

Pharmaceutical Concentrations and Loads in Hospital Effluents: Is a Predictive Model or Direct Measurement the Most Accurate Approach?

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Abstract The pharmaceutical concentration and load in a hospital effluent may be known through the adoption of predictive models based on medicament consumption data or through direct measures. Both methods present strengths and weaknesses and advantages and drawbacks. This chapter presents and compares the predicted and measured concentrations and loads found by different authors for a large number of pharmaceuticals in hospital effluents. It then discusses the main factors influencing the predicted values, as well as those affecting measured ones, and estimates the range of variability of each model parameter (pharmaceutical consumption data, excretion factor, and wastewater volume). It then presents the results of the sensitivity analysis carried out for the predicted concentrations and the uncertainty analysis for measured ones (in the latter case, by evaluating the contribution due to sampling protocol, chemical analysis, and flow rate measurement) and discusses the most critical parameters in both strategies. The study concludes with some recommendations for reducing uncertainties in measured and predicted data, thus improving the accuracy and reliability of the results.

Keywords Consumption data, Measured concentrations, Pharmaceuticals, Predicted concentrations, Uncertainty analysis

Contents

- 1 Introduction
- 2 Models Proposed for Predicting the Concentration and Load of PhCs in Hospital Effluents

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- 3 Overview of Studies and Investigations on the PEC and PEL of PhCs in HWW
 - 4 Model Parameters
 - 4.1 Consumption Data
 - 4.2 Excretion Factor
 - 4.3 Flow Rate Prediction
 - 5 Comparison Between Measured and Predicted Concentrations and Loads
 - 6 Potential Factors Influencing PEC and PEL
 - 6.1 Inaccurate Estimation of PhC Consumption Within the Hospital
 - 6.2 Variation in Consumption Over the Year
 - 6.3 Differences Between Pharmacy Consumption Data and Effective Administration
 - 6.4 Inaccuracy in the Excretion Factor Assumed for the Evaluation of PEC
 - 6.5 Wastewater Flow Variations
 - 6.6 Improper Disposal of Unused Medicines (in Household Waste or via the Toilet)
 - 6.7 Biodegradation/Biotransformation or Adsorption Processes Occurring in the Sewage System Before the Sampling Point
 - 7 Factors Affecting MEC and MEL
 - 7.1 Sampling Protocols
 - 7.2 Analytical Errors
 - 7.3 Sewer Layout and Fluctuation of the Concentration Throughout the Day and the Week
 - 7.4 Flow Rate Measurement
 - 7.5 Degradation Processes During Sampling and Transportation
 - 8 Uncertainties in Predicted and Measured Concentrations and Loads
 - 8.1 Uncertainties in Concentration and Load Predictions
 - 8.2 Uncertainties in Concentration and Load Measurements
 - 9 Conclusions and Perspectives
- References

Abbreviations

HWW	Hospital wastewater
ICM	Iodinated contrast media
MEC	Measured concentration
MEL	Measured load
PEC	Predicted concentration
PEL	Predicted load
PhCs	Pharmaceutical compounds
WWTP	Wastewater treatment plant

1 Introduction

In the last 15 years, increasing attention has been paid to improving knowledge of the pollutant content of hospital effluents in terms of conventional pollutants (namely, COD, BOD₅, suspended solids, nitrogen compounds, and phosphorus compounds) and micropollutants (pharmaceuticals, detergents, disinfectants, heavy metals, microorganisms, and viruses) [1–4] in order to evaluate how to

manage them better [5–7], to test the most adequate treatments [8], and to evaluate the environmental risk posed by the residues of PhCs in hospital effluents [9, 10].

Pharmaceuticals are still unregulated compounds with regard to their occurrence in the aquatic environment (surface and ground water, domestic and hospital wastewater). The European Community has recently set a *watch list* including substances which might be included in the list of priority compounds and therefore subject to regular monitoring [11, 12]. The current list includes 17- α -ethinylestradiol, 17 β -estradiol, estron, diclofenac, azithromycin, clarithromycin, and erythromycin. The results collected in ongoing and future investigations will lead to the inclusion or exclusion of these compounds in the priority list as well as new proposals for the watch list.

In the United States, the contaminants which might be included in a national priority list are the antibiotic erythromycin and the estrogens 17 α -ethinylestradiol, 17 β -estradiol, equilenin, estriol, estrone, mestranol, and norethindrone [13].

In Switzerland, investigations carried out during 2006–2010 led to the so-called Micropoll Strategy and to the definition of a list of priority compounds (including 22 pharmaceuticals and two hormones). The main goal consisted of the reduction of the total micropollutant load released by the largest WWTPs (greater than 100,000 inhabitants). They had to guarantee a reduction of 80% of the influent micropollutant load through upgrade, consisting of the adoption of end-of-pipe treatments (namely, ozonation and powdered activated carbon, PAC) [14].

Hospital effluents are quite often discharged into public sewage and co-treated with urban wastewater. A lively debate is ongoing among scientists regarding the environmental risks posed by this practice [6, 15, 16].

It is well known that a deep and exhaustive knowledge of the PhC content in hospital effluents is necessary to better evaluate the most adequate management and treatment method. Chemical characterization may be carried out by two approaches: direct measurements of their concentrations or the adoption of models to predict them.

Both strategies include advantages and drawbacks and strengths and weaknesses. This chapter presents and discusses models commonly used to predict PhC concentrations and loads in hospital effluents. Based on literature data, predicted and measured concentrations are compared for a wide group of PhCs in hospital effluents and the factors affecting the accuracy and reliability of both predicted and measured concentrations are presented, along with an evaluation of their uncertainty. The chapter concludes with suggestions for reducing uncertainty in direct measures and predictions.

2 Models Proposed for Predicting the Concentration and Load of PhCs in Hospital Effluents

Heberer and Feldmann [17] presented a model for predicting the (weekly) load of active pharmaceutical ingredients based on their consumption amounts and pharmacokinetic data. For each compound the weekly load (kg/week) was estimated by Eq. (1):

$$M_{\text{tot week}} = \sum_{i=1}^n a_i \times b_i \times m_i \times s_i [(1 - R_p) + R_p(x_p + x_c)]_i \times 10^{-6} \quad (1)$$

where a_i is the number of the dispensed packages per week for each brand or formulation i ,

b_i is the number of units per package for each brand or formulation i ,

m_i is the content of each active ingredient per unit (expressed in mg) for each formulation or brand,

s_i is the release rate of active ingredients from the individual formulation or brand i ,

R_p is the absorption rate which depends on the mode of application of each brand or formulation i ,

x_p is the portion of the active compound excreted as a parent compound after its adsorption, and

x_c is the percentage excreted as conjugate.

As R_p , x_p , and x_c are generally reported as a minimum-maximum range, Eq. (1) is refined in Eqs. (2) and (3):

$$M_{\text{tot week [min]}} = \sum_{i=1}^n a_i \times b_i \times m_i \times s_i [(1 - R_{p [\text{max}]}) + R_{p [\text{max}]}(x_{p[\text{min}]} + x_{c[\text{min}]})]_i \times 10^{-6} \quad (2)$$

$$M_{\text{tot week [max]}} = \sum_{i=1}^n a_i \times b_i \times m_i \times s_i [(1 - R_{p [\text{min}]}) + R_{p [\text{min}]}(x_{p[\text{max}]} + x_{c[\text{max}]})]_i \times 10^{-6} \quad (3)$$

and the evaluation leads to a minimum-maximum predicted load of each active ingredient in the investigated effluent.

In their investigations, Feldmann and colleagues [17, 18] compared (minimum and maximum) predicted loads for the selected PhCs (diclofenac, carbamazepine, and metamizole) on the basis of the seven values of measured concentrations $c_{d,i}$ (24-h composite water samples, $\mu\text{g/L}$) and daily sewage flow rate (L/d) as shown in Eq. (4):

$$M_{\text{meas week}} = \sum_{i=1}^7 c_{d,i} \times V_{d,i} \times 10^{-9} \quad (4)$$

They defined percentage recovery REC (%) as the ratio between the measured and predicted load on a weekly basis:

$$\text{REC}(\%)_{[\text{min}]} = \frac{M_{\text{meas week}}}{M_{\text{tot week}[\text{max}]}} \times 100 \quad (5)$$

$$\text{REC}(\%)_{[\text{max}]} = \frac{M_{\text{meas week}}}{M_{\text{tot week}[\text{min}]}} \times 100 \quad (6)$$

In 2011, Escher et al. [19] made a first evaluation of predicted PhC concentrations in hospital effluents by adopting a simpler predictive model:

$$\text{PEC}_{\text{HWW}} = \frac{M \times F}{Q_{\text{HWW}}} \quad (7)$$

where M is the amount of active ingredients dispensed within the hospital in the reference period,

F is the excretion factor of the unchanged active ingredient in urine and feces, and Q_{HWW} is the volume of wastewater produced in the hospital in the same reference period.

M is the sum of all the amounts m_i of active ingredient administered in the different formulations or brands; m_i was obtained on the basis of the number of units U_i for each brand or formulation and the amount of active ingredient in each unit $m_{U,i}$ (Eq. 8):

$$M = \sum_{i=1}^n m_i = \sum_{i=1}^n U_i m_{U,i} \quad (8)$$

This method was preferred to the previous one and used by other authors, as reported in the following sections.

3 Overview of Studies and Investigations on the PEC and PEL of PhCs in HWW

The main studies dealing with both the predicted concentrations and loads of PhCs in hospital effluents and the measured ones are reported in Table 1, along with their main features. This table also includes studies that critically analyze sampling protocols and provides suggestions for estimating uncertainties in PEC and PEL,

Table 1 Main studies referring to PEC, PEL, MEC, and MEL of pharmaceuticals in hospital effluents

Ref	Main contents
Kümmerer and Helmers [20]	This study deals with measured and predicted concentrations of gadolinium (Gd) in the effluent of the Freiburg University Hospital (1,700 beds). MECs were based on time proportional composite water samples – samples were taken from the main hospital drain every 10 min; 12 mixed samples, each covering an interval of 2 h over a 24 h period, were withdrawn. PECs were based on the annual water consumption within the hospital and downscaling the available national hospital consumption data of Gd (referring to 110,000 beds, which are the beds available in German hospitals) to Freiburg hospital (1,700 beds). An excretion factor of 0.9 was assumed for Gd
Heberer and Feldmann [17]	Authors present a model able to predict the <i>load</i> of pharmaceuticals in a hospital effluent, based on consumption and pharmacokinetic data. It was applied to a military hospital in Berlin for diclofenac and carbamazepine. PEL was compared to MEL over a time period of 1 week
Mahnik et al. [21]	This study evaluates the concentrations of selected cytostatics in the sewer system of an oncologic inpatient treatment ward of the Vienna University Hospital (Austria) on the basis of the exact dispensed substances in that ward during the observation period. It then compares them to the concentrations measured during the same period in which the monitored substances were dispensed in the ward
Feldmann et al. [18]	This study applies the model described in Heberer and Feldmann [17] for metamizole to the same military hospital and compares PEL and MEL over a time period of 1 week
Weissbrodt et al. [22]	This study was carried out at one of the 10 largest Swiss hospitals (415 beds) and dealt with an investigation on the occurrence of a selection of common cytostatics and iodinated contrast media (ICM) in the hospital effluent. MELs were based on 24-h flow proportional composite water samples. PELs were assessed from the actual consumption levels over 9 consecutive days. A comparison between MELs and PELs leads the authors to establish the quantity of selected compounds excreted on-site, in the hospital sewer network. Fluctuations of the load emitted for the selected compounds are also reported over the day and the whole investigation period
De Souza et al. [23]	The authors evaluated the environmental risk assessment due to intravenous antibiotics dispensed in the intensive care unit of a hospital in Curitiba (Brazil). In this unit (16 beds), antibiotic consumption amounts to 25% of the total consumption within the hospital (160 beds). The authors also presented consumption fluctuations over a year for the class of antibiotics
Ort et al. [16]	The aim of the study is to accurately evaluate the contribution of the PhC load emitted by an Australian hospital (190 beds) to the load in the corresponding WWTP influent (catchment area of about 45,000 inhabitants) for 59 compounds, using direct measurements. This experimental data, which refers to a limited time period is then compared to readily available audit data in order to evaluate if the same kind of information can be used for other locations to make a prediction, without planning specific monitoring campaigns

(continued)

Table 1 (continued)

Ref	Main contents
Ort et al. [24, 25] Ort and Gujer [26] Lai et al. [27]	The first two studies represent reference papers for evaluating uncertainties in the MECs and MELs of PhCs in wastewater. They discuss potential uncertainties in detail and provide guidelines for the proper selection of sampling frequency and sampling mode in order to reduce them. In particular, Table SI_3A and SI_3B (in the Supplementary Information linked to Ort et al. [24]) estimate the increment in sampling errors due to a sampling mode different from the reference one consisting of flow proportional composite sampling. Ort and Gujer [26] discuss sampling mode to obtain representative micropollutant loads in sewer systems. Finally, an interesting discussion is reported in Lai et al. [27] on how to evaluate and reduce uncertainties in direct measurements and predictions with regard to a selection of PhCs in wastewater
Mulot et al. [28]	The study reports the average MECs for 10 PhCs in the effluent of three French hospitals and the PECs for three PhCs with regard to only one hospital (evaluated on the basis of their corresponding daily – when available – or annual consumption data). It then compares PEC and MEC for these three compounds for 14 days, during three sampling campaigns. The study concludes with a comparison between measured and estimated load for the 10 compounds
Escher et al. [19]	This study consists of an evaluation of PEC and PEL for a wide spectrum of compounds emitted by a cantonal hospital and a psychiatric center in Switzerland in order to evaluate the ecotoxicological potential of the top 100 PhCs administered in the two health-care structures for different scenarios (raw hospital effluent, after dilution in the sewer with the urban effluent, and after a common biological treatment by activated sludge process with and without dilution due to mixing with urban wastewater). They assumed that all PhCs administered in the hospital would also be excreted there
McArdell et al. [29]	The authors carried out a comparison of predicted and measured loads in the effluent of a Swiss hospital (346 beds) with regard to the top 30 PhCs and, in particular, to ICM and cytostatics. An analysis was also carried out for disinfectants and metals consumed within the hospital and detected in the hospital effluent
Le Corre et al. [30]	Prediction of the concentrations of PhCs in a hospital effluent represents the first step in the consumption-based approach which is able (1) to assess the contribution of health-care structures to the WWTP influent load of PhCs and (2) to provide a list of critical compounds through the ratio between effect threshold (ET, depending on the acceptable daily intake of each PhC) and PEC for each compound (the so-called margin of exposure $MOE = ET/PEC$)
Coutu et al. [31]	The study deals with temporal (monthly) variability in consumption of nine antibiotics in the main hospital in Lausanne. These consumptions were then upscaled to all the hospitals located in Lausanne. PECs were evaluated for both hospital and urban settlement wastewater in order to assess the concentration at the entrance of the WWTP
Helwig et al. [32]	Within the European Pills Project, an analysis of the fluctuations in hospital consumption of selected PhCs was carried out, in particular with regard to weekdays and the weekend in psychiatric facilities and

(continued)

Table 1 (continued)

Ref	Main contents
	radiology departments, as well as the laundry effluent (if present). Moreover, a discussion of the annual PhC consumption in six different hospitals located in different countries is provided, with regard to their type and size
Herrmann et al. [15]	PEC and MEC were evaluated for a selection of six psychiatric drugs dispensed in a psychiatric hospital, a nursing home, and a general hospital in Germany. An analysis of the uncertainty in MECs is presented and discussed
Daouk et al. [33]	The study refers to the characterization of the effluent of the Geneva University Hospitals, in Switzerland, in terms of PEC and MEC for 15 PhCs. MECs were based on 24-h time proportional composite water samples; PECs were based on data regarding the annual consumption of the selected PhCs. Moreover, the daily load was also evaluated. In doing this, HWW flow rate was estimated by means of height measure in the pipe and the Kindsvater-Carter equation
Verlicchi and Zambello [34]	The authors compared PEC and MEC in a hospital effluent for 38 PhCs belonging to 11 different therapeutic classes. MECs are based on time proportional water sampling carried out in two different seasons (summer and winter). PECs are based on yearly consumption. Comparisons are reported with regard to the two seasons and the whole year
Klepiszewski et al. [35]	The authors provide an analysis of the importance of a priori accuracy checks in defining the sampling protocol in a PhC monitoring campaign in a hospital sewer

as well as in MEC and MEL. Compounds included in the current study are compiled in Table 2.

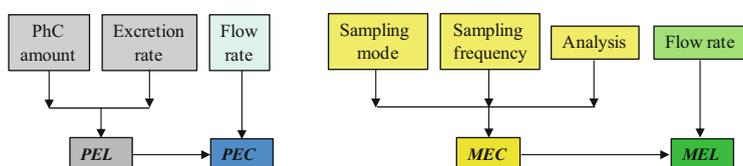
4 Model Parameters

According to Eq. (4), the parameters requested by the predictive model are PhC consumption data, PhC excretion factor and the wastewater volume generated within the health-care structure during the period of interest. Figure 1 shows the parameters necessary for the evaluation of PhC load and concentration (left) and their correlation, as well as the parameters that must be set in the case of direct measurement of PhC concentrations and loads (Fig. 1, right). Sampling mode includes continuous mode and discrete mode (namely, grab samples, composite samples based on time, volume or flow proportional mode).

The following paragraphs include a discussion regarding the parameters necessary to evaluate PEC and PEL.

Table 2 Compounds included in this chapter grouped according to their therapeutic class

Analgesics/anti-inflammatories	Acetaminophen, codeine, dexamethasone, diclofenac, ibuprofen, indomethacin, ketoprofen, mefenamic acid, metamizole
Anesthetic	Propofol, thiopental
Antibiotics	Amoxicillin, azithromycin, cefazolin, chloramphenicol, chlortetracycline, cilastatin, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, gatifloxacin, metronidazole, moxifloxacin, norfloxacin, ofloxacin, sulfadiazine, sulfamethoxazole, trimethoprim
Anti-diabetics	Glibenclamide
Antihypertensives	Enalapril, hydrochlorothiazide, lisinopril, valsartan
Antineoplastics or cytostatics	5-Fluorouracil, cyclophosphamide, cisplatin, carboplatin, doxorubicin, oxaliplatin, gemcitabine, ifosfamide, tamoxifen
Beta-agonists	Salbutamol
Beta-blockers	Atenolol, metoprolol, propranolol, sotalol, timolol
Contrast agents	Diatrizoate, iobitridol, iohexol, iomeprol, iopamidol, iopromide, ioxitalamic acid
Diuretics	Furosemide
Hormones	Progesterone
Lipid regulators	Atorvastatin, pravastatin
Psychiatric drugs	Amisulpride, carbamazepine, diazepam, doxepin, fluoxetine, gabapentin, levetiracetam, lorazepam, paroxetine, pregabalin, quetiapine
Rare metals	Gadolinium (Gd), platinum (Pt)
Receptor antagonists	Ranitidine

**Fig. 1** Main parameters defining predicted and measured concentrations and loads of PhCs

4.1 Consumption Data

The adopted models assume that an even and uniform consumption of each compound occurs over the whole observation period (year, month). Generally, consumption data are available on an annual basis, rarely per quarter, month or shorter periods.

Weissbrodt et al. [22] compared the average estimated consumption of some ICM and cytostatics in a hospital and the exact consumption referred to the observation period of 8 days. They found good agreement for ICM but an overestimation (4.5 times) for cytostatics with respect to the exact consumption. An analysis of the exact daily consumption of ICM highlights that higher consumption occurs on weekdays with respect to the weekend and, on Fridays in particular consumptions are the highest, as the radiology department operates at its highest capacity. During

weekends, only the emergency computer tomography applications are in operation, and the only ICMs used on those days are iomeprol and ioxitalamic acid.

Daouk et al. [33] analyzed the variability of the mean daily loads for a group of PhCs over a week and found that it is in the range of 50–150% of the mean value for compounds widely consumed on a regular basis (namely, acetaminophen, morphine, and ibuprofen). The fluctuations are more pronounced (up to 400%) for less administered PhCs such as diclofenac, mefenamic acid, gabapentin, and carbamazepine. Gadolinium (present in ICM) and platinum (in many cytostatics) exhibited high deviation from the average value during the weekend.

De Souza et al. [23] highlighted that the consumption of PhCs varies among the departments and wards within the structure. They found that in the investigated Brazilian hospital, the intensive care unit contributes more than 25% to the consumption of antibiotics, and monthly fluctuations from the average value are very small and limited to only a few months, whereas fluctuations are more frequent and more pronounced for the whole structure (whose percentage variation varies between -45% and $+27\%$).

Consumption patterns of the different therapeutic classes and of specific compounds have not been thoroughly investigated and results are not always comparable. de Souza et al. [23] reported the profile in terms of the number of units of antibiotics used in the Brazilian hospital and in intensive care units, whereas Coutu et al. [31] reported the monthly fluctuations of antibiotic sales for a hospital normalized to the annual mean.

Analysis of the consumption profiles over the year are available for the group of antibiotics, and for some specific active ingredients, namely, cefazolin and carbamazepine, for some case studies referring to the whole hospital. They are reported in Table 3 as the percentage variation with respect to the monthly average consumption.

Table 3 Percentage variation of the monthly consumption with respect to the average monthly value of some active pharmaceutical ingredients and the whole class of antibiotics

Month	Variation for antibiotics (%)	Variation for carbamazepine (%)	Variation for carbamazepine (%)	Variation for cefazolin (%)
January	3.9	-34	-0.61	-3
February	-12.2	87	-75	24
March	-7.0	-48		26
April	0	-20		-14
May	5.3	14	-66	-16
June	-8.9	-72	-0.61	-3
July	4.4	4	128	30
August	12.8	38	-65	-6
September	16.8	97	38	-36
October	2.7	7	3.53	-3
November	-19.9	-45	38	13
December	2.2	-27		-11
	[36]	[36]	[37]	[37]

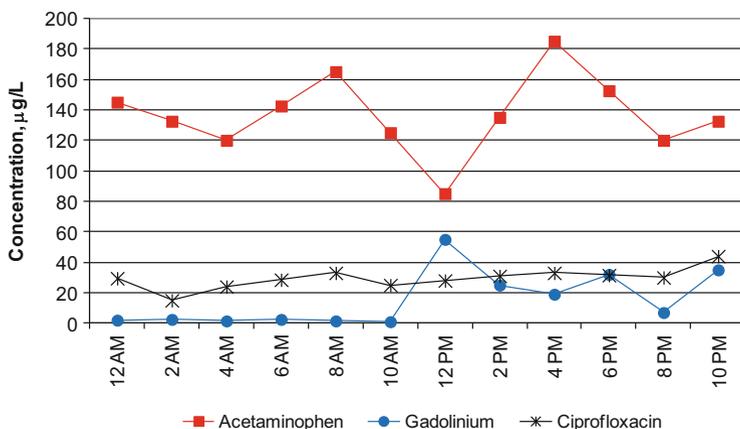


Fig. 2 Hourly fluctuations in concentrations of acetaminophen, gadolinium, and ciprofloxacin in hospital effluents. Data from [20, 39, 40]

Lenz et al. [38] highlighted no consistent difference in the consumption of the cancerostatic platinum compound CPC (namely, cisplatin, carboplatin, oxaliplatin, and 5-fluorouracil) over 18 months.

With regard to consumption in different years, Coutu et al. [31] reported a slight variation for most of the investigated antibiotics, whereas in the analysis carried out by Le Corre et al. [30], based on Australian hospitals, the year-to-year variability amounts from 22 to 44%, depending on the PhCs.

As discussed in Verlicchi and Zambello [34], consumption patterns in health-care structures differ from those observed in urban settlements. With regard to antibiotics, fluctuations are more evident in urban consumption, with typical seasonal peaks, while in hospitals fluctuations exist, but are less pronounced and in any case, they are site-specific. These considerations lead to the supposition that antibiotic use in hospitals is disconnected from nonhospital use, perhaps due to different protocols and the types of diseases treated with them.

It is difficult yet possible to obtain daily consumption patterns for some compounds. It is important to remember that PhCs are dispensed over the day to patients and the resulting concentration presents fluctuations over the day. Profiles of hourly variation of PhC concentrations (MEC) in a *typical day* are compound-specific and available only for a limited number of active ingredients. Figure 2 reports some of these with regard to hospital effluents. Profiles referring to other substances are reported and discussed in [2].

Weissbrodt et al. [22] report daily profiles for concentrations of some ICM and cytostatics, as well as for hospital effluent flow rates and highlights that the maximum concentrations do not always correspond to maximum load (concentration \times flow rate), and this must be kept in mind in order to have a representative sample in the case of MEC, or to decide when sampling to obtain the maximum occurrence (for environmental risk assessment) or to evaluate the daily load (hourly contributions may differ).

4.2 Excretion Factor

The excreted amount of a specific compound depends on many factors, mainly related to administration routes, human health and metabolism. This is confirmed by the different values reported in literature by many authors for each compound. With regard to the selection of substances considered in this study, the observed ranges are reported in Fig. 3.

In predicting concentrations of PhCs based on their consumption, the assumed value of excretion may greatly influence the resulting concentration, as remarked by Weissbrodt et al. [22]. Suggestions are available in literature – for instance,

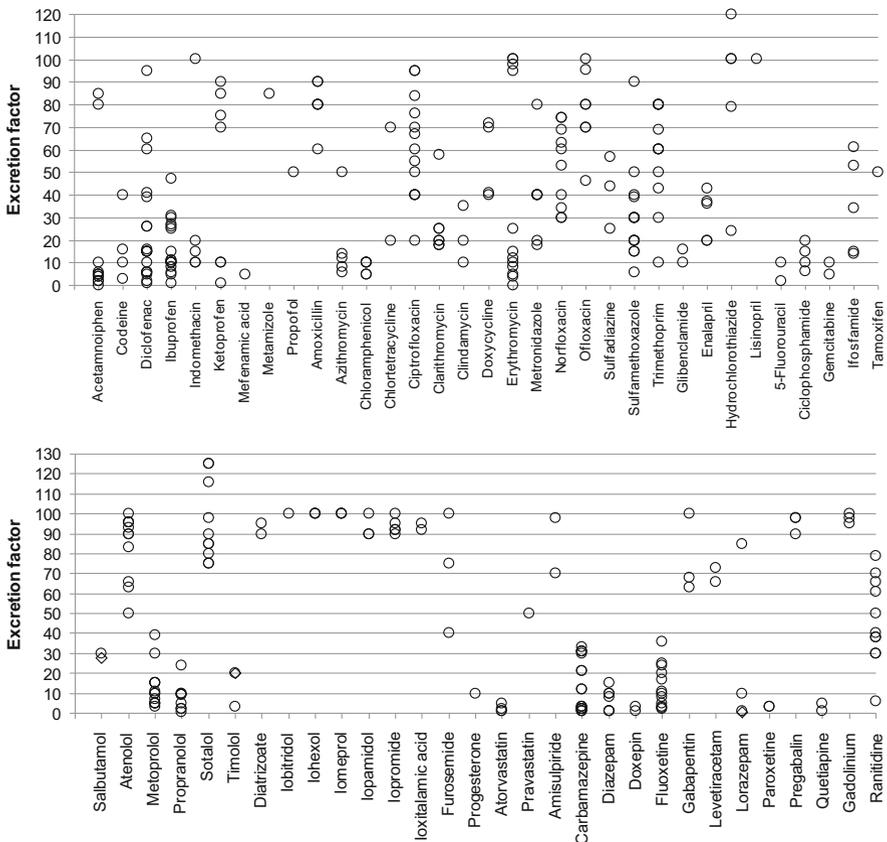


Fig. 3 Range of variability of the excretion factors reported in literature for the selected compounds. Data from: [2, 7, 10, 15, 17, 18, 22, 28, 31–33, 41–52; <http://www.bioagrimix.com/hacpp/html/tetracyclines.htm>; <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC90863>; <http://www.ncbi.nlm.nih.gov/pubmed/3557734>; <http://www.medsafe.govt.nz/profs/datasheet/Daoniltab.pdf>; <http://www.medsafe.govt.nz/profs/datasheet/b/Buventolinhalpwd.htm>; <http://dmd.aspetjournals.org/content/3/5/361>; <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1428960/pdf/brjclinpharm00307-0061.pdf>; www.torino.medica.it]

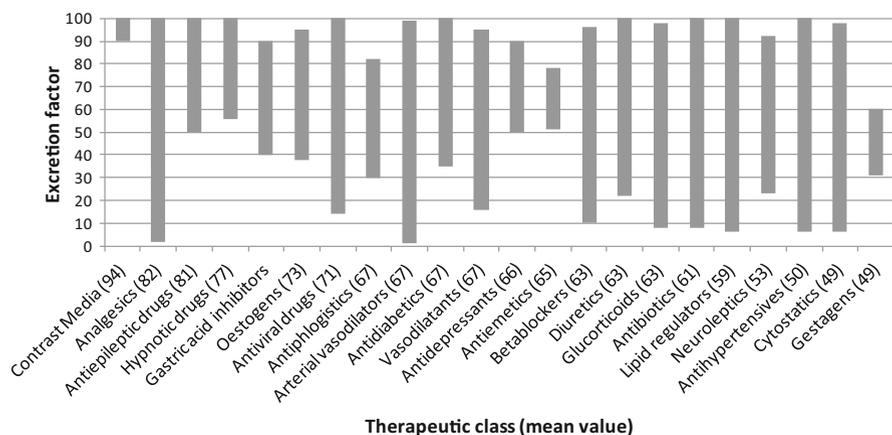


Fig. 4 Range of variability of percentage excretion factors for therapeutic classes. The number in brackets after each compound corresponds to the mean value based on collected data. Data from: [46]

Escher et al. [19] assumed an excretion of 75–100% for active ingredients being used as creams, since wash off from the skin is also a source of water contamination without undergoing metabolism in the human body. Lienert et al. [47] provide rules for evaluating excretion data in case of uncertainties and inconsistencies regarding the fraction excreted via urine and feces. Other researchers used the values they evaluated considering excretion of the parent compound in urine as well as feces, others assumed a literature value, without discussing the criteria used for its selection. In their investigation, Verlicchi and Zambello [34] assumed that the excretion factor was equal to the average value defined on the basis of a collection of literature data, with the intention of accounting for different scenarios in terms of formulation, administration route, metabolism and gender.

Lienert et al. [46] provided an interesting panorama of the variability ranges of excretion factor for some therapeutic classes, as well as the corresponding average values. In Fig. 4 the intervals are reported for 22 groups of compounds and the suggested average value is reported in brackets, after the name of the group.

It is worth noting that there are compounds, such as iodinated contrast media and cytostatics, that are largely excreted by human beings, but they are not completely released into the internal sewer network. In fact, most of them are administered to outpatients, who spend a period of time in hospital which is shorter than the typical excretion time. Weissbrodt et al. [22] found that only 49% for ICM and 5.5% for cytostatics are released in the hospital effluent.

4.3 Flow Rate Prediction

The hospital wastewater flow rate was evaluated based on hospital specific water consumption and hospital size (namely, number of beds) that is the water volume per bed per day. It is known that there is not a clear correlation between hospital size and water consumption [2], and that specific consumption is related to many factors, including water availability and geographical conditions. Values found worldwide are between 200 and 1,200 L/ (bed d), but generally those adopted vary between 400 and 800 L/ (bed d).

Authors have sometimes assumed a fraction of the estimated water consumption, which is generally 0.65–0.85 [53, 54].

Altin et al. [55] estimated water usage amounts for some hospitals in Turkey on the basis of the different kinds of user (personnel, beds, guests, laboratory, laundry and cafeteria). They found that this theoretical value was in good agreement with 80% of the average flow rate consumption resulting from 24-h flow measurements at different times for a medium-size hospital. They remarked that 20% of the consumed water was used for irrigation and cleaning.

In [34], the average daily flow rate results from a mass balance at the investigated hospital, considering water consumption (provided by the internal technical service), inlet contributions due to water bags used in surgery rooms, human excreta due to inpatients, outpatients, staff and visitors and also water losses due to an old water 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 pattern.

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. This concept is clearly shown in the graphs of Fig. 5, which refer to the daily flow rate measured in the Indonesian hospital (538 beds, 1,225 staff) investigated by [56] over three months (March, April and May).

It emerges that the percentage variation compared to the average daily flow rate ranged between -12% and $+13\%$. This could be explained by the fact that during the weekend, laboratory and diagnosis activities and outpatient presence within the hospital are reduced.

Consistent variations were also found with regard to the *monthly* flow rate over the whole year. Figure 6 refers to two medium-size Italian hospitals discussed in [34] where the flow rate was regularly measured and recorded at the end of each month for a whole year. The percentage variation varied between -41% and $+72\%$ with respect to the average monthly value. The highest flow values occurred during the hot season. It is also important to observe that although the investigated hospitals had a similar size, the profile of wastewater was different in the two structures.

An analysis of flow rate variation over the year will lead to the definition of an expected range of flow rate variability on an annual basis, for a general hospital. This will be useful in carrying out a sensitivity analysis of the prediction model.

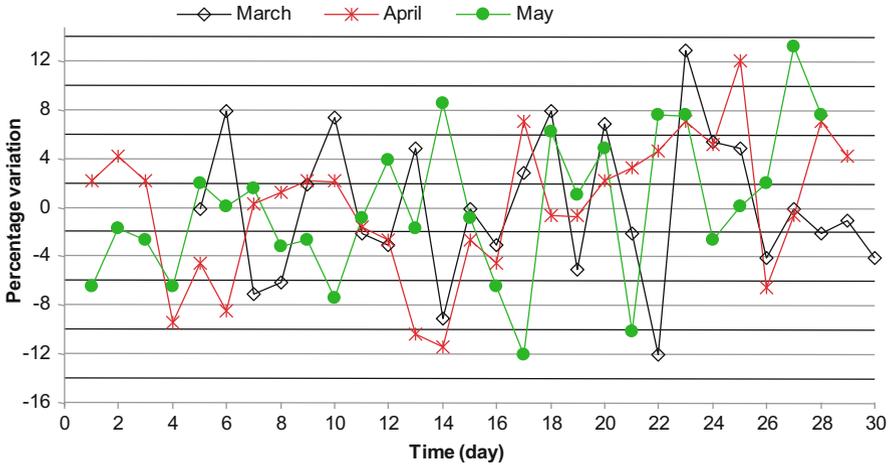


Fig. 5 Percentage variation of the daily flow rate over 3 months in an Indonesian hospital

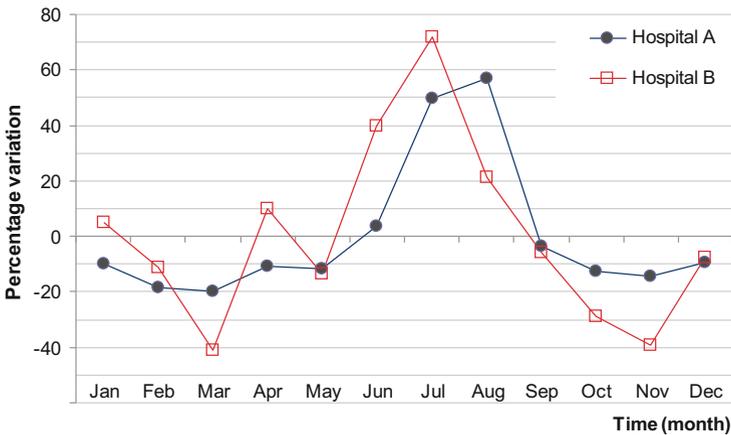


Fig. 6 Percentage variation of the monthly flow rate with respect to the monthly average value in two Italian hospitals: Hospital A: 450 beds, 9,407 m³/month. Hospital B: 400 beds, 9,960 m³/month

The analysis of the observed variation of the flow rate concludes with the analysis of the profiles of the percentage variation with respect to the hourly flow rate. Figure 7 refers to three profiles observed in medium-sized hospitals in a typical day. In France the hospital has 655 beds and an average hourly flow rate of 27.3 m³/h [1], in Mauritius the hospital has 535 beds and an average flow rate of 23.3 m³/h [57] and in Turkey, 324 beds with an average flow rate of 7.8 m³/h [55].

Due to these hourly variations, a (24-h) composite flow proportional water sampling mode is preferable with respect to grab samples, as in this way, analysis

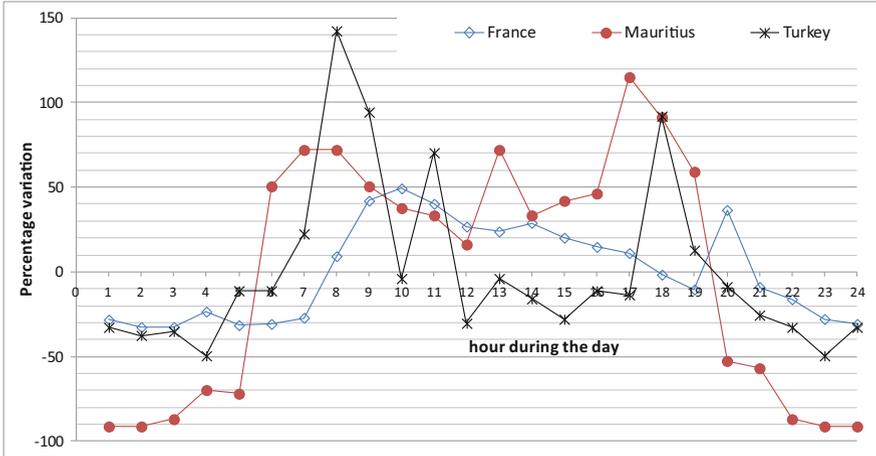


Fig. 7 Percentage variation of the hourly flow rate with respect to the average daily flow rate in three hospitals [1, 55, 57]

of the resulting water samples will weight variations both in occurrence and in flow rate and samples will be more representative of the real conditions (this will result in lower uncertainty, as discussed by [24, 27, 35]).

5 Comparison Between Measured and Predicted Concentrations and Loads

Table 1 briefly reports studies and investigations that have dealt with predicted and measured concentrations and loads for a selection of PhCs in hospital effluents. The data discussed in these studies are reported in Fig. 8 in terms of the ratio between PEC and MEC for each compound.

The accuracy evaluation criteria followed in this chapter is that proposed by Ort et al. [58] and already applied in Daouk et al. [33], Verlicchi et al. [51], and Verlicchi and Zambello [34]. It sets that:

- If $0.5 \leq \text{PEC}/\text{MEC} \leq 2$, then PEC is acceptable.
- If $\text{PEC}/\text{MEC} < 0.5$, then PEC is unacceptably low.
- If $\text{PEC}/\text{MEC} > 2$, then PEC is unacceptably high.

As remarked in Verlicchi and Zambello [34], although these criteria are labeled for accuracy evaluation, MECs are not considered a priori more accurate and reliable than PECs, or vice versa, and the criteria are applied to evaluate how different the results of the two approaches are.

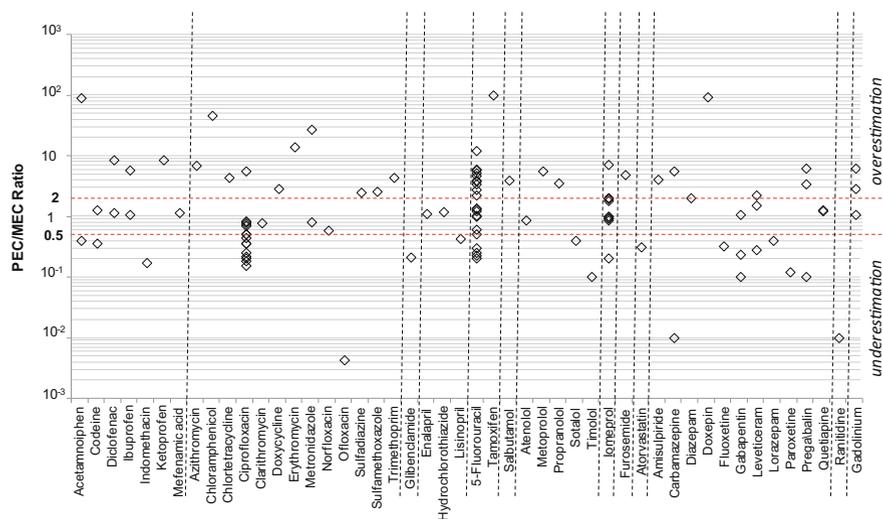


Fig. 8 Ratio between PEC and MEC for a selection of compounds grouped according to their therapeutic class. *Horizontal dotted lines* (corresponding to PEC/MEC equal to 0.5 and 2) define overestimation and underestimation regions as well as good accordance according to the criteria suggested by Ort et al. [58]. Data from: [15, 20, 21, 28, 33, 34]

An analysis of the dispersion of data in Fig. 8 in the three regions defined by the criteria shows that 32% of the data is in the acceptable interval and, for the remaining 64% of data, PEC is too high or too low.

The discussion reported in Sect. 4 regarding the choices necessary in order to define the parameters requested in PEC and PEL model application may be useful in explaining overestimation or underestimation with respect to the direct measures of concentrations. An in-depth analysis of the potential factors influencing the accuracy and reliability of PECs, PELs, MECs, and MELs will be carried out in Sects. 6 and 7.

A good level of accordance was found by [21, 38], who compared PEC and MEC for cytostatics in the effluent of the (only) oncologic inpatient treatment ward of the Vienna University Hospital (18 inpatients), considering minimal excretion rates for the investigated compounds ($E = 0.02$). In particular, Lenz et al. [38] provided MECs and PECs for a group of cytostatics, called cancerostatic platinum compounds (CPCs) including cisplatin, carboplatin, oxaliplatin, and 5-fluorouracil, whereas Mahnik et al. [21] mainly investigated 5-fluorouracil and doxorubicin (an anthracycline). This trend was confirmed by McArdell et al. [29], who compared MEL and PEL for cyclophosphamide in the effluent of the oncologic ward of a 346-bed hospital in Baden, Switzerland.

The same authors [29] investigated predicted and measured loads of a wider spectrum of compounds (the top 11 dispensed in the hospital in Baden) and also found good accordance for ICM in the effluent of the radiologic ward; for many of the most administered active ingredients, they found a ratio PEL/MEL of about

0.33. The loads of valsartan measured were 6 times higher than predicted, which was justified by the fact that other angiotensin receptor blockers may transform to valsartan and contribute to the load being higher than expected. Seasonal variations could also account for higher loads (predictions were based on annual consumption data of PhCs). PELs which were significantly higher than corresponding MELs were found for azithromycin (23 times), cilastatin (25 times), cyclophosphamide (7 times), dexamethasone (14 times) diclofenac (6 times), erythromycin (28 times), and thiopental (41 times). These discrepancies could be due to the fact that annual consumption figures are not representative for the measurement period (summer), as a seasonal fluctuation is expected for most of them.

With regard to cytostatics and ICM, consistent discrepancies were found between measured and predicted values by Weissbrodt et al. [22] who compared PEL and MEL in the effluent of a medium-sized hospital. These differences can be attributed to the fact that most of these compounds are administered to outpatients (70% for cytostatics and 50% for ICM) and therefore only a part of the dispensed amount is excreted within the hospital. Predicted values were in general much higher than measured ones.

Mullot et al. [28] compared MEL and PEL for a selection of compounds in three different French hospitals and found that the ratio between the average values of measured and predicted load was in the range 0.7–1.1 for atenolol, sulfamethoxazole, ciprofloxacin, 5-fluorouracil, and ketoprofen. For cyclophosphamide, the ratio was 0.67 and for propofol it was equal to 0.12.

The authors recognize that the evaluation of this ratio minimizes the fluctuations. In fact, if it is evaluated for a specific hospital, it varies in a wider range – for ifosfamide it becomes 0.30 and for iobitridol 2.1.

Ort et al. [24] remarked that pollutant loads are in general underestimated when flow and concentrations are positively correlated.

Discussion regarding discrepancies between predictions and direct measurements of PhC concentrations and loads has to consider different factors, depending both on the compound itself and the investigated point.

According to Mullot et al. [28], a strong correlation exists for PEC and MEC mainly for those compounds with short elimination half-lives and a weak human metabolism. For other PhCs, prediction of concentrations should also consider various parameters, including outpatient use, pharmacokinetic data, and molecule stability in wastewater.

The prevailing opinion is that predictive models could be extremely useful tools, but intrinsic uncertainties are unavoidable due to the necessary adoption of default or literature values, which should be carefully evaluated case by case in order to reduce the inaccuracy of the estimation. Direct measurements provide a snapshot of a particular situation and time of occurrence and load of PhCs. The main problem consists of evaluating how representative of the situation and time these values could be. As many factors affect PEC and MEC and PEL and MEL, an in-depth analysis was carried out discussing the specific characteristics.

6 Potential Factors Influencing PEC and PEL

6.1 *Inaccurate Estimation of PhC Consumption Within the Hospital*

PEC values are estimated on the basis of (annual) PhC consumption. This datum generally contains all the PhCs dispensed by the hospital structure to inpatients and outpatients.

In predicting PhC concentrations, the following factors should be kept in mind:

- PEC corresponds to an average value based on consumption and does not consider potential fluctuations of patients treated in the hospital over the year.
- 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).
- Inpatients may take their usual medicaments with them from home to the hospital when they are hospitalized. Therefore, these compounds are not considered in the hospital consumption data.
- Day-hospital patients staying in the hospital for only a few hours a day for analyses or therapy requiring specific agents, such as cytostatics, or diagnosis agents or outpatients do not totally excrete the administered compounds in the structure [19, 22, 28]. Escher et al. [19] underlined that a large quantity of PhCs are consumed within the hospital but excreted at home by outpatients. They stated that it is difficult to estimate the fraction released into the internal sewage. Weissbrodt et al. [22] found that only 49% of ICM and not more than 5.5% of cytostatics were excreted there, the remaining percentage was carried home. With regard to the effluent of the oncological ward investigated by Lenz et al. [38], it was found that only 27–34% of the total administered platinum (occurring in the dispensed cancerostatic platinum compounds CPC: cisplatin, carboplatin, and oxaliplatin), is excreted in the internal sewage network which can be explained by the short length of time spent in hospital in comparison to the biological half-life of CPC. Lower still is the percentage of the administered amount of 5-fluorouracil (0.5–4.5%) and doxorubicin (0.1–0.2%) released in the structure:
 - Lack of patient compliance may be of great importance – Bianchi et al. [59] found that for antipsychotics the mean adherence to therapy was 64%.
 - In addition, the hospital pharmacy provides PhCs to discharged patients or outpatients for starting or continuing their treatment at home. This is the case, for instance, for antineoplastics and psychiatric drugs [2, 59]. These substances are neither administered nor excreted in the hospital. Antivirals may be prescribed and delivered in the hospital but are likely to be excreted at home by outpatients [33].
 - 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 entire hospital consumption [60].

- Finally, pharmacy consumption data may differ from real consumption data due to lack of patient compliance, as well as due to outside consumption for leaving patients [61].

6.2 Variation in Consumption Over the Year

As highlighted in Sect. 4.1, there are classes of compounds with seasonal variability in consumption (for instance antibiotics), whereas for other classes fluctuations are not pronounced. Consumption data referring to the whole year does not provide information about the real consumption pattern. PEC and PEL will provide an average value on an annual basis.

6.3 Differences Between Pharmacy Consumption Data and Effective Administration

It should be noted that the consumption data in the hospital database correspond to the amounts supplied by the pharmacy to individual wards and not to the amounts effectively administered within each ward or department. Some unused drugs for inpatients may be collected on the wards and returned to the pharmacy for reuse or proper disposal. It is generally not hospital policy to discard drugs in the (solid or liquid) waste system, both for financial and environmental reasons. Hence, these drugs do not contribute to the load in the hospital effluent. Ort et al. [16] remarked that these amounts are generally very limited. Moreover, there could be a lag time between delivery to the ward and actual consumption.

6.4 Inaccuracy in the Excretion Factor Assumed for the Evaluation of PEC

The excretion factor varies according to the kind of formulation, as well as characteristics of the individual who assumed the PhC. The estimated value should consider the excretion data of a large set of individuals as the variations of a small number of patients are not significant.

As discussed in Sect. 4.2, for a given active ingredient, literature quite often provides ranges of excretion factors, resulting from different studies and investigations, showing the minimum-maximum observed range. In many cases, excretion factors refer to investigations carried out some decades ago [7, 45] and do not

consider that new generation PhCs (i.e., gatifloxacin and moxifloxacin) are designed to provide better therapeutic effects, improving the human absorption rate and, at the same time, reducing the excretion rate [62].

It is questionable whether it is still correct, from a scientific view point, to assume existing (and old) literature data for these compounds. This could lead to an overestimation of the predicted concentrations.

When adopting the excretion rate for a given compound, particular attention must be paid to the correct value as it may refer to the unchanged compound or to the corresponding metabolites [47]. If both are considered for the evaluation of the predicted concentrations, an overestimation will occur. Moreover, attention is required regarding the application mode of the active pharmaceutical ingredient, resulting in different excretion rates [17, 19].

In addition, another difficulty is to accurately evaluate the fraction of the sorbed drug which is eliminated unchanged during each of the subsequent days [28]. However, their selected PhCs are mainly polar and not subject to a significant adsorption on suspended matter.

Le Corre et al. [30] suggested considering the total excretion of each PhC to counterbalance other uncontrolled parameters (i.e., improper disposal or unused PhCs). In this way there could only be an overestimation and false negative results would be prevented.

With regard to application mode, Heberer and Feldmann [17] identified dermal application as the main source for the occurrence of diclofenac residues in the hospital effluent, as a low absorption rate is reported for this type of application. For this reason, high excretion values (75–100%) are generally recommended for creams and ointments but, paradoxically, this assumption could also lead to a high level of inaccuracy. A low recovery of these active ingredients could be found as they may be absorbed by clothes or bandages. If a laundry is present within the hospital, part of these compounds might be found in its effluent. If the laundry is not present, this contribution will not be accounted for.

A proper assumption of excretion factor should weigh the administered amount of each active ingredient by considering the contributions of application mode of the different formulations containing the same pharmaceutical.

6.5 Wastewater Flow Variations

The hospital effluent flow rate is often assumed equal to hospital water consumption [19, 33], sometimes as a fraction of water consumption: 65–85% [53], 75% [54], and 80% [55]. Verlicchi and Zambello [34] evaluated the hospital wastewater flow rate on the basis of a water balance at the investigated structure, taking into consideration potable water consumption and the contributions due to water bags used in surgery rooms, wastewater produced by staff, inpatients, outpatients and visitors, as well as estimated losses due to leakage in the old water distribution system within the structure. As discussed in Sect. 4.1, this flow rate presents hourly,

daily, and monthly fluctuations. Uncertainties in the estimation of flow rate may greatly affect the predictions. Moreover, it is important to consider that PEL is strictly correlated to flow rate as well as the dispensed amount of the selected PhC in the same period, and uncertainties depend on both factors, as discussed later.

6.6 Improper Disposal of Unused Medicines (in Household Waste or via the Toilet)

Improper disposal of unused medicines, i.e., by flushing them down the toilet or throwing them out with the household waste rather than returning them to the internal pharmacy will also affect prediction accuracy [34]. In the case of a hospital, this factor could be of minor importance compared to investigations carried out for urban wastewater, as the disposal of medicaments is managed by the personnel of the structure, who should return the waste PhCs to an authorized supplier or reverse distributor.

For registered entities such as hospitals, there are no clear guidelines for the disposal of PhCs in the USA [63], but any such disposal must be done in accordance with local environmental regulations. Usually, the US Drug Enforcement Administration (DEA) may dispose of controlled substances by returning them to the manufacturer, by transferring them to a reverse distributor, or by destroying them using a procedure specified by federal regulation (to date, no such procedures exist). Authors remarked that liquids are more frequently discharged than those dispensed in tablet form. In particular, they found that 50% of dispensed acetaminophen and codeine were wasted in the analyzed academic center hospital.

6.7 Biodegradation/Biotransformation or Adsorption Processes Occurring in the Sewage System Before the Sampling Point

Within the internal sewer system, PhCs occurring in the wastewater may be subjected to a biodegradation process, as remarked by Weissbrodt et al. [22] with regard to cytostatics.

According to Lai et al. [27] the effect of biodegradation should be considered more or less constant within a given sewer system and over a short sampling period (i.e., days) and that inter-day variability should be negligible. This may not hold true when data among different locations or within a location over a longer time span (i.e., year, seasonal effects) are compared.

Compounds with a high sorption potential, like azithromycin, may be affected by desorption processes as they may sorb onto sludge and particles present in the

sewer and can also be released at a later time depending on environmental conditions [51].

7 Factors Affecting MEC and MEL

7.1 Sampling Protocols

A PhC mainly reaches the internal hospital sewer through toilet flushes. Not all the toilet flushes may contain the dispensed active ingredients. This depends on the human metabolism and, in particular, on the half-life of the compound. It could be assumed that in a day there are 5 toilet flushes for each individual staying within the structure all day. Real short-term variations, expected and observed in a sewer, will depend on the total number of toilet flushes containing the compound of interest discharging into the sewage network. As a consequence, the occurrence of PhCs may vary greatly throughout the day, exhibiting the so-called short-term variations, and therefore it is crucial to plan and adopt a proper sampling protocol, namely, sampling frequency and mode, which is able to provide *representative* wastewater samples for the specific compound [24, 64].

Researchers may choose between different sampling *modes*: they may collect grab samples from one side and time, flow, or volume proportional composite water samples from the other side. Generally, automatic sampler devices are used to collect a number of discrete samples over a 24 h period. According to Ort et al. [24] the continuous flow proportional sampling mode is the most accurate (true and precise) sampling mode for loads of dissolved compounds.

Depending on the dynamic of a PhC in the sewer, the adoption of a specific sampling protocol will lead to different levels of uncertainty. In the study by Ort et al. [24], an in-depth analysis and comparison of the resulting sampling uncertainties are carried out with regard to three active ingredients presenting very different behavior: ranitidine, carbamazepine, and iopromide. The main results are that sampling errors increase with a decreasing number of wastewater pulses per day (i.e., toilet flushes containing the specific compound under study) containing the compound of interest and also with decreasing sampling frequency.

Selection of the most appropriate sampling *frequency* is discussed in Ort and Gujer [26] in order to contain sampling errors. Moreover, in Ort et al. [24, 25] a method for evaluating sampling uncertainties is presented through the discussion of some case studies, referring to compounds of different behavior (gadolinium, ranitidine, iopromide, and carbamazepine). The method is based on sewer type (gravity or pressurized, separate, or combined) and wastewater packets of the compound of interest. The latter parameter considers the number of total pulses reaching the sewer based on the PhC administered amount and daily defined dose and total number of toilet flushes. Examples of applications of this theory are available in [34, 51, 65, 66].

Suggestions for the selection of an accurate sampling protocol resulting in representative water samples and “quite accurate” MECs are provided in [24, 25].

When sampling we can find real variation (due to the pattern consumption of PPCPs) and additional variation due to analytical error (including transport preservation, storage, preparation, and instrumental errors). This uncertainty may become a dominant source of error if not managed.

A continuous flow proportional sampling mode is conceptually the most accurate (true and precise) sampling mode when sampling for loads of dissolved compounds [16, 24]. However, it is not always economically and technically sustainable. It is sometimes recommended to plan sampling periods over several weeks, as done in [17, 21].

To reduce the uncertainties, a precautionary high sampling frequency (<5 min) is recommended by Ort et al. [24, 25] if the dynamics for the substances of interest are not well known or not properly assessed, or to take into account different composite sampling modes, considering that the choice is highly dependent on the site-specific boundary conditions.

For the compounds that have great variation throughout the year, it is very important to decide the most adequate sampling campaign. Measuring only in one season may imply an over- or underestimation of the yearly load. In calculating PEC, the consumption should be considered on a monthly basis for compounds that have a strong seasonal variation.

For estimating the environmental risk posed by PhCs in water, a grab sample in the hour of maximum discharge may be a better choice, since acute toxicological aspects are not only related to the load and even the maximum concentration must be considered. Ort et al. [24, 25] have discussed the main aspects to be considered to ensure the reliability of the measured data and reduce relative uncertainty.

7.2 Analytical Errors

Instrumental and human errors should be considered when calculating the uncertainties related to chemical analysis. These kinds of errors may cause high uncertainties, especially for those compounds detected at very low concentrations (some ng/L) [34, 51]. Johnson et al. [64] measured different subsamples of the same sample in different laboratories, reporting that the PhC concentrations did not guarantee accurate results with these compounds as the standard deviation ranged up to 60%.

With regard to analytical methods, it should be underlined that they only analyze the compound dissolved in the water phase. For the compounds with high sorption potential, a fraction might have sorbed to suspended solids phase and consequently is not analyzed in the water samples.

7.3 *Sewer Layout and Fluctuation of the Concentration Throughout the Day and the Week*

In planning a monitoring campaign, it is essential to obtain data on the sewer type and layout (gravity or in pressure, combined or separate, potential infiltration contributions, network framework) and also to be aware of the potential fluctuations of the different PhCs throughout the day [24, 25]. In fact, for some compounds (namely, Gd, contract media, cytostatics, and Pt), MECs remain quite low during the night and exhibit several peaks in the morning as well as in the afternoon, following different consumption and excretion patterns [20, 22]. Interesting analyses are reported in [21] with regard to the dynamic of concentrations of 5-fluorouracil in a week, [28] referring to iomeprol, 5-fluorouracil, and ciprofloxacin over 14 days, and [22] with regard to ICM and cytostatics over the day and a week.

These discrepancies with respect to the corresponding daily average value confirm that analytical investigations on PhCs must be performed on 24-h composite water samples in order to measure the average concentrations for the different compounds which would better represent the potential impact of the hospital wastewater [2].

7.4 *Flow Rate Measurement*

In order to estimate hospital flow rate, Daouk et al. [33] measured the water height in the sewer pipe (by means of a sharp-crested rectangular weir and an ultrasonic flow meter device upstream of the weir) every 2 min (accuracy checking every 2 weeks) and evaluated flow rate on the basis of the Kindsvater-Carter equation [67]:

$$Q = C_e \frac{2}{3} \sqrt{2g} b_e (h_e)^{1.5} \quad (9)$$

where Q is the discharge (m^3/s), C_e the discharge coefficient ($\text{m}^{0.5}/\text{s}$), g is the gravity acceleration (m/s^2), b_e is the effective width (m), and h_e is the effective height (m).

Heberer and Feldmann [17] continuously measured flow rate using a flow meter device calibrated with a magnetic inductive flow meter. Weissbrodt et al. [22] and Ort et al. [16] routinely measured the flow rate at a high temporal resolution during the test phase. Verlicchi and Zambello [34] instead evaluated the daily flow rate by means of a mass balance, as described in Sect. 6.5.

7.5 *Degradation Processes During Sampling and Transportation*

As highlighted in Sect. 6.7, biodegradation and biotransformation may occur within the discharge point and the sampling point, as well as during the transportation of the withdrawn samples. In the latter case there could also be photodegradation processes leading to a lower MEC.

8 **Uncertainties in Predicted and Measured Concentrations and Loads**

Both predicted and measured concentrations and loads are affected by unavoidable uncertainties due to intrinsic fluctuations of the parameters discussed above (Sects. 6 and 7).

8.1 *Uncertainties in Concentration and Load Predictions*

The magnitude of uncertainty in PEL and PEC was determined by literature (excretion factor), by internal staff (flow rate), or a combination of both approaches (PhC consumption).

Uncertainty in flow rate – Lai et al. [27] assumed a conservative uncertainty estimate equal to $\pm 20\%$ in the case of a gravity sewer network, appearing reasonable on the basis of other studies (among them [68]).

Verlicchi and Zambello [34] assumed a wider range of variability for the hospital flow rate (between -51% and $+81\%$) resulting from literature data (regarding specific hospital flow rates in two medium-size hospitals and throughout the year, as well as weekdays and weekends).

Uncertainty in excretion factor – The assumed uncertainty is compound-specific and very different ranges were found for different PhCs, as remarked by Herrmann et al. [15] who set $\pm 100\%$ for doxepin and quetiapine and $\pm 4\%$ for pregabalin and Verlicchi and Zambello [34] who considered 38 compounds belonging to different therapeutic classes. The ranges they reported are extremely different, starting from $\pm 3\%$ for salbutamol and arriving at ± 99 for lorazepam.

Uncertainty in PhC consumption – Verlicchi and Zambello [34] found a modest uncertainty for analgesics and anti-inflammatories ($\pm 15\%$), a slightly higher uncertainty for antibiotics (-36 to $+30\%$), and much higher uncertainty for carbamazepine (-75 to $+120\%$). For compounds whose fluctuations were not clear, a default uncertainty range was assumed equal to $\pm 50\%$.

With regard to the neurological drugs investigated by Herrmann et al. [15] in psychiatric hospitals and nursing homes, very different uncertainty ranges were

found for the same compound in different structures. This underlines the importance of carrying out site-specific studies and being careful when considering results obtained in other investigations or referring to different health-care structures to be valid.

On the basis of the reported sensitivity analysis of adopted models for PEC and PEL, it emerges that E always has a great influence on PEC and PEL values for most compounds. In addition, in Verlicchi and Zambello [34], wastewater flow rate has a more consistent influence than drug consumption, whereas in Herrmann et al. [15] the consumption amount highly influences the results. Unfortunately, consumption patterns are scarce and only available for a few compounds, mainly 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.

8.2 *Uncertainties in Concentration and Load Measurements*

The evaluation of the total uncertainty in MELs and MECs is carried out using Eq. (9):

$$U_{\text{total}} = \sqrt{U_{\text{Sampling}}^2 + U_{\text{Analysis}}^2 + U_{\text{Flow rate}}^2} \quad (10)$$

which considers the contributions due to sampling, chemical analysis and flow rate measurement (the latter parameter has to be considered only for uncertainty in MEL, as remarked in Fig. 1).

Sampling Uncertainties These are often correlated with toilet flushes and the adopted average sampling interval as suggested by [24, 25]. To have an idea of how toilet flushes may influence sampling uncertainty, the evaluation made by Weissbrodt et al. [22] in the case of an average sampling interval of 8 min and different toilet flushes could be useful:

- In the case of 1 or 2 toilet flushes (this is the case of a patient who received the treatment in the hospital and then excreted part of the administered PhC also at home), a sampling uncertainty between -100% and $+130\%$ was evaluated.
- For 18 flushes (corresponding to 2–5 patients per day with 4.5 toilet flushes per patient) the sampling uncertainty is $\pm 50\%$.
- In the case of 50 toilet flushes, the uncertainty reduces to $\pm 30\%$.

A continuous flow proportional sampling will result in the lowest uncertainty interval (theoretically equal to 0%). Kovalova et al. [69] adopted continuous flow proportional sampling and sampling was synchronized with the real-time potable water consumption at the investigated hospital and assumed U_{sampling} equal to

0. Although Lai et al. [27] adopted a continuous flow proportional mode for their 24-h composite wastewater samples, they assumed an uncertainty of 5% to account for unknown or unforeseen uncertainties.

This sampling protocol is time and money consuming. Different sampling modes (time proportional and grab samples) as well as frequency (discrete samples over a day) may be selected, but the associated sampling uncertainties may consistently increase. An estimation of the increment in the uncertainty ranges is provided in the supplementary data by [24].

Weissbrodt et al. [22] adopted a flow proportional composite water sampling mode and estimated a sampling uncertainty equal to 30–40% for the most administered ICMs (iomeprol, iohexol and ioxitalamic acid) and between 120 and 130% for the investigated cytostatics 5-fluorouracil and gemcitabine. This higher value was explained by the authors with the fact that there is a high chance that toilet flushes containing cytostatics are missed during the sampling.

The sampling uncertainty evaluated by Verlicchi and Zambello [34] in their investigations based on 24-h time proportional hospital effluent sampling varies from 25% to over 100%, depending on the compound (its related consumption amount and expected toilet flushes).

Chemical Analysis Uncertainty due to chemical analysis was estimated from the relative recoveries, intraday instrumental precision, and other uncertainty factors (see Eq. 11), as discussed in [27, 51, 65, 69].

$$U_{\text{Analysis}} = \sqrt{U_{\text{recovery}}^2 + U_{\text{precision}}^2 + U_{\text{other}}^2} \quad (11)$$

In the investigations by Ort et al. [16] uncertainties due to analysis were estimated equal to 20% for all compounds, in Herrmann et al. [15] U_{Analysis} was evaluated between 5 and 24% for neurological drugs, and in Verlicchi and Zambello [34], it varied between 4 and 16% for all 38 compounds. In Kovalova et al. [69] for 35% of the investigated compounds it was estimated less than 14%, for 32% between 15 and 29%, for 25% between 30 and 100%, and for the remaining 7% greater than 100%.

Uncertainty in Flow Rate Flows in completely filled pressurized pipes may be measured in more accurate way than flows in a gravity sewer. Ort et al. [16] assumed an uncertainty for flow rate measurement of 6% in the case of pressurized pipes, whereas Lai et al. [27] assumed a conservative uncertainty estimate equal to 20%, appearing reasonable on the basis of other studies (i.e., [68]) and considering the gravity flow.

More accurate evaluations were carried out by Daouk et al. [33], whose measurement methods were described in Sect. 7.4 and who assumed an uncertainty equal to 5%.

Le Corre et al. [30] assumed an uncertainty of 50% to account for the seasonal or day-to-day variability of dry weather wastewater volumes and flow measurement

errors. Herrmann et al. [15] evaluated a maximum uncertainty interval in flow rate equal to -19% and $+14\%$. Finally, Verlicchi and Zambello [34] assume a wider range of variability for the hospital flow rate (between -51% and $+81\%$) resulting from literature data (regarding specific hospital flow rates in two medium-size hospitals and throughout the year as well as on weekdays and at the weekend).

An analysis of the different contributes appearing in Eq. (9) highlights that the parameter which contributes the most to the total uncertainty for MEC is the sampling mode, with only a few exceptions. If a flow proportional sampling mode was adopted, the sampling uncertainty would be at the 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%.

9 Conclusions and Perspectives

The analysis carried out above has highlighted that each strategy (prediction models and direct measurements) presents strengths and weaknesses. The advantage of one approach is often the disadvantage of the other, so it is recommended to use them both in a complementary manner.

The use of PECs is advised to reduce the cost of sampling campaigns, which are however necessary when greater precision is required. The predicted approach can be used with some confidence for substances where no analytical method exists to experimentally determine concentrations and loads or where the limit of quantification is not low enough [24], in situations where it would be hard to sample wastewater due to complex and inaccessible sewer systems around the hospital, and, finally, in cases where the collection of representative samples is impossible [24, 30].

The PEC approach could be useful in the phase of identifying priority compounds and during an initial attempt to assess environmental risk with regard to the effluent of the whole health-care structure or of a specific wing [23]. It is worth noting that predicted data do not identify strong fluctuations and, instead, result in average values [32].

Only predicted models could be used to assess new marketed PhCs, whereas MECs can only be used for the risk management of substances that are already marketed. For estimating environmental risk, a grab sample in the hour of maximum discharge may be a better choice, as acute toxicological aspects are not only related to load, and even the maximum concentration must be considered.

To sum up, citing the words by [70], it should be noted that:

- Great efforts have been made in assessing the occurrence of PhCs in hospital effluents (*known known*).
- More needs to be done (*unknown known*), as for some compounds analytical methods are not yet available or not yet validated.
- Future efforts are required to improve our knowledge (*unknown unknown*).

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