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# Determining the fraction of pharmaceutical residues in wastewater originating from a hospital

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ABSTRACT

Pharmaceutical residues in water are frequently analysed and discussed in connection with sewage treatment, ecotoxicity and, natural and drinking water quality. Among different localities hospitals are suspected, or implied, to be a major and highly variable source of pharmaceuticals that substantially contribute to the total wastewater load. In this study, the contribution of pharmaceuticals from a hospital to a sewage treatment plant (STP) serving around 45,000 inhabitants was evaluated. Approximately 200 hospital beds result in a hospital bed density of 4.4 beds per 1000 inhabitants, which is a typical value for developed world countries. Prior to sampling, a sound systems analysis was performed, and a sophisticated continuous flow-proportional sampling regime was applied. Hence, overall experimental uncertainty was reduced to a minimum, and measurements provide clear evidence that, for 28 of 59 investigated substances, over 85% of the pharmaceutical residue loads do not originate from the hospital when applying a conservative error estimation. Only for 2 substances, trimethoprim (18%) and roxithromycin (56%), was the maximum observed contribution of the hospital >15%. On average, the contribution of the hospital for the compounds detected in both, hospital effluent and sewage treatment plant influent was small and fairly constant. Five compounds were only detected in hospital wastewater, and 24 neither in the hospital wastewater nor in the total wastewater at the influent of the STP. For these compounds no experimental contribution could be calculated. For the compounds where audit data for both the national consumption and the specific hospital under investigation were available, a prediction of the fraction of pharmaceuticals originating from the hospital was performed. Three quarters of the compounds, classified with the existing audit data, were in the same "hospital contribution category" as determined by measurements. For most of the other compounds, plausible reasons could be identified to explain the observed deviations.

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## 1. Introduction

### 1.1. Brief overview

Hospital wastewater (HWW) is normally discharged directly, without pre-treatment, to sewers. Despite mostly being only a small fraction of the total wastewater volume in the influent of a sewage treatment plant (STP), HWW has gained increasing scientific and public attention in the last decade. This is, in part due to the observation and expectation that HWW is a source for undesirable constituents, such as (multi-)antibiotic-resistant bacteria (Baquero et al., 2008; Kummerer, 2004). In other

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publications, the emission from hospitals was estimated for antibiotics, anaesthetics, disinfectants, heavy metals, AOX (Adsorbable Organic Halogens), iodised X-ray contrast media and cytostatic agents (e.g. Kummerer, 2001). The latter were also investigated in detail by Lenz et al. (2007). Furthermore, a number of toxicity assays were performed (Boillot et al., 2008; Ferk et al., 2009; Hartmann et al., 1998). As a result, it has been suggested in some studies that pre-treatment of HWW prior to discharge into the sewers provides a reasonable solution (Gautam et al., 2007; Lenz et al., 2007; Pauwels and Verstraete, 2006). However, this view is not unanimously supported. The separate treatment of HWW to reduce the development of resistant bacteria was questioned (Kummerer, 2009): the substantial amount of antibiotics used outside of hospitals (in Germany more than 75%) seems to be a plausible reason that resistant bacteria are also abundant in wastewater not receiving any HWW. Additionally, Boillot et al. (2008) found quantitatively far fewer microorganisms in the effluents of hospitals than in urban wastewaters which is consistent with other studies. With regard to pharmaceuticals, Lenz et al. (2007) report that 1) for some pharmaceuticals merely a small fraction of the amounts administered in the hospital were actually found in its effluent (i.e. 0.1–0.2% for doxorubicin, 0.5–4.5% for 5-fluorouracil and 27–34% for total platinum) and 2) a complete onsite wastewater treatment process is needed to significantly remove targeted pharmaceuticals. This includes full physical and biological treatment steps, not only advanced processes. Capturing all sources within a hospital (wards, laboratories) may be further complicated by the fact that different facilities discharge through different pipes to the common sewer. This particularly holds true for large existing hospital complexes.

Therefore, local circumstances need to be considered and the contribution of an individual hospital needs to be assessed in relation to the total load in a STP catchment. To our knowledge, only a few publications explicitly quantify pharmaceutical residues (subsequently referred to as 'pharmaceuticals') excreted within hospitals compared to the total pharmaceutical load in the corresponding STP influents (Feldmann et al., 2008; Heberer and Feldmann, 2005; Thomas et al., 2007). However, these studies are limited to a small number of pharmaceuticals, or make an assumption on the water flow instead of measuring the wastewater flow onsite to determine actual loads.

In view of the local situation in South East Queensland where it is proposed to recycle wastewater for indirect potable reuse, it is sensible to consider whether pre-treatment of HWW will provide a significant benefit. From two previous research papers relevant for the region of interest also dealing with pharmaceuticals the contribution of hospitals cannot be derived (Khan and Ongerth, 2004; Watkinson et al., 2009).

Therefore, the goal of our study is to determine accurately the contribution of a hospital to the total pharmaceutical load found at the inlet of the corresponding STP by means of measurements. Additionally, this experimentally data obtained from a limited time period is then compared with readily available audit data. It shall be assessed whether the contribution of a hospital can be predicted reliably without any additional administrative effort, i.e. without extra surveys on the hospital wards for day-specific consumptions. If measurements matched with the prediction, the same kind (comprehensiveness and quality) of information can be used at other locations to make a prediction, a priori without laborious measurements.

The focus of this research is on dissolved pollutants which cannot be eliminated in conventional wastewater treatment. Pollutants showing poor to moderate biological removal need to be transformed by chemical reactions (e.g. oxidation) or separated by physical processes (e.g. adsorption onto activated carbon).

### 1.2. *Systems analysis*

The prediction and experimental quantification of pharmaceutical mass fluxes in the wastewater of a specific STP catchment are laborious. A sound understanding of the whole system is required prior to setting up a predictive model, and performing a confirmative sampling campaign. This particularly holds true when attempting to attribute different fractions to a multitude of individual sources, for example if there are several hospitals and multiple smaller health care facilities in a catchment. Due to the lack of generally accessible consumption data at sufficiently high spatial and temporal resolution, models often provide only a prediction of an average load. Additionally, the latter is prone to uncertainty due to varying transformations of pharmaceuticals during human metabolism.

While it would be ideal to have a list of all health care facilities with size, services provided and precise pharmaceutical consumption, just obtaining generally available consumption data is a tedious task in itself. The ''institutional resolution'' is often not sufficient without additional administrative effort, i.e. temporary surveys of the wards in the hospital(s) under investigation (Feldmann et al., 2008; Kummerer, 2001). Furthermore, the (average) household pharmaceutical consumption needs to be estimated from national or state-wide sales and/or prescription data if regional data is not available.

Moreover, collecting representative samples requires a thorough knowledge of the sewer layout and awareness of potentially highly variable concentrations and loads in the course of a day. Clearly, accurate chemical analysis of a non-representative sample is not adequate to characterise a real full-scale system.

### 1.3. *Sampling issues*

Accurately quantifying pharmaceutical loads in hospital effluents or sewers close to any source (sub-catchments, households or industry) is a demanding undertaking. It requires a substantial experimental effort and is still prone to uncertainties. The latter are extremely hard to quantify if sampling is carried out with conventional (unsophisticated) devices, i.e. auto-samplers operated in a discrete sampling mode with (too) long time intervals, or grab samples. Rarely are fluctuations of concentrations and loads assessed in separate experiments at high temporal resolution prior to the ''real'' measuring campaigns. These pre-experiments are very expensive and may not provide the data to answer the actual research question. However, if the applied sampling protocol does not result in the collection of a representative sample, then the care taken in the following

processes of transport, storage, preparation and chemical analyses with a sophisticated method cannot make up for this deficiency (de Gruijter et al., 2006). Subsequent (even sophisticated) statistical analyses of non-representative samples are unreliable and the resulting conclusions will therefore be of limited value. In some cases, the large variation observed in previous studies may not be "true natural variation" but instead, may simply be an artefact caused by inadequate sampling (Ort et al., in preparation).

Therefore, strong emphasis has been put on obtaining representative samples for this study. In Ort and Gujer (2006) a method was presented to estimate the required sampling frequency in order to not exceed a certain sampling error. In gravity sewers this results in fairly short time intervals if the substance of interest is contained in a small number of "wastewater pulses" per day (e.g. toilet flushes containing a specific excreted pharmaceutically active compound). Sampling frequencies that are too low result in large sampling uncertainties, especially in the case of only a few patients per day (Weissbrodt et al., 2009). The often claimed problem of "limited storage capacity in an auto-sampler" can be easily solved by replacing the glass bottles more than once per day. This may be more laborious, but it is a much better solution than using a time-proportional sampling mode, which does not take samples weighted according to the flow in the sewer. In contrast, physical boundary conditions such as deep sewers resulting in long dead times for purging the sampling hose or limited access to pressurised sewers are more difficult to overcome.

## 2. Material and methods

### 2.1. Sewage treatment plant and catchment characteristics

A total of approximately 45,000 inhabitants in two geographically separated sub-catchments, Morayfield and Caboolture, are connected to the South Caboolture STP (subsequently only referred to as STP) which is operated with two sequencing batch reactors (SBRs). It treats a daily dry weather flow of approximately 10,000 $m^3$. During long dry periods with high level water restrictions, this value can drop to 7500 $m^3\ day^{-1}$.

Morayfield is drained by gravity sewers and contributes two thirds of the total wastewater. It is only pumped once, at the STP itself. Caboolture makes up for one third of the total influent and is a largely pressurised sewer system with numerous pumping stations. At specific times of the day the flow is diverted at the influent of the STP and stored in two large buffer tanks (800 $m^3$ each) before being pumped to the SBRs. This combination of sewers and the complex influent layout of the STP results in very high hydraulic fluctuations (see Fig. 1). Hours with almost zero flow contrast with hours around 250–300 $L\ s^{-1}$ and in between, the flow varies rapidly and significantly. During wet weather the relative flow variations are less significant due to higher base flow.

### 2.2. Hospital characteristics

Caboolture Public Hospital has 190 beds and offers all services of a modern regional hospital (listed in Table SI 1, see supporting information). A small private hospital providing mainly day surgery (only around 10 beds) and a small dental surgery also drain into the same sewer. The wastewater from the private hospital cannot be accessed separately. Other small health care facilities within this sewer catchment make consultations to out-patients, and therefore, the wastewater from these facilities are not expected to significantly add to the pharmaceutical load of the STP. The hospital bed density for the whole STP catchment is 4.4 beds per 1000 inhabitants. All HWW is collected in a sewage pumping station (SPS CT-51, subsequently referred to as SPS) before being pumped to the primary rising main. There is no residential wastewater contributing to this SPS and the hydraulic residence time in the main sewer to the STP is approximately 30 min to 1 h (hydraulic calculations provided by the Regional Council for the decisive time in the morning when samples at the SPS and the STP needed to be coordinated). The average daily volume during dry periods pumped at the SPS is approximately 75 $m^3$ which is 1% of the total wastewater volume discharged to the STP. The occupancy of hospital beds in Caboolture during the sampling period was close to 100% which is representative for the year to date average.

Unfortunately no comprehensive database exists with regard to other health care facilities in the catchment of the STP. Hence, an internet search was performed. Four aged care facilities with a total capacity of 443 beds were found (297 high care and 146 low care) with an unknown occupancy rate. Furthermore, a total of 14 addresses for doctors plus 12 dentists were found. If mass fluxes at the influent of the STP were significantly higher than expected from average national consumption and hospital usage, further investigations of these facilities would be warranted.

### 2.3. Sampling

Continuous flow-proportional sampling modes were applied in this study to minimise sampling error. Continuously diverting a small flow-proportional side stream is conceptually the best solution to obtain representative samples for dissolved compounds. However, low velocities in the side stream prevent proper sampling of solids and long-term operation may lead to biofilm growth. Due to the limited time of sampling biofilm growth is not considered problematic in this instance.

Sampling over consecutive days was preferred to the alternative option of collecting samples on single days distributed over a longer period. This drastically reduces the effect of unknown system behaviour: missing a "decisive" HWW packet at the STP is then limited to the first hour of the first day and the last hour of the last day. All other water packets are captured, although they might be attributed to the STP sample a day later. However, this would merely lead to higher variability of the hospital's contribution and not to a non-quantifiable effect.

#### 2.3.1. Sampling protocol for Caboolture Hospital (SPS CT-51)

The HWW is not easily accessible before it enters the SPS. Furthermore it would have been very difficult to set up an accurate flow meter to measure flow in a small open channel with intermittent, partially very low flows and to use this data

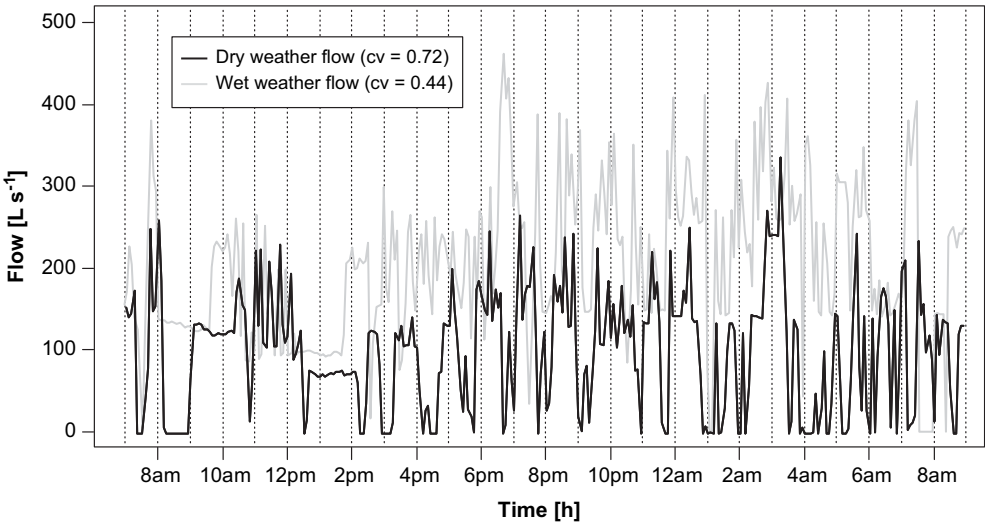


**Fig. 1 – Two examples for typical flow patterns at the influent of the sewage treatment plant; cv = coefficient of variation (standard deviation/mean).**

to control the speed of the sampling pump. Instead, plumbers from the Regional Council fitted a tap in the rising main of the SPS (see Fig. 2). The tap is upstream of the non-return valve before the HWW enters the primary rising main leading to the STP. Electricians from the Regional Council installed an actuator after the tap which only opens when the pump of the SPS empties the wet well. Water runs without a sampling pump due to the pressure in the rising main. Under normal operating conditions there are about 24 pumping cycles per day, triggered automatically based on to the water level in the SPS. While it was found that the flow during one cycle is fairly constant, it can vary significantly among cycles due to variable hydraulic conditions in the primary rising main. Therefore, a manual operating mode was adopted, disabling the auto level control. This allowed for using the full storage capacity of the wet well. Starting at 7 AM it was emptied again at 12 PM, 6 PM and 7 AM the following day which required personnel to be present three times per day (confined space). The pump operates at about 2500 L $min^{-1}$ and the sampling side stream was adjusted with the tap to approximately 1 L $min^{-1}$, resulting in a sampling volume of about 10 L per pump cycle. In comparison, the dead volume of the tap installation including hose was 0.5 L (ca. 5% of the sampling volume).

The three samples were collected in separate glass bottles, and analysed separately. The concentrations of the individual samples were multiplied with the flow for the corresponding pump cycle, and summed to obtain a 24-h load. Rough diurnal variations could also be determined with this sampling procedure, but they are not relevant for the system and time scales under investigation, and hence they are not further discussed in this paper.

#### 2.3.2. *Sampling protocol at the sewage treatment plant*

To sample for the same ''water packets'' as at the SPS, sampling started at 7:45 AM in the influent of the STP. The storage tanks start filling at 8 AM and are emptied completely during night

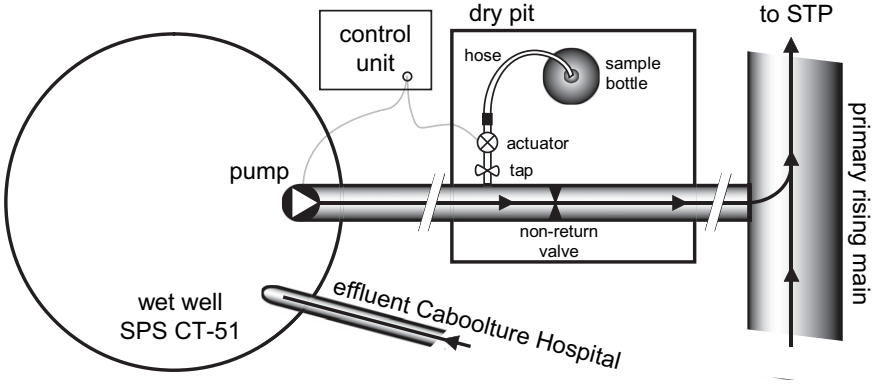


**Fig. 2 – Schematic drawing of the sampling point at the sewage pumping station (SPS) CT-51 (not to scale): All hospital wastewater is discharged to the wet well of the SPS and intermittently pumped to the primary rising main leading to the sewage treatment plant (STP). Upstream of the non-return valve a stand pipe with a tap and an actuator was fitted. This allows for taking flow-proportional samples during individual pump cycles.**

time, and in the early morning hours. This guarantees that wastewater is not stored and dragged on over different 24-h sampling periods. Flow rates in the influent are routinely measured at high temporal resolution. A wire connected to an analogue digital converter provides a 4–20 mA signal from the PLC (programmable logic controller) linear to the flow in the sewer to control the speed of the sampling pump. The peristaltic pump (Watson Marlow 520UN, programmable interface, water proof casing, equipped with a 520R2 pump head and 3.2 mm tube bore) was tested in the lab to ensure its linear behaviour over the full speed range under similar physical boundary conditions (suction height approximately 2 m, pressure height negligible). The pump speed was set to 0 rpm (revolutions per minute) for 0 L $s^{-1}$ in the sewer (pumping 0 mL $min^{-1}$) and to 34 rpm for 1000 L $s^{-1}$ (pumping 69.4 mL $min^{-1}$). The finest increment of the pump is 0.1 rpm equivalent to 2.9 L $s^{-1}$ wastewater flow in the influent of the STP. With this setup approximately 15 L of wastewater were collected in a 20 L glass bottle which was located in a refrigerated container. Two field blanks were collected: to this end 0.5 L of MilliQ water was used to rinse the sampling tube and subsequently 0.5 L MilliQ water was pumped through the tube to be analysed in the laboratory. No substances were detected above the limit of quantification.

### 2.4. Chemical analyses

After collection, the continuously refrigerated samples were transported to the laboratory where they were filtered the same day and preserved before analysis. All samples were analysed for 59 substances by Queensland Health Forensic and Scientific Services (QHFSS). A detailed description of the method consisting of solid phase extraction followed by concentration prior to quantification by LC–MS/MS (liquid chromatography coupled with tandem mass spectrometry) is given in the supplementary information SI 2, accompanied with an alphabetical list of all compounds (Tables SI 2.2 and SI 2.3).

As the method does not allow for correction of absolute analytical extraction recoveries in raw wastewater samples, we report relative loads. In order to compare hospital effluent samples with samples from the influent of the STP, it is necessary to assume that matrix effects between these sample types are similar. Any systematic error in recovery is therefore cancelled out when calculating ratios of loads, i.e. contribution of HWW to the total influent of the STP.

### 2.5. Uncertainty assessment

Flows in completely filled pressurised pipes can be measured more accurately than flows in open water channels (gravity flow). For this study a maximum error of ±10% was assumed, which equals to ±6% ($=10/3^{0.5}$) as single standard deviation of a normal distribution. For chemical analysis a random uncertainty (reproducibility) of ±20% for all compounds was chosen (see Tables SI 2.1–2.3). The two errors are independent, and Gaussian error propagation results in an overall uncertainty estimate for calculated loads of ±21% ($=[6^2+20^2]^{0.5}$).

The flow-proportional continuous sampling procedure covers all fluctuations in the wastewater over time. Since it is a reasonable assumption that dissolved compounds are completely mixed over the whole pipe cross section in the influent works, no additional errors need to be taken into account due to sampling.

### 2.6. Pharmaceutical audit data

#### 2.6.1. National consumption

An extract from the DUSC database (Drug Utilisation Sub-Committee) for the year 2008 is listed for the compounds investigated in this study (see supporting information, Table SI 3). It comprises the sum of subsidised drugs (subsidised under the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS) and processed by Medicare Australia) and non-subsidised drugs (under PBS co-payment and private prescriptions). The amounts of non-subsidised drugs were estimated from continuous data on all prescriptions dispensed from a validated sample of 370 community based pharmacies. The available data do not include drugs dispensed to public hospital in-patients, pharmacy over-the-counter drugs (i.e. non-prescription) and drugs supplied by supermarkets.

#### 2.6.2. Amounts administered to in-patients in Caboolture Public Hospital

No specific survey was carried out during the sampling period on the wards. Routinely stored audit data for a current 12-month period (2007–2008) was made available by the pharmacy of the Caboolture Public Hospital. For each pharmaceutical, a specific database query was performed to derive the amounts exclusively used for hospitalised in-patients; pharmaceuticals given to out-patients (in consultations and pharmacy) were not considered, since they will be taken and excreted at home. The total annual hospital load was determined after summing the contributions of all medications containing the pharmaceutically active compound of interest.

It has to be noted that the amounts derived from this database are amounts supplied by the pharmacy to the individual wards and not the amounts effectively administered. However, it is generally not the hospital's policy to discard drugs to the (solid or liquid) waste system, both from a financial and environmental point of view. Nevertheless, some unused drugs for in-patients may be collected on the wards and returned to the pharmacy for reuse or proper disposal. Hence, these drugs do not contribute to the load in the HWW. However, in discussion with relevant hospital staff these amounts are considered to be very limited and are not assessed within this study.

## 3. Results and discussion

### 3.1. Evaluation of wastewater volumes

The four consecutive weekdays, mid-February 2009 when sampling took place, were during a wet period, with flows 1.5–2 times higher than normal dry weather flow (i.e. surface runoff in catchments and infiltration to sewage pumping stations). In Table 1 the flows at the two sampling locations over the corresponding 24-h periods are summarised. During the sampling period, the hospital contributed less than 1% of the total wastewater flow to the STP.

**Table 1 – Wastewater volumes over 24 h at the SPS CT-51 (hospital wastewater) and the influent to the STP.**

| | | Influent STP [m³] | Hospital wastewater (flow at SPS) | |
|---|---|---|---|---|
| | | 7:45 AM – 7:45 AM of the following day | 7 AM–7 AM of the following day [m³] | Fraction of influent STP [%] |
| Day 1 | 16/2/09 | 14,064 | 109 | 0.8 |
| Day 2 | 17/2/09 | 16,921 | 129 | 0.8 |
| Day 3 | 18/2/09 | 19,059 | 138 | 0.7 |
| Day 4 | 19/2/09 | 14,347 | 127 | 0.9 |

### 3.2. *Evaluation of relative pharmaceutical loads*

To obtain relative pharmaceutical loads, measured concentrations were multiplied with the corresponding 24-h flow at each sampling location and normalised by the highest STP influent load. Four examples representing four different groups of pharmaceuticals are charted in Fig. 3. Absolute concentration values are not reported because they are difficult to compare among different studies; they highly depend on the sewer system (separate or combined) and on the hydraulic conditions (dry or wet weather flow). The key figures chosen for statistical evaluation are presented in Table 2, and discussed subsequently in detail for one example (atenolol, a beta-blocker, see also Fig. 3A).

The numbers in black circles (❶) refer to the corresponding column in Table 2:

❶ Concentration values for atenolol in the influent of the STP were, on average, 10 times higher than the limit of quantification (LOQ).

❷ The concentrations in the hospital effluent were on average 2 times higher than in the STP influent.

❸ The STP influent loads show only little day-to-day variation (cv = 0.06, cv = coefficient of variation = standard deviation/mean). Day-to-day variation is smaller than the estimated overall uncertainty.

❹ The loads in the hospital effluent varied more (cv = 0.27).

❺ On average the hospital contributed only 1.8% to the total atenolol load in the influent of the STP.

❻ For a conservative error estimation, a maximum contribution of the hospital was calculated by dividing the upper uncertainty value of the hospital effluent by the lower uncertainty value of the STP influent for each day (see Fig. 3). Over all four days, the highest maximum contribution for atenolol was 3.5%.

❼ Over all four days, the smallest minimum contribution for atenolol was 0.9% (analogue procedure as in ❻).

❽ The prediction for an average contribution of the hospital based on audit data is 0.6% (see more details in Section 3.4).

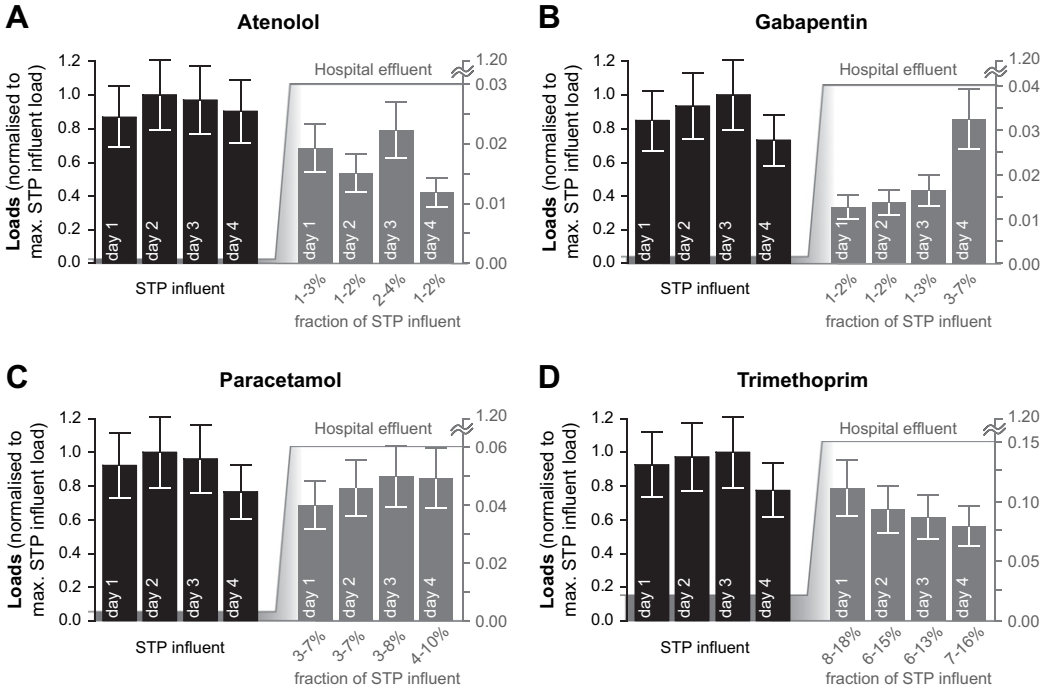


**Fig. 3 – Measured, relative pharmaceutical loads over 24-h periods in the influent of the STP and effluent of the hospital for four consecutive weekdays. Error bars include uncertainty of flow measurements (±6%) and chemical analysis (±20%), resulting in an overall uncertainty of ±21% (single standard deviation). Note the different scales for the y-axis of STP influent and hospital effluent.**

**Table 2 – Classification of substances according to the contribution of the hospital to the total load in the influent of the STP (see Section 3.3 for more explanations of key figures marked with black circles ❿). LOQs for all compounds are between 0.1 and 2 μg $L^{-1}$.**

| Classification ❾ | Substance | Therapeutic group [f] | $\frac{\bar{C}_{STP}}{LOQ}$ ❶ | $\frac{\bar{C}_{Hospital}}{\bar{C}_{STP}}$ ❷ | Coefficient of variation for loads | | Contribution of hospital wastewater [% of total STP influent] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Measured | | | average predicted with audit data[d] ❽ |
| | | | | | Influent STP ❸ | Hospital ❹ | Min ❼ | Mean ❺ | Max ❻ | |
| Max ≤ 5% | Atenolol | BB | 10.7 | 2.0 | 0.06 | 0.27 | 0.9 | 1.8 | 3.5 | 0.6 |
| | Atorvastatin | HL | <LOQ | – | – | 0.47 | – | 3[c] | – | 0.9 |
| | Caffeine | – | 296.4 | 3.0 | 0.07 | 0.17 | 1.4 | 2.6 | 4.4 | – |
| | Carbamazepine | AC | 6.3 | 0.6 | 0.17 | 0.65 | 0.0 | 0.4 | 1.3 | 1.9 |
| | Cephalexin[a] | AB | 33.8 | 0.9 | 0.21 | 1.33 | 0.0 | 0.4 | 1.2 | 5.9 |
| | Citalopram | AD | <LOQ | – | – | 0.19 | – | 4[c] | – | 1.6 |
| | Codeine | AG | 1.6 | 1.8 | 0.08 | 0.47 | 0.5 | 1.5 | 3.7 | 6.6 |
| | DEET | IR | 24.2 | 0.2 | 0.22 | 0.18 | 0.1 | 0.2 | 0.3 | – |
| | Diclofenac | AI | <LOQ | – | – | 0.53 | – | 1[c] | – | 1.8 |
| | Hydrochlorthiazide | DI | 8.7 | 2.7 | 0.24 | 0.30 | 1.1 | 2.0 | 3.7 | 0.5 |
| | Iopromide[b] | XC | 1.3 | 3.9 | 0.20 | – | 1.4 | 2.1 | 3.2 | – |
| | Naproxen | AI | 1.9 | 3.0 | 0.11 | 0.34 | 0.8 | 2.3 | 4.4 | 0.3 |
| | Oxazepam | AL | 5.5 | 1.2 | 0.08 | 0.41 | 0.4 | 1.2 | 2.8 | 1.5 |
| | Oxycodone | AG | <LOQ | – | – | 0.33 | – | 3[c] | – | 5.0 |
| | Sulphamethoxazole | AB | 6.7 | 1.1 | 0.05 | 0.65 | 0.2 | 0.8 | 2.2 | 6.7 |
| | Temazepam | SE | 2.3 | 1.9 | 0.06 | 0.23 | 0.7 | 1.6 | 3.1 | 4.3 |
| | Venlafaxine | AD | 11.2 | 2.6 | 0.16 | 0.27 | 0.9 | 2.0 | 5.0 | 2 |
| 5 % < max < 15 % | Erythromycin | AB | 7.7 | 2.8 | 0.41 | 0.28 | 0.8 | 2.6 | 5.5 | 4.3 |
| | Furosemide | DI | 13.3 | 6.9 | 0.20 | 0.17 | 2.6 | 5.8 | 13.7 | 5.9 |
| | Gabapentin | AC | 56.5 | 3.2 | 0.13 | 0.49 | 1.0 | 2.3 | 6.8 | 4.6 |
| | Gemfibrozil | HL | 3.9 | 5.3 | 0.26 | 0.85 | 0.7 | 4.1 | 10.0 | 0.4 |
| | Ibuprofen | AI | 70.6 | 6.3 | 0.08 | 0.18 | 2.7 | 4.6 | 8.5 | 49 |
| | Metoprolol | BB | 3.5 | 4.6 | 0.19 | 0.29 | 2.0 | 4.1 | 7.0 | 2.3 |
| | Paracetamol | AG | 1293.6 | 6.8 | 0.11 | 0.10 | 2.8 | 5.1 | 9.8 | 10 |
| | Ranitidine | HB | 3.2 | 6.2 | 0.12 | 0.38 | 1.3 | 4.9 | 11.0 | 5.7 |
| | Salicylic acid | m | 60.1 | 4.9 | 0.26 | 0.18 | 1.8 | 4.9 | 10.8 | 11 |
| | Tramadol | AG | 11.0 | 3.4 | 0.18 | 0.26 | 1.2 | 2.5 | 6.0 | 6.7 |
| | Triclosan | BI | <LOQ | – | – | 0.25 | – | 6[c] | – | – |
| max > 15% | Roxithromycin | AB | 1.4 | 28.4 | 0.22 | 0.20 | 11.68 | 25.66 | 56.0 | 19 |
| | Trimethoprim | AB | 3.4 | 13.3 | 0.11 | 0.15 | 5.7 | 10.14 | 18.3 | 14 |
| All values at STP < LOQ | Ciprofloxacin | AB | <LOQ | – | – | 0.24 | – | – | ≥50[h] | 10 |
| | Desmethyl Citalopram | m | <LOQ | – | – | 0.27 | – | – | ≥5[h] | – |
| | Indomethacin | AI | <LOQ | – | – | 0.44 | – | – | ≥15[h] | 10 |
| | Lincomycin[g] | AB | <LOQ | – | – | 0.53 | – | – | ≥50[h] | – |
| | Sertraline | AD | <LOQ | – | – | 0.22 | – | – | ≥5[h] | 1.2 |
| All values < LOQ[e] | Acetylsalicylic acid (11%),[e] Chloramphenicol (0.1%) Chlortetracycline, Cyclophosphamide (1.6%), Dapsone, Desmethyl Diazepam (11%), Diazepam (11%), Doxylamine, Enrofloxacin, Fluoxetine (0.8%), Fluvastatin, Ifosfamide, Norfloxacin (3.2%), Oxytetracycline, Phenytoin (4.2%), Praziquantel, Propranolol (0.8%), Simvastatin (0.5%), Sulphasalazine (0.7%), Sulphadiazine, Sulphathiazole, Tetracycline, Tylosin, Warfarin (1.9%) | | | | | | | | | |

– Not available.

a Only detected twice in hospital (influent STP four times).

b Only detected once in hospital (influent STP twice).

c Calculated with average loads measured in the influent of the same STP (three non-consecutive days in 2008 during very low dry weather flows).

d Audit data for hospital 2007–2008, audit data for national consumption 2008 (DUSC database).

e Numbers in brackets are the fraction of the hospital based on audit data (same as for column ❽ for the other compounds).

f AB = antibiotic, AC = anticonvulsant, AD = antidepressant, AG = analgesic, AI = anti-inflammatory, AL = anxiolytic, BB = beta-blocker, BI = biocide, DI = diuretic, HB = histamine blocker, HL = hypolipidemic agent, IR = insect repellent, m = metabolite, SE = sedative, XC = X-ray contrast media.

g More than 97% of national consumption used in agriculture (Watkinson et al., 2009).

h When assuming $C_{STP}$ = LOQ.

**Table 3 – Comparison with other hospital wastewater studies.**

| Number of hospitals | Number of beds per 1000 inhabitants | Investigated substances (% in influent of the corresponding STP originating from hospitals) | Location of study |
|---|---|---|---|
| 2 | 4.4 | diclofenac (1.4)[a]<br>ibuprofen (0.7) [a]<br>metoprolol (1.5) [a]<br>paracetamol (12) [a]<br>tetracycline (0.5) [a]<br>trimethoprim (14) [a] | Oslo, Norway (Thomas et al., 2007) |
| 1 | 3.6 | 5 X-ray contrast media (50) [b]<br>cytostatics (max 7.5) [b] | Winterthur, Switzerland (Weissbrodt et al., 2009) |
| More than 5 | 12.1 | carbamazepine (15) [c]<br>diclofenac (10) [c] | Berlin, Germany (Heberer and Feldmann, 2005) |
| More than 5 | 12.1 | metamizol (50) [c] | Berlin, Germany (Feldmann et al., 2008) |

a Concentrations measured over 12 weeks, loads estimated with water consumption, sum of the two major hospitals (an unknown number of other smaller hospitals/health care facilities are located in the catchment).
b Influent STP was not measured in this study, percentage refers to loads of pharmaceuticals quantified in the hospital's effluent compared to day-specific administered amounts.
c Only measured in the effluent of one hospital and then extrapolated for the whole catchment based on audit data of the other hospitals.

❾ Classification of all substances according to maximum observed contribution from the hospital (❻).

The consistent results for atenolol are reflected across most of the 30 detected substances. Representatives of other pharmaceutical groups show also fairly constant loads over the four-day period: gabapentin (an anticonvulsant), paracetamol (an analgesic) and trimethoprim (an antibiotic, see Fig. 3B–D).

From the 59 substances, 5 were detected only in the HWW but not in the influent of the STP and 24 substances were not detected above the LOQ in any of the samples. The 30 substances detected at both locations were classified for the hospital's contribution to the total influent of the STP. To this end, the maximum observed contribution including uncertainty as a conservative estimate was used (see description before in ❻). The hospital's contribution for 17 substances was at all times "smaller than 5%", 11 additional substances fall in the category "smaller than 15%" and only 2 substances were "above 15%" (trimethoprim and roxithromycin with a worst case estimate of 18% and 56% respectively). For most substances quantified in both STP influent and hospital effluent, the variations of the loads in the HWW were on average 2.4 times higher than in the influent to the STP. The small number of hospital patients compared to the potentially large number of individuals taking these pharmaceuticals at home is a valid explanation for this observed difference in variation.

Four out of the 5 substances only detected in the HWW were just above the LOQ. With the 100 fold dilution in the influent of the STP the LOQ would have to be at least three orders of magnitude lower to reliably quantify the hospital's (high) contribution. When assuming that the concentrations in the influent of the STP were equivalent to the corresponding LOQ, only a one-sided estimation with regard to the hospital's contributions from >5% up to >50% can be made. However, in some cases this deviates from the prediction based on audit data (see chapter 3.3).

### 3.3. *Comparison with audit data*

If the consumption of pharmaceuticals in a STP catchment can be estimated from existing national sales or prescription data, and audit data for the hospital are available, the contribution of the hospital can be calculated with the following equation

$$\text{contribution(hospital)} = \frac{\text{Cons}_{\text{Cab.Hosp.}} \cdot \text{excretion ratio}}{\text{Cons}_{\text{Cab.Pop.}} \cdot \text{excretion ratio} + \text{Cons}_{\text{Cab.Hosp.}} \cdot \text{excretion ratio}} \cong \frac{\text{measured load(hospital)} \cdot \text{recovery} \cdot \text{accuracy}}{\text{measured load(STP catchment)} \cdot \text{recovery} \cdot \text{accuracy}} \text{ with } \text{Cons}_{\text{Cab.Pop.}} = \frac{\text{Cons}_{\text{AUS}}}{20,000,000} \cdot 45,000 \quad (1)$$

where Cons is the consumption, Cab stands for Caboolture, Pop. for population, AUS for Australia and Hosp. for hospital. It becomes evident that the transformation due to human metabolism (excretion ratio) cancels out of the equation when assumed to be similar for patients in the hospital and for people at home. The consumption of pharmaceuticals in the STP catchment is estimated by calculating an average per capita consumption from the national consumption data multiplied with the number of inhabitants in the catchment. The consumption of in-patients in the hospital is added to the

domestic consumption to obtain an estimate for the total STP influent load (see also Table SI 3).

The prediction for 27 compounds where both national and hospital audit data were available, in some cases deviated significantly from the experimentally determined values. However, only 8 substances would have been classified differently based on audit data when applying strict boundaries for the classification which does not change the overall picture substantially.

Possible reasons for three examples are briefly discussed: 1) The overestimation in the case of ibuprofen may be reasonably explained by the fact that the national consumption is likely to be substantially underestimated because ibuprofen can also be obtained over the counter and in supermarkets without prescription. 2) A patient who regularly takes histamine blockers (at home) is likely to take them with him if he is being hospitalised (for any treatment not related or interfering with histamine blockers). This is one of the cases where patients may bring their own medication to the hospital and is also assumed to be valid for beta-blockers and diuretics. 3) In some countries trimethoprim is often applied together with sulphamethoxazole (combination item) and hence would be expected in a similar ratio. In Australia, the consumption pattern is different: 70% of trimethoprim is sold as single item (general public) and in the hospital under investigation even 90% are administered as individual compound.

In other cases the explanation may be sought in a higher or lower than average number of patients being treated during the sampling period in the hospital. However, if the number of treated patients shall be estimated from measurements, the excretion ratio and absolute recoveries for chemical analyses need to be taken in to account (see Eq. (1)). This makes it difficult to compare measured influent loads from a STP with audit data from an individual health care facility to reliably calculate the health care facility's contribution to the total influent of the STP.

### 3.4. *Comparison with other studies*

The Caboolture catchment, with 4.4 beds per 1000 inhabitants, is comparable with two other studies (3.6 and 4.4 beds per 1000 inhabitants, see Table 3). Without audit data for the hospitals and general public, the load estimations based on measured concentrations and an estimate for wastewater based on average water consumption in the study by Thomas et al. (2007) make a direct comparison difficult. However, higher contributions were also found for paracetamol and trimethoprim. In the study by Weissbrodt et al. (2009) the loads at the influent of the STP were not measured. The percentage determined in this study is the amounts measured in the sewer divided by the amounts administered on the corresponding days. The compounds investigated in the Swiss study are iodinated X-ray contrast media and cytostatics, both compounds almost exclusively administered in hospitals. Only 50% of the X-ray contrast media and a maximum of 7.5% of the cytostatics were quantified in the hospital's effluent, implying that the remaining part is most likely "carried home" by patients and excreted in household toilets. In the studies by Heberer and Feldmann (2005) and Feldmann et al. (2008) the hospital bed density is significantly higher (12.1 beds per 1000 inhabitants) with a sub-catchment bed density of 24. Pharmaceutical loads were measured in the influent of the STP and in selected hospital effluents. With day-specific hospital consumption data the contribution of the other hospitals was estimated, resulting in a total hospital contribution of 15% (carbamazepine), 10% (diclofenac) and 50% (metamizole, not measured in our study). Although the results seem to be in good agreement with our study, the limited number of compounds, the various approaches used, and the different catchment characteristics preclude a comprehensive comparison.

### 3.5. *Hospital wastewater treatment and catchments in South East Queensland*

Over 800 pharmaceuticals, disinfectants and other substances are recorded in the DUSC and the hospital database. Whilst the 59 substances analysed for in this study presents one of the more comprehensive studies of the relative contribution of a hospital to total load in wastewater, we do not claim that these results can be extrapolated for each of these 800 substances, at all hospitals, or medical research activities in general. As is often the case, the selection of these 59 substances was based upon the availability of a validated analytical method. Despite this "limitation", even if there were substances that originate almost exclusively from hospital wastewater, or if measures were taken to prevent pharmaceutical residues entering hospital wastewater (source control, separate collection of urine and faeces (Heinzmann et al., 2008)) or if hospital wastewater was treated on site, over 85% of the total load for the majority of the pharmaceuticals investigated in this study would still reach to the STP because they are excreted by the public at home in their households. Even for very specific compounds, almost exclusively administered in hospitals, the trends in many health care systems are moving towards shorter hospitalisations or even treatment of out-patients (particularly diagnostics). Two examples are the iodinated X-ray media and cytostatics: although administered in high amounts in hospitals, they cannot be recovered to 100% and hence solely attributed to hospital effluent (Weissbrodt et al., 2009).

Relevance to other catchments in South East Queensland (SEQ): The three catchments of main interest within SEQ, the ones with advanced water treatment plants for providing purified recycled water to the region (for planned indirect potable reuse scheme), have approximately 8 hospital beds per 1000 inhabitants (Luggage Point, eleven hospitals), 0.4 (Gibson Island, one hospital) and 1.7 (Bundamba, five hospitals). While the hospital in Caboolture (this study) contributes 4.2 beds per 1000 inhabitants (total in the catchment 4.4), the biggest individual hospital in the catchment of Luggage Point accounts for only 1.5. A desktop exercise analysing audit data from the sum of all hospitals in these catchments is proposed to evaluate if further steps are required. This includes the planning of future sampling campaigns and the potential benefit of treating some hospitals' wastewater at the source.

## 4. Conclusions

- *Measurements:* For several, widely applied pharmaceuticals, an individual hospital seems to be a small additional point

source in the catchment of a sewage treatment plant. In this study a hospital with 4.4 hospital beds per 1000 inhabitants contributed less than 15% to the total load in the influent of the sewage treatment plant for 28 substances, detected in both hospital effluent and STP influent, which is in good agreement with estimates from other studies. Considering a conservative worst case uncertainty estimation, the hospital contribution only exceeded 15% for two substances, roxithromycin (max. 56%) and trimethoprim (max. 18%).

- *Audit data:* The contribution of the hospital calculated with audit data and the chosen classification reveals good agreement with actual measurements for three quarters of the substances. National audit data to calculate the consumption by the general public in a catchment and hospital data for in-patients appear to be good predictors. This approach can be used with some confidence for substances where no analytical method exists to experimentally determine concentrations and loads or where the LOQ is not low enough. This needs to be tested for other countries (dependant upon the comprehensiveness and quality of national and hospital audit data).
- *Sampling in general:* Sampling campaigns in hospital wastewater are prone to high uncertainty due to a highly dynamic system (flow and concentrations). All effort should be undertaken to understand the system (behaviour) prior to setting up a sound sampling protocol to ensure that representative samples can be obtained.
- *Other catchments in South East Queensland:* The preliminary analysis based on hospital bed densities suggests focusing on the catchment of the STP at Luggage Point (approximately 8 hospital beds per 1000 inhabitants). However it has to be noted that this hospital bed density consists of 3 major public hospitals and a series of private hospitals. Since measurements will be very expensive to assess all hospitals' contributions. A detailed desktop analysis of all audit data is planned to identify if there are major sources and if measurements at selected locations may be appropriate.
- *Hospital wastewater treatment:* If, for whatever motivation, hospital wastewater shall be treated separately onsite, it must be noted, that for many substances no major overall reduction can be achieved since many pharmaceuticals are taken on a regular basis at home. With the current trend to shorter hospitalisations and treatments (diagnostics) of outpatients, this also holds true for compounds mainly administered in hospitals.

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## Appendix. Supplementary information

Information about the supplementary material can be found at doi:10.1016/j.watres.2009.08.002.

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