume an uncertainty of (50 %, +50), which is the same value proposed by Le Corre et al., (2012) and considered “conservative”.

Based on data reported on Table 7, it emerges that *E* and wastewater volume greatly influence PEC values for most compounds. Only for ofloxacin, glibenclamide, tamoxifen, salbutamol, atenolol and sotalol, does the excretion factor not represent the most influencing factor, as expected uncertainties in administered amount and wastewater flow rate are consistently higher. Unfortunately, consumption patterns are scarce and available only for some antibiotics and carbamazepine. This underlines the need for further investigations to improve knowledge of consumption trends in hospitals over the year and to better evaluate the influence of PhC consumption on PEC uncertainty.

It is important to underline that water consumption increases during summer time (Fig. SD-1 and SD-2) and a lower demand generally occurs in winter. In this season a higher consumption of antibiotics was found (and expected), resulting in higher antibiotic concentrations in the hospital effluent with respect to the predicted ones based on average PhC and average water consumption.

**Tab. 7**

In order to reduce uncertainties in PEC approach, great attention should be paid to the *most appropriate* adopted values of excretion factors, according to the evolution of new formulations as well as types of medicaments mostly used within the structure of interest, PhC consumption amounts (it would be recommended to use monthly consumption data), and wastewater flow rate.

## 6 Conclusions and perspectives

Knowledge of PhC concentrations in hospital effluents is essential for identifying proper management and treatment of the wastewater produced and also for carrying out an environmental risk assessment due to PhC residues in order to preserve the receiving environment.

This study outlines and compares the concentrations of 38 compounds belonging to 11 different therapeutic classes, resulting from direct measurements of the effluent of a large hospital and from a prediction model based on the documented annual consumptions within the structure.

It emerges that predicted concentrations are generally higher than measured ones, and for only a few compounds they are quite similar. It is not possible to establish which approach is more reliable and accurate for all the compounds since both options are affected by uncertainties, depending on the specific compounds and expected temporal variability. The uncertainty and sensitivity analysis carried out pointed out that PECs are generally mainly affected by the parameters of wastewater volume (from -45 to +104% for each compound) and excretion factor (different ranges, from -99 % to +99 %))and MECs by sampling mode (> 100 %).

Thus, measured or predicted concentration values should be carefully *handled* during subsequent analysis by scientists, practitioners and administrators.

It is quite difficult to suggest which strategy to adopt for a more accurate characterization of a hospital effluent. It is well known that a wide spectrum of compounds is used within a hospital. It would be quite hard to provide a snapshot including the occurrence of *all* the compounds. Both prediction or measurement would take too long, as well as being unsustainable efforts.

The starting step would be to define the prioritization criteria (Helwig et al., 2013; Daouk et al., 2015; Jean et al., 2012) for selecting a list of compounds for specific health-care structures. For instance, psychiatric and geriatric hospitals are likely to use a quite different range of drugs than general hospitals. For some of them, investigations have already highlighted the collection of greater concern (Helwig et al., 2013; Herrmann et al., 2015; Mendoza et al., 2015; Yuan et al., 2013).

Thus, a hybrid approach could be the best solution, as it combines the adoption of a model to (roughly) predict concentrations of selected PhCs based on their annual consumption, wastewater volume and average excretion factors and of specific sampling campaigns covering the (expected) most critical periods during the year. Moreover, the use of PECs should be used with some confidence for substances where no analytical method is available to experimentally determine concentrations or where the limit of

quantification is not low enough , as remarked by Ort et al. (2010b). This strategy should lead to a refinement of hospital effluent chemical characterization and would lead to a more accurate identity card of the health care structure, reflecting its singularity.

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# Tables

**Table 1.** Selection of compounds and corresponding therapeutic class

| Therapeutic Class | Selected Compounds | Number of compounds |
|---|---|---|
| Analgesics/Anti-inflammatories (A) | Acetaminophen, Codeine, Diclofenac, Ibuprofen, Indomethacin, Ketoprofen | 6 |
| Antibiotics (B) | Azithromycin, Chloramphenicol, Chlortetracycline, Ciprofloxacin, Clarithromycin, Doxycycline, Erythromycin, Metronidazole, Norfloxacin, Ofloxacin, Sulfadiazine, Sulfamethoxazole, Trimethoprim | 13 |
| Antidiabetics (C) | Glibenclamide | 1 |
| Antihypertensives (D) | Enalapril, Hydrochlorothiazide, Lisinopril | 3 |
| Antineoplastics (E) | Tamoxifen | 1 |
| Beta-agonists (F) | Salbutamol | 1 |
| Beta-blockers (G) | Atenolol, Metoprolol, Propranolol, Sotalol, Timolol | 5 |
| Diuretics (H) | Furosemide | 1 |
| Lipid regulators (I) | Atorvastatin | 1 |
| Psychiatric drugs (J) | Carbamazepine, Diazepam, Fluoxetine, Lorazepam, Paroxetine | 5 |
| Receptor antagonists (K) | Ranitidine | 1 |

**Table 2** Annual consumption data and weight percentage for the selected compounds in the investigated hospital; range of variability for the excretion factor *E* and average values assumed in this study for each compound for PEC evaluation (=$PEC_0$)

| Therapeutic class | Compound | **Amount [kg/year]** | **% in weight to the total** | ***E (range)*** | ***E* average** |
|---|---|---|---|---|---|
| Analgesics/anti-inflammatories | Acetaminophen | 101.31 | 59.24 | 0.02-0.85 | 0.44 |
| | Codeine | 1.25 | 0.73 | 0.03-0.40 | 0.22 |
| | Diclofenac | 1.07 | 0.63 | 0.05-0.95 | 0.49 |
| | Ibuprofen | 6.91 | 4.04 | 0.01-0.47 | 0.24 |
| | Indomethacin | 0.0573 | 0.03 | 0.10-1.00 | 0.55 |
| | Ketoprofen | 3.75 | 2.19 | 0.01-0.90 | 0.46 |
| Antibiotics | Azithromycin | 1.94 | 1.14 | 0.06-0.50 | 0.28 |
| | Chloramphenicol | 0.866 | 0.51 | 0.05-0.10 | 0.075 |
| | Chlortetracycline | 0.116 | 0.07 | 0.20-0.70 | 0.45 |
| | Ciprofloxacin | 20.7 | 12.12 | 0.20-0.95 | 0.58 |
| | Clarithromycin | 2.13 | 1.25 | 0.18-0.58 | 0.38 |
| | Doxycycline | 0.062 | 0.04 | 0.40-0.72 | 0.56 |
| | Erythromycin | 0.534 | 0.31 | 0.05-1.00 | 0.53 |
| | Metronidazole | 6.037 | 3.53 | 0.20-0.80 | 0.50 |
| | Norfloxacin | 0.040 | 0.02 | 0.30-0.74 | 0.52 |
| | Ofloxacin | 0.0178 | 0.01 | 0.70-0.80 | 0.75 |
| | Sulfadiazine | 0.233 | 0.14 | 0.25-0.57 | 0.40 |
| | Sulfamethoxazole | 2.78 | 1.62 | 0.15-0.40 | 0.28 |
| | Trimethoprim | 0.555 | 0.32 | 0.10-0.80 | 0.45 |
| Antidiabetics | Glibenclamide | 0.0221 | 0.01 | 0.10-0.16 | 0.13 |
| Antihypertensives | Enalapril | 0.132 | 0.08 | 0.20-0.43 | 0.32 |
| | Hydrochlorothiazide | 0.407 | 0.24 | 0.24-1.20 | 0.72 |
| | Lisinopril | 0.0146 | 0.01 | 0.95-1.00 | 0.98 |
| Antineoplastics | Tamoxifen | 0.0033 | 0,002 | 0.30-0.50 | 0.40 |
| Beta-agonists | Salbutamol | 0,176 | 0,10 | 0.28-0.30 | 0.29 |
| Beta-blockers | Atenolol | 0,7854 | 0.46 | 0.50-1.00 | 0.75 |
| | Metoprolol | 3.293 | 1.93 | 0.10-0.30 | 0.25 |
| | Propranolol | 0.27 | 0.16 | 0.005-0.24 | 0.13 |
| | Sotalol | 0.2 | 0.12 | 0.75-1.25 | 1. |
| | Timolol | 0.0046 | 0.00 | 3-20 | 0.12 |
| Diuretics | Furosemide | 6.79 | 3.97 | 0.40-1.00 | 0.70 |
| Lipid regulators | Atorvastatin | 0.343 | 0.20 | 0.01-0.05 | 0.03 |
| Psychiatric drugs | Carbamazepine | 2.66 | 1.55 | 0.01-0.61 | 0.31 |
| | Diazepam | 0.121 | 0.07 | 0.01-0.15 | 0.08 |
| | Fluoxetine | 0.00728 | 0.00 | 0.025-0.60 | 0.31 |
| | Lorazepam | 0.0634 | 0.04 | 0.003-0.85 | 0.43 |
| | Paroxetine | 0.0437 | 0.03 | 0.03-0.04 | 0.03 |
| Receptor antagonists | Ranitidine | 5.29 | 3.1 | 0.06-0.79 | 0.43 |

**Table 3** Concentration range and mean value for selected compounds in the hospital effluent (adapted from Verlicchi et al. 2012) [ng/L] (*n* = 4 for each period).

| Class | Compound | *Summer* | | | *Winter* | | | *Year* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Min** | **Max** | **Mean** | **Min** | **Max** | **Mean** | **Min** | **Max** | **Mean** |
| A | Acetaminophen | 3,450 | 4,658 | 4,054 | 1,426 | 3,390 | 2,536 | 1,426 | 4,658 | 3,143 |
| | Codeine | 422 | 636 | 529 | 410 | 3,167 | 1,886 | 410 | 3,167 | 1,343 |
| | Diclofenac | 176 | 271 | 223 | 476 | 527 | 510 | 176 | 527 | 395 |
| | Ibuprofen | 380 | 813 | 597 | 2,230 | 3,220 | 2,623 | 380 | 3,220 | 1,813 |
| | Indomethacin | 895 | 3,409 | 2,152 | 403 | 607 | 533 | 403 | 3,409 | 1,181 |
| | Ketoprofen | 829 | 1,417 | 1,123 | 1,066 | 1,765 | 1,400 | 829 | 1,765 | 1,289 |
| B | Azithromycin | 46 | 50 | 47 | 577 | 1,044 | 797 | 46 | 1,044 | 497 |
| | Chloramphenicol | <lod | <lod | <lod | <lod | 10 | 8 | 4 | 6 | 5 |
| | Chlortetracycline | 62 | 93 | 77 | <lod | <lod | <lod | 62 | 93 | 77 |
| | Ciprofloxacin | 1,379 | 1,889 | 1,634 | 14,944 | 26,167 | 21,389 | 1,379 | 26,167 | 13,487 |
| | Clarithromycin | 50 | 64 | 57 | 9,330 | 13,500 | 10,943 | 50 | 13,500 | 6,589 |
| | Doxycycline | 56 | 97 | 76 | <lod | <lod | <lod | 56 | 97 | 76 |
| | Erythromycin | 79 | 86 | 82 | 91 | 227 | 157 | 79 | 227 | 127 |
| | Metronidazole | 261 | 392 | 326 | 853 | 1057 | 956 | 261 | 1,057 | 704 |
| | Norfloxacin | 23 | 44 | 34 | 224 | 513 | 347 | 23 | 513 | 222 |
| | Ofloxacin | 3,262 | 4,049 | 3,656 | 24,538 | 36,538 | 30,949 | 3262 | 36,538 | 20,032 |
| | Sulfadiazine | 77 | 119 | 98 | 271 | 383 | 328 | 77 | 383 | 236 |
| | Sulfamethoxazole | 900 | 2,670 | 1,785 | 936 | 3,364 | 2,011 | 900 | 3,364 | 1921 |
| | Trimethoprim | 449 | 860 | 654 | 68 | 359 | 182 | 68 | 860 | 371 |
| C | Glibenclamide | 66 | 71 | 68 | 72 | 113 | 96 | 66 | 113 | 85 |
| D | Enalapril | 85 | 176 | 131 | 244 | 404 | 311 | 85 | 404 | 239 |
| | Hydrochlorothiazide | 536 | 816 | 676 | 1,838 | 2,388 | 2,185 | 536 | 2,388 | 1,582 |
| | Lisinopril | 89 | 337 | 213 | <lod | <lod | <lod | 89 | 337 | 213 |
| E | Tamoxifen | <lod | <lod | <lod | <lod | <lod | <lod | <lod | <lod | <lod |
| F | Salbutamol | 26 | 30 | 28 | 99 | 140 | 121 | 27 | 140 | 83 |
| G | Atenolol | 2,208 | 2,586 | 2,397 | 5,050 | 6,550 | 5,750 | 2,208 | 6,550 | 4,409 |
| | Metoprolol | 507 | 970 | 739 | 862 | 1,193 | 1,054 | 507 | 1,193 | 928 |
| | Propranolol | 76 | 94 | 85 | 30 | 61 | 43 | 30 | 94 | 60 |
| | Sotalol | 352 | 613 | 483 | 3,306 | 6,723 | 5,074 | 352 | 6,723 | 3,238 |
| | Timolol | <lod | <lod | <lod | 22 | 39 | 33 | 22 | 39 | 33 |
| H | Furosemide | 6,389 | 7,717 | 7,053 | 5,297 | 6,281 | 5,766 | 5,297 | 7,717 | 6,280 |
| I | Atorvastatin | 80 | 173 | 127 | 244 | 308 | 268 | 80 | 308 | 212 |
| J | Carbamazepine | 758 | 1,183 | 971 | 748 | 1,083 | 947 | 748 | 1,183 | 956 |
| | Diazepam | <lod | <lod | <lod | 21 | 38 | 31 | 21 | 38 | 31 |
| | Fluoxetine | 24 | 33 | 29 | 35 | 69 | 56 | 24 | 69 | 45 |
| | Lorazepam | 167 | 198 | 183 | 464 | 698 | 601 | 167 | 698 | 433 |
| | Paroxetine | <lod | <lod | <lod | 56 | 76 | 67 | 56 | 76 | 67 |
| K | Ranitidine | 1,077 | 1,511 | 1,294 | 1,407 | 4,107 | 3,033 | 1,077 | 4,107 | 2,338 |

Lod = limit of detection

**Table 4.** Analysis of the dispensed medicaments in terms of number of products handled for each therapeutic class, and administered amount of each class (weight and percentage to the total).

| | **Type of Phamaceutical products** | **Dispensed products [#]** | **Administered amount [kg/year]** | **Percentage to the total [%]** |
|---|---|---|---|---|
| A | Analgesics and anti-inflammatories | 19 | 114.36 | 66.9 |
| B | Antibiotics | 31 | 36.04 | 21.1 |
| C | Antidiabetics | 2 | 0.0221 | 0.0129 |
| D | Anti-hypertensives | 4 | 0.513 | 0.323 |
| E | Antineoplastics | 1 | 0.0033 | 0.00193 |
| F | Beta-agonists | 5 | 0.177 | 0.103 |
| G | Beta-blockers | 12 | 4.55 | 2.66 |
| H | Diuretics | 4 | 6.79 | 3.97 |
| I | Lipid regulators | 4 | 0.343 | 0.20 |
| J | Psychiatric drugs | 12 | 2.89 | 1.69 |
| K | Receptor antagonists | 2 | 5.29 | 3.10 |
| | **All pharmaceutical products** | 96 | 171 | 100 |

**Table 5.** Analysis of the ratio between predicted and measured concentrations in the different observation periods, with a focus on the specific therapeutic classes.

| **PEC/MEC$_{av}$** | **Summer period** | **Winter period** | **Whole Year** |
|---|---|---|---|
| < 0.5, PEC *underestimation* | 4 compounds: 1 antihypertensive, 1 antidiabetic, 1 analgesic, 1 antibiotic | 11 compounds: 3 antibiotics, 3 psychiatric drugs, 2 beta blockers, 1 analgesic, 1 lipid regulator, 1 antidiabetic | 10 compounds: 3 psychiatric drugs, 2 beta blockers, 1 lipid regulator, 1 antidiabetic, 1 analgesic, 1 antihypertensive, 1 antibiotic |
| between 0.5 and 2, *good overlapping between PEC and MEC* | 4 compounds: 2 psychiatric drugs; 1 lipid regulator, 1 beta blocker | 5 compounds: 2 anti-hypertensives, 1 antibiotic, 1 analgesic, 1 beta blocker. | 7 compounds: 2 antibiotics, 2 antihypertensives, 1analgesics, 1 betablocker, 1 psychiatric drug |
| > 2, PEC *overestimation* | 30 compounds: 12 antibiotics, 5 analgesics/anti-infl.,4 beta blockers, 3 psychiatric drugs, 2 anti-hypertensives, 1 antineoplastic, 1 beta agonist, 1 receptor antagonist, 1 diuretic | 22 compounds: 9 antibiotics, 4 analgesics/anti-infl., 2 psychiatric drugs, 2 beta blockers, 1 antineoplastic, 1 receptor antagonist, 1 beta agonist, 1 diuretic, 1 anti-hypertensive. | 21 compounds: 10 antibiotics, 4 analgesics and anti-inflammatories, 2 betablockers, 1 antineoplastic, 1 diuretic, 1beta agonist, 1 receptor antagonist |

**Table 6.** Excretion percentages suggested for different therapeutic classes (Lienert et al., 2007a).

| Percentage of excretion | Therapeutic classes |
|---|---|
| > 80 % via urine | X ray contrast media |
| | Analgesics |
| | Antiepileptic drugs |
| > 70 % via urine | Hypnotic drugs |
| | Gastric acid inhibitors |
| | Antiviral drugs |
| > 60 % via urine | Antiphlogistics |
| | Arterial vasodilatators |
| | Vasodilatants |
| | Antidepressants |
| | Antiemetics |
| | Betablockers |
| | Diuretic drugs |
| | Glucorticoides/corticosteroids |
| | Antibiotics |
| > 50 % via urine | Antilipidaemics |
| | Neuroleptics |
| | Antihypertensives |
| | Cytostatics |
| | Gestagens |

**Tab. 7.** Results of the uncertainty and sensitivity analysis in terms of minimum and maximum percentage of variation of MEC or PEC value for each PhC and for each parameter, varying within the assumed range discussed in the text. The letter appearing in brackets after the name corresponds to the therapeutic class of the compound (see Table 1).

| **Compound** | ***MEC - Uncertainty analysis (%)*** | | | ***PEC - Sensitivity analysis (%)*** | | |
|---|---|---|---|---|---|---|
| | $U_{sampling}$ | $U_{analysis}$ | $U_{total}$ | ***E*** | ***Mi*** | ***WW volume*** |
| Acetaminophen (A) | 35 | 5 | 35 | -95/+95 | -15/+15 | -45/+104 |
| Codeine (A) | 38 | 4 | 38 | -86/+86 | -15/+15 | -45/+104 |
| Diclofenac (A) | 38 | 7 | 39 | -96/+96 | -15/+15 | -45/+104 |
| Ibuprofen (A) | 45 | 7 | 46 | -96/+96 | -15/+15 | -45/+104 |
| Indomethacin (A) | 98 | 6 | 98 | -82/+82 | -15/+15 | -45/+104 |
| Ketoprofen (A) | 37 | 6 | 37 | -98/+98 | -15/+15 | -45/+104 |
| Azithromycin (B) | 50 | 6 | 50 | -79/+79 | -36/+30 | -45/+104 |
| Chloramphenicol (B) | >100 | 16 | >100 | -33/+33 | -36/+30 | -45/+104 |
| Chlortetracycline (B) | >100 | 6 | >100 | -56/+56 | -36/+30 | -45/+104 |
| Ciprofloxacin (B) | 38 | 4 | 38 | -65/+65 | -36/+30 | -45/+104 |
| Clarithromycin (B) | 60 | 6 | 60 | -53/+53 | -36/+30 | -45/+104 |
| Doxycycline (B) | 100 | 9 | 100 | -29/+29 | -36/+30 | -45/+104 |
| Erythromycin (B) | 100 | 10 | >100 | -90/+90 | -36/+30 | -45/+104 |
| Metronidazole (B) | 50 | 6 | 50 | -60/+60 | -36/+30 | -45/+104 |
| Norfloxacin (B) | >100 | 6 | >100 | -42/+42 | -36/+30 | -45/+104 |
| Ofloxacin (B) | >100 | 15 | >100 | -7/+7 | -36/+30 | -45/+104 |
| Sulfadiazine (B) | >100 | 6 | >100 | -44/+44 | -36/+30 | -45/+104 |
| Sulfamethoxazole (B) | 70 | 3 | 70 | -45/+45 | -36/+30 | -45/+104 |
| Trimethoprim (B) | 70 | 5 | 70 | -78/+78 | -36/+30 | -45/+104 |
| Glibenclamide (C) | 60 | 7 | 60 | -23/+23 | *-50/+50* | -45/+104 |
| Enalapril (D) | 38 | 10 | 39 | -37/+37 | *-50/+50* | -45/+104 |
| Hydrochlorothiazide (D) | 38 | 11 | 40 | -67/+67 | *-50/+50* | -45/+104 |
| Lisinopril (D) | 70 | 6 | 70 | | *-50/+50* | -45/+104 |
| Tamoxifen (E) | >100 | 4 | >100 | -25/+25 | *-50/+50* | -45/+104 |
| Salbutamol (F) | 25 | 7 | 26 | -3/+3 | *-50/+50* | -45/+104 |
| Atenolol (G) | 38 | 8 | 39 | -33/+33 | *-50/+50* | -45/+104 |
| Metoprolol (G) | 38 | 3 | 38 | -59/+59 | *-50/+50* | -45/+104 |
| Propranolol (G) | 70 | 7 | 70 | -96/+96 | *-50/+50* | -45/+104 |
| Sotalol (G) | 70 | 12 | 71 | -25/+25 | *-50/+50* | -45/+104 |
| Timolol (G) | >100 | 10 | >100 | -74/+74 | *-50/+50* | -45/+104 |
| Furosemide (H) | 30 | 6 | 31 | -43/+43 | *-50/+50* | -45/+104 |
| Atorvastatin (I) | 38 | 9 | 39 | -67/+67 | *-50/+50* | -45/+104 |
| Carbamazepine (J) | 50 | 6 | 50 | -97/+97 | -75/-128 | -45/+104 |
| Diazepam (J) | 38 | 15 | 41 | -88/+88 | *-50/+50* | -45/+104 |
| Fluoxetine (J) | >100 | 6 | >100 | -92/+92 | *-50/+50* | -45/+104 |
| Lorazepam (J) | 38 | 5 | 38 | -99/+99 | *-50/+50* | -45/+104 |
| Paroxetine (J) | 60 | 10 | 61 | | *-50/+50* | -45/+104 |
| Ranitidine (K) | 38 | 9 | 39 | -86/+86 | *-50/+50* | -45/+104 |

## *Captions of figures*

**Figure 1** Comparison of predicted and measured average (annual) concentrations for the spectrum of selected substances. Compounds appear in descending order according to the assessed PEC/MEC ratio (for tamoxifen $MEC_{av,}$ <lod, we virtually assigned a really high value for the ratio).

**Figure 2**. Analysis of the ratio between PEC and average MEC based on data collected in summer for the selected compounds (for compounds whose $MEC_{av,SUMMER}$<lod, we virtually assigned a really high value for the ratio)

**Figure 3**. Analysis of the ratio between PEC and average MEC referring to the winter season for the selected compounds (for compounds whose $MEC_{av,WINTER}$ <lod, we virtually assigned a really high value for the ratio).

**Figure 4**. Comparison between PEC and MEC concentrations for the selection of compounds. Green rectangles correspond to compounds whose PEC is between min and max MEC

**Figures**

Click here to download Figure: 1 Revised Figures.docx

## Figures

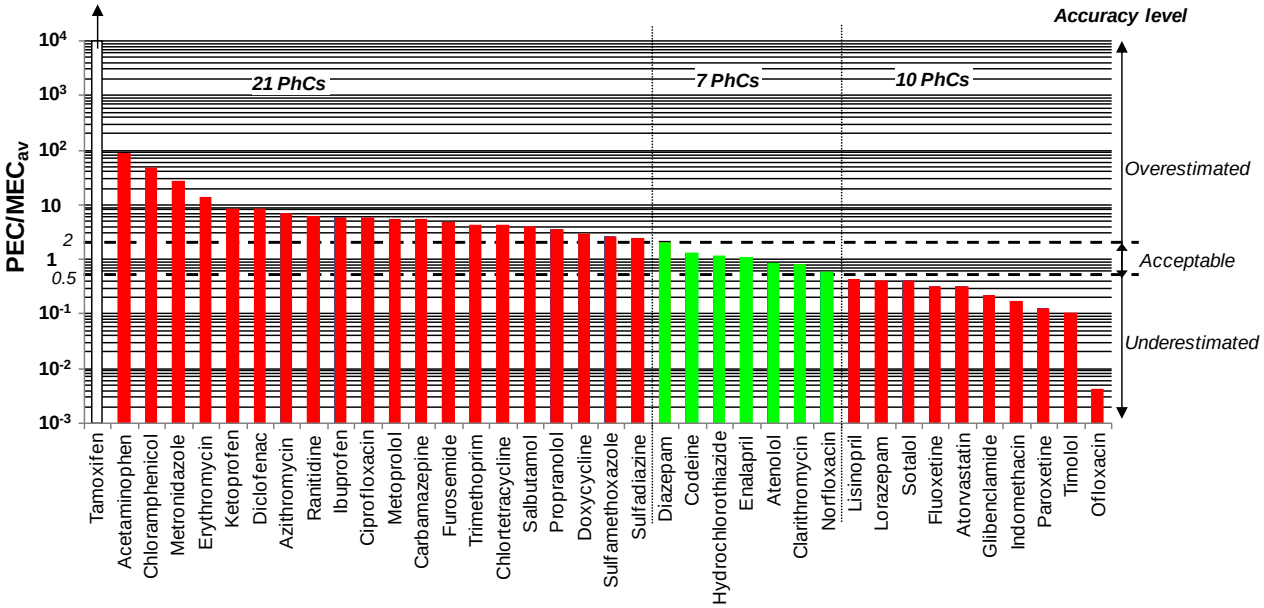


**Figure 1**

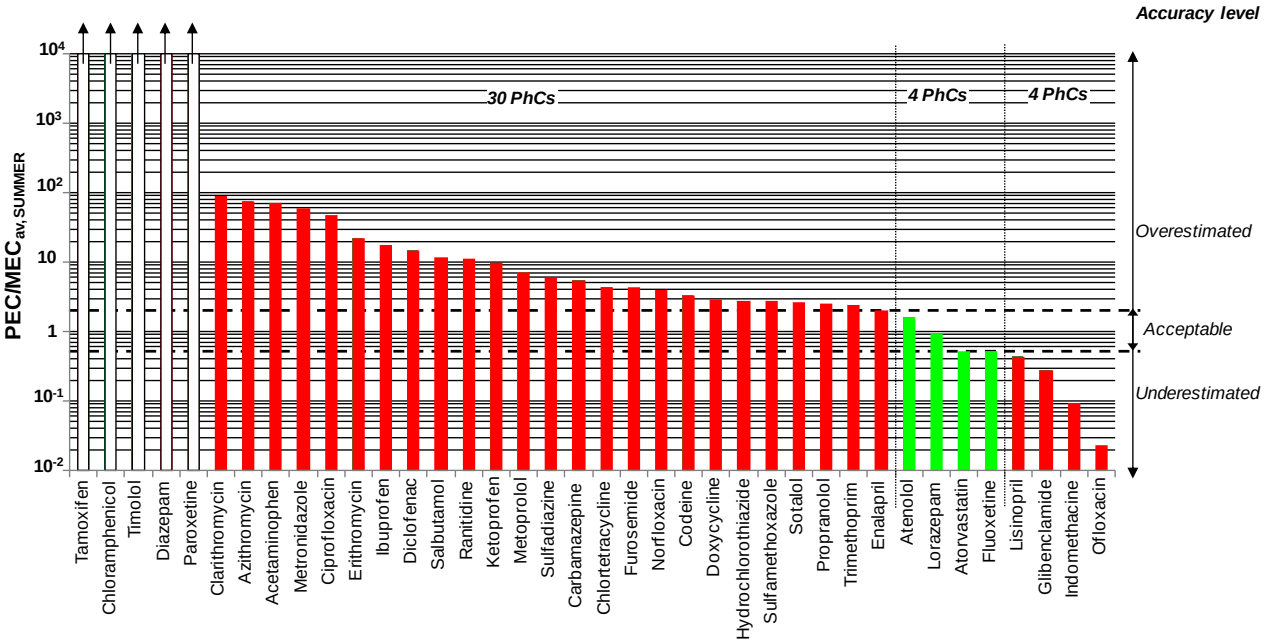


**Figure 2**.

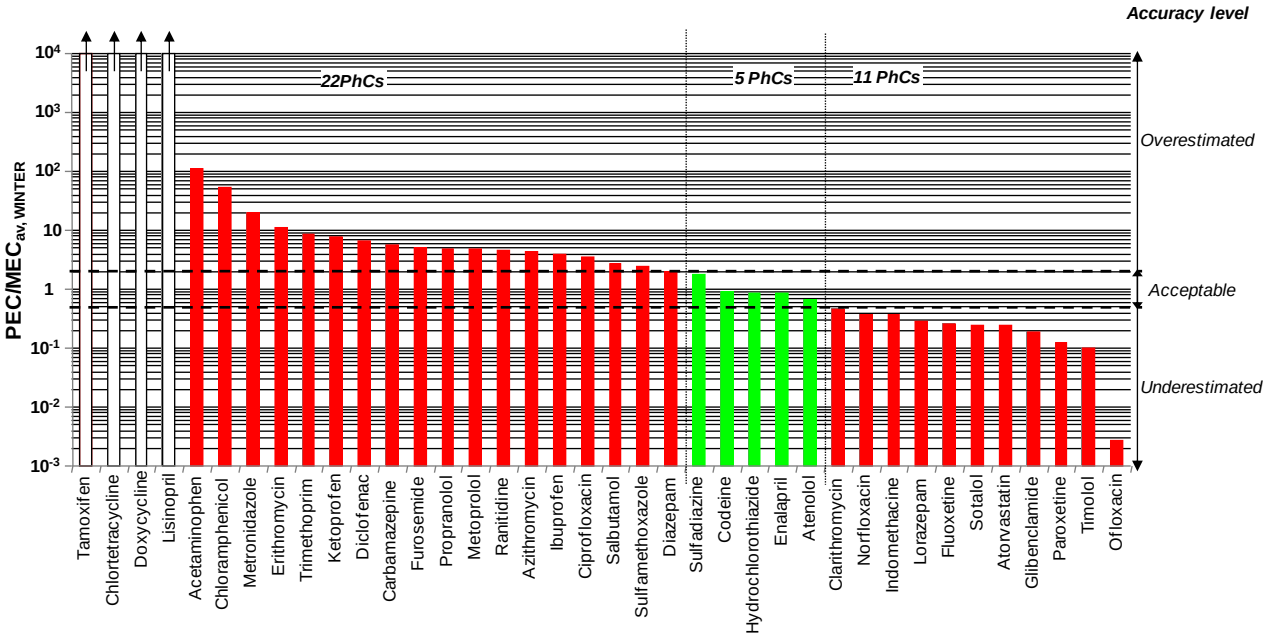


**Figure 3**.

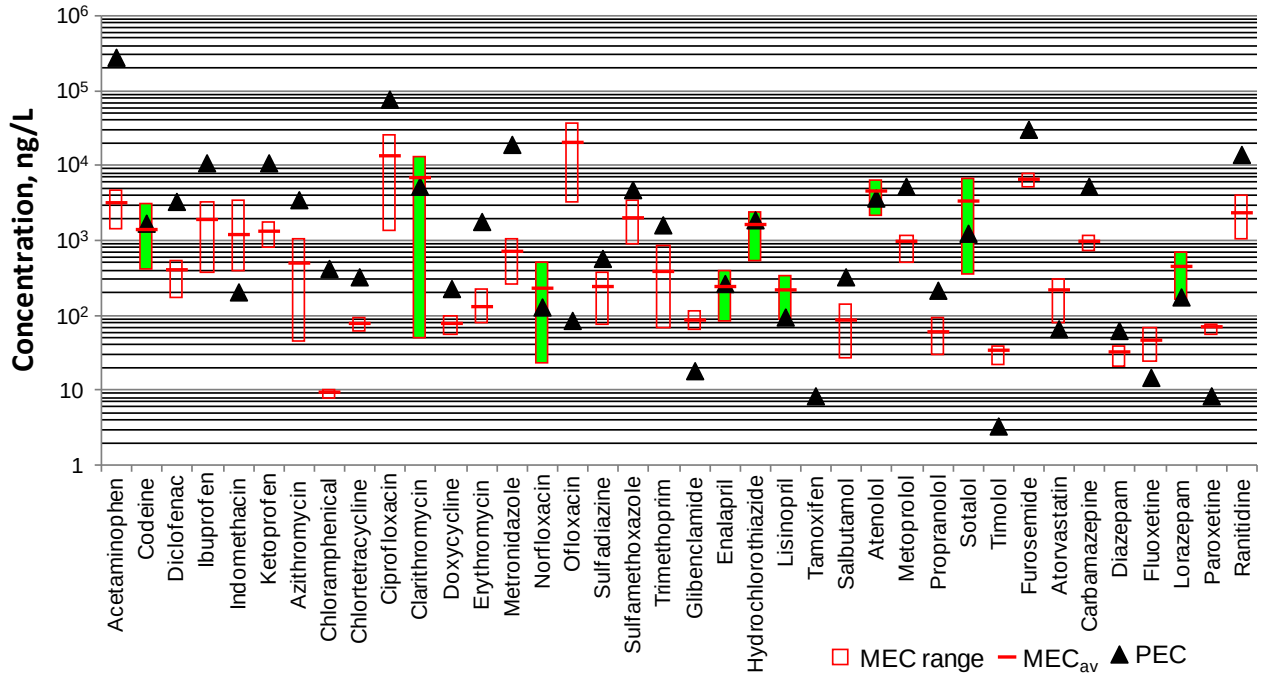


**Figure 4**.

**Supplementary material for on-line publication only**

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