Hard data on hard drugs? - Assessing illicit drug loads in sewers

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ABSTRACT

The monitoring of illicit drugs in wastewater is an appealing idea within an emerging field. Objective, evidence-based data on drug-use can be obtained from urban drainage systems in real-time and without the limitations of population surveys. While current analytical techniques are sensitive enough to quantify arrays of substances in wastewater, current models to assess community consumption figures from substance loads are too simplistic and neglect relevant influence factors, such as sewer transport and transformation. In a case study of community cocaine use, observed substance loads show significant hourly variations, which demonstrates the need to consider the effect of short-time variations in the assessment of community drug use. Although the results from an integrated stochastic model are in general agreement with population surveys, further work is needed regarding the conceptualisation of drug use epidemiology, sewer processes and parameter estimation procedures.

KEYWORDS
Urban Drainage System; Cocaine; Benzoylecgonine; Stochastic modelling; Sewer epidemiology

LEARNING FROM SEWERS/WASTEWATER

Drug abuse has devastating social and economic consequences, with annual cost estimated at more than a hundred billion dollars in the U.S. alone. Although it would be important to assess the timely nature and magnitude of drug abuse and to closely monitor trends across communities, it is impossible to measure drug abuse directly, because, among other things, drug use is illegal and stigmatized. Instead, general population surveys are performed, which are affected by uncertainty from sampling, non-response and self-reporting (Sloboda, 2005).

To overcome these difficulties, environmental researchers suggest monitoring illicit drugs in surface water and wastewater (Chiaia and Field, 2007; Daughton and Jones-Lepp, 2001; Zuccato *et al.*, 2005), which is an appealing idea: Objective, evidence-based data on drug-use can be obtained from water quality studies in real-time and at only a fraction of the cost of population surveys. To avoid confounding results, the analyses often focus on metabolites and drug target residues (DTRs), which are unique to human consumption.

Currently, the field is driven by environmental chemists, who develop sophisticated analytical techniques for arrays of DTRs (Chiaia and Field, 2008; Hummel *et al.*, 2006; Postigo *et al.*, 2008). However, the models that are used to interpret the data are currently conceptually weak and miss potentially important aspects (e.g., transport and fate of substances in sewers, bias from inadequate sampling procedures). Regarding some of these weaknesses, the engineering community can make important contributions, because engineers 1) have developed a thorough understanding of sewer processes, 2) have already begun to include society as a variable in their integrated models (Peters *et al.*, 2002; Rauch *et al.*, 2003) and 3) are familiar with modelling stochastic processes (Ort *et al.*, 2005a; Rauch *et al.*, 2003).

The two main contributions of this work are 1) to present the first monitoring data of cocaine and its major metabolites in sewers, at hourly resolution, which provide new insight into short-time fluctuations of illicit drug loads, and 2) to suggest a stochastic simulation model for the assessment of community drug use that predicts time series of substance mass fluxes in wastewater systems for a given population of drug users. In this article, the analytical tandem mass spectrometry technique is first described briefly. Second, the results of a monitoring campaign for a medium-sized urban catchment in southern California are presented and an integrated stochastic model is suggested for the prediction of sewer substance loads. Third, the measured data are compared with model results for different scenarios and the most important findings are discussed. The paper ends with a summary of the main conclusions.

MONITORING AND MODELLING ILLICIT DRUG LOADS IN SEWERS

Selecting appropriate drug target residues (DTRs)

In recent months, several new analytical methods have been developed (Chiaia and Field, 2008; Huerta-Fontela *et al.*, 2007; Hummel *et al.*, 2006; Postigo *et al.*, 2008) to detect illict drugs and corresponding DTRs. However, very little has been reported regarding the interpretation of drug load figures. One challenge is the unique relation of the target drug and its metabolite to drug use to avoid bias from legal industrial or private use. So far, most of the studies concentrated on cocaine, as the metabolism for cocaine is relatively well understood and metabolite is unique to human consumption. Although other substances (e.g., methamphetamine, LSD) are detectable, the focus of this study is on the assessment of mass fluxes of cocaine (CO) and its major metabolite Benzoylecgonine (BE) to obtain comparable results. In addition to BE, results for Norbenzoylecgonine (NB) and Norcocaine (NC) are reported, but are not being used for modelling.

Analysing DTRs in wastewater with tandem mass spectrometry

Drug residues in wastewater are often so diluted that their analysis requires Liquid Chromatography Tandem Mass Spectrometry (LC-MS-MS). LC-MS-MS is very popular for the analysis of single or multiple specific substances in complex matrices because it combines the physical separation capabilities of liquid chromatography (LC) with the mass analysis capabilities of mass spectrometry (Castiglioni *et al.*, 2006). In this work, the novel Large Volume Injection Method has been used to quantify CO, BE, NBE, NCO, by injecting larger amounts of sample volume (up to 1800 μl) directly into the LC unit (Chiaia and Field, 2008). This omits the common solid phase extraction, which results in lower processing times and greater analytical precision. The recoveries, limits of detection (from 0.5 ng/l), and quantification (1 ng/l) of the compounds in wastewater were obtained as described in Chiaia and Field (2008). Although only results for cocaine and its major residues are reported here, one analytical run yields precise concentrations for an array of 11 illicit and prescribed drugs and their main metabolites and biomarkers such as creatinine and caffeine, in total 22 substances. While comprehensive error analysis is still ongoing, first analysis suggests that relative errors are around ±15% (single standard deviation) for CO and BE.

Patterns of cocaine use in a sub-catchment of a community in Southern California

To assess patterns of cocaine use, a monitoring campaign was performed in a sub-catchment of a community in the greater San Diego region, where level of cocaine use was estimated to 2.85% of the population (SAMHSA, 2006). The catchment is drained by a separate sewer system and has approximately 52000 inhabitants. GIS layers of the network topology for foul sewers, census tracts and demographic information were incorporated into a Geodatabase

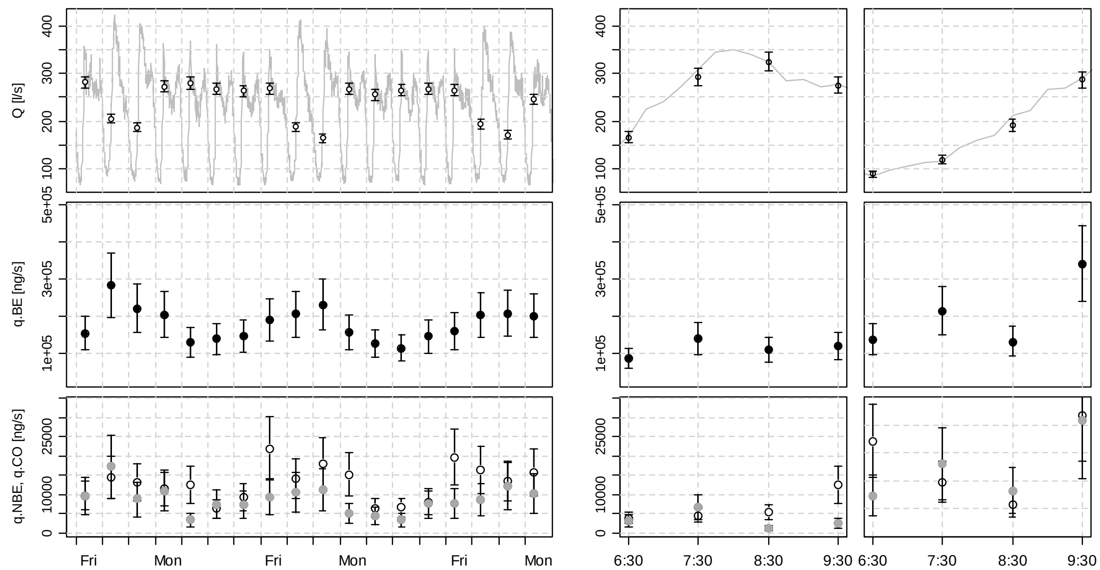

Figure 1 Illicit substance loads from a catchment of ca. 52000 inhabitants. Left column: 4hr average data. Middle and right column: 1hr average data. Top row: Discharge measurements, dots represent 4-hr average values, Middle row: BE loads (error bars 95% confidence interval based on analytical precision and uncertainty of discharge measurements). Bottom row: CO (circles dots) and NBE (grey dots) loads.

using ArcGIS 9.1 (ESRI, Redlands, CA, USA). The flow distances obtained from network analysis were in the range of 0.150 to 15.6 km.

Discharge at the monitoring point is measured on a routine basis by ADS Environmental (Huntsville, AL, USA) with an ADS proprietary sensor. Depth is measured by ultra-sound (4 sensors) and a simultaneous pressure sensor, velocity is measured by Ultrasonic-Doppler and all readings are recorded and stored in 15 min intervals. The calibration of the sensors is checked on a regular basis. Here, it was in the order of a few percent for both water level and velocity sensors. The sewer at monitoring point has a circular profile with a diameter of 0.775 m and an average daily flow rate of 221.6 l/s, velocity of 0.771 m/s and water level of 0.473 m. Grab samples were taken using an autosampler (ICSO 6700, Teledyne ISCO, Lincoln, NE, USA), which was calibrated on a daily basis with volumetric measurements.

CO, BE, NBE and NCO loads were monitored for 18 consecutive days, starting on 30.11.2007, which ensured that no special holiday or event (e.g., concert, football game) occurred during the sampling period. 100 ml grab samples were collected from 6:00 a.m. until 10:00 a.m., with a sampling interval of 3 min and 5 batches of samples were pooled to one batch. From these batches, flow-proportional samples of 1-hour averages and 4-hour averages were produced in the lab. Samples were cooled with Blue Ice immediately after collection and deep frozen after the production of composite samples, which was no later than 2 hours after collection of the last sample. Figure 1 (left) shows the results for 4-hour average flow-proportional samples. Also, 1-hour samples for Wednesday 12.12. (middle) and Sunday 16.12. (right) are given.

4-hr composites: The mean discharge in the morning hours was 239.2 l/s (0.17), BE mass fluxes 1.8E5 ng/s (0.25), CO 1.29E4 ng/s (0.35) and NBE 8.67E3 ng/s (0.39), in brackets the corresponding coefficients of variation for the composite samples. On average, the load of BE for the morning hours was 0.175 g/4 hrs (0.25), which was lower on weekdays (0.152 (0.18)) and higher on weekends (0.219 (0.14)). NCO concentrations were below the detection limit.

1-hr composites: The mid-week pattern shows little hourly variations, which points to relatively steady signal. On the weekend, however, large hourly variations are observed, which points to a underlying signal that is very dynamic. A highly dynamic signal on weekends seems reasonable, because only a few percentage of people seem to consume cocaine and not necessarily on a regular basis. However, the observed substance loads pose two important questions: 1) Do the observed variations reflect real fluctuations or rather the overall measurement uncertainty? 2) How does the observed load compare to the survey information, which usually is a percentage of the population?

The uncertainty of the observed substance loads was assessed by means of Monte Carlo Simulation with 10000 iterations. Errors in pipe geometry, water level measurement, velocity measurements and substance concentrations were considered as described in Rieckermann *et al.* (2007).

The resulting 95% credibility intervals are depicted as error bars in Figure 1. The results demonstrate that the observed variability is not due to measurement uncertainty and that substance loads vary significantly in the order of hours and minutes. In turn, this means that the observed loads are biased if the sampling interval is too large. To account for sampling uncertainty in the assessment of cocaine loads (question 2), a model is necessary.

Assessing cocaine loads in wastewater systems

The general causal processes that observed substance loads to community usage figures are relatively well defined (Figure 2). However, the formulation of a mathematical model requires the analyst to make various assumptions, which usually depend on the specific focus of the model. In the following, the current state-of-the art model to assess community drug use from measured substance loads is presented and its limitations are discussed briefly. Then, an integrated model is suggested that predicts dynamic load patterns and thus can be used to assess the representativeness of different sampling schemes.

Steady state model: To infer consumed amounts of the parent drug CO from measured BE loads, Zuccato *et al.* (2005) suggest a linear model based on average consumption and excretion figures (equation 1). It has been used in other studies in a similar fashion (Batchelor, 2007; Bones *et al.*, 2007; IBP, 2006).

$$n_{d,1000} = q_{BE} \cdot M_{CO} / M_{BE} \cdot \left(k_{CO2BE} \cdot m_{d,CO,in} \cdot n_{d,occ}\right)^{-1} \qquad \text{eq. (1)}$$

where $n_{d,1000}$= number of typical doses per thousand people, q_{BE}= daily load of benzoylecgonine, M_{CO}= molar mass of parent drug (303 [g/mol]), M_{BE}= molar mass of main metabolite (289 [g/mol]), k_{CO2BE}= pharmacokinetic parameter, describing what fraction of the parent drug is excreted as the metabolite (0.45), $m_{d,CO,in}$= typical dose consumed by the most common route (25 [mg] intranasal, a “line” of cocaine), $n_{d,occ}$= typical number of doses per occasion (4 [lines]). In comparison to Figure 2, important simplifying assumptions are 1) a single user class, single average drug dose, 2) steady-state average metabolism, 3) uniform voiding pattern over the entire monitoring period, 4) no mobility of the population in the

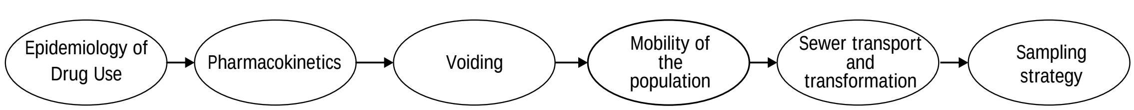

Figure 2 Schematic representation of the major influence factors for observed drug loads in sewers

catchment and over its boundaries, 5) immediate sewer transport without dynamics, transformation or losses, 6) disregard of the applied sampling strategy. While many of these assumptions might be reasonable in large catchments, Ort *et al.* (2005b) showed that short-time fluctuations affect the representativeness of observed substance loads in sewers. To overcome some of these weaknesses, an integrated stochastic model has been developed.

Integrated stochastic model: The stochastic model was developed to predict dynamic load patterns at a given monitoring point. It incorporates the following sub-models (Figure 3): 1) Epidemiology of drug use, 2) Pharmacokinetics, 3) Temporal urination patterns, 4) Sewer transport, and 5) Sampling strategy. The mobility of population and substance degradation are currently not considered due to insufficient information. For details on the model and chosen parameter values, see Rieckermann et al. (2008). Capital letters refer to the factors depicted in Figure 3.

1) Epidemiology of cocaine use: The epidemiological sub-model follows the approach used in Chitwood (1985) and Cohen (1994) to conceptualise and quantify cocaine use. Specifically, it considers three use levels (B: low, medium, high), with conditional probabilities for three different routes of administration (C: smoking, injection, intranasal), the amount of drug mass consumed (D) and different weekly (E) and daily use patterns (F). Also, different degrees of purity are considered (G). Parameter values have either been taken from literature or elicited from local experts.

2) Pharmacokinetics: Pharmacokinetics is concerned with what the body does to the drug. Here, the pharmacokinetic sub-model computes bladder input fluxes of CO and BE (K) from the dose masses (I), times (J) and routes (C), and NBE and NCO are currently not implemented. The transformation is based on the clinical trials reported in Cone *et al.* (2003), where detailed excretion profiles of cocaine and its metabolites were recorded for controlled

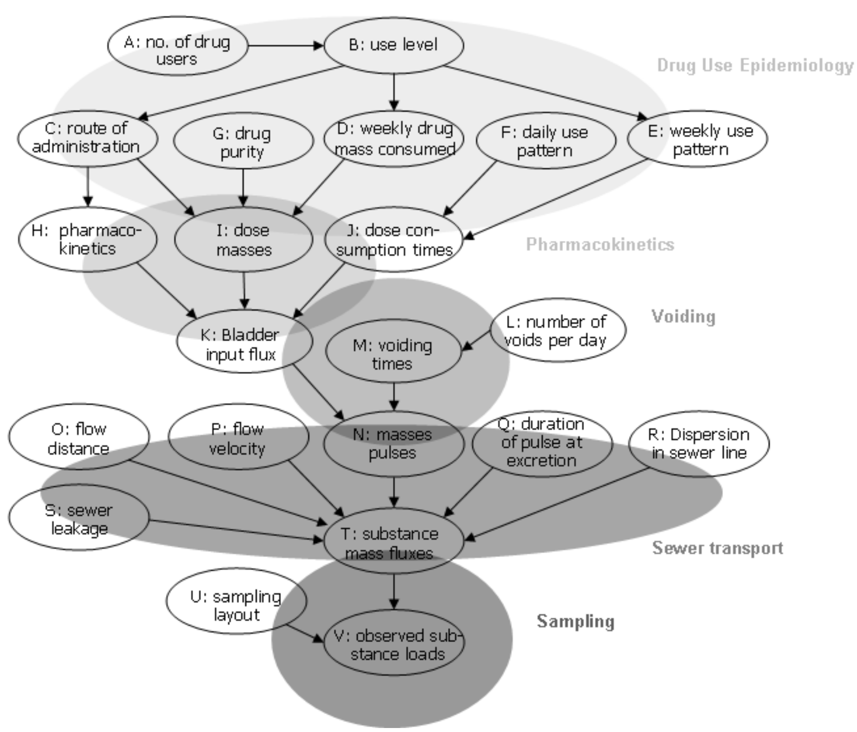

Figure 3 Schematic representation of the integrated stochastic model

administrations of cocaine for the different intake routes. Human cocaine metabolism is modelled with cumulative lognormal density functions that have been fitted to the data of CO and the main metabolite BE. Excretion rates of BE are in the range of 2 to 43% of administered cocaine.

3) Temporal urination patterns: Clinical information on urination (voiding), also knowledge on temporal excretion patterns. From the distribution of number of voidings per day (M) (Boedker *et al.*, 1989) and temporal voiding patterns (L) (Friedler *et al.*, 1996; Rauch *et al.*, 2003), voiding times are computed for each user. Voiding times are then used together with the cumulative bladder loads (K) to compute substance masses for BE and CO that are discharged with each toilet use (P).

4) Sewer transport and transformation: For each drug user, pulses of substance masses (P) are discharged to the sewer at a house drain and then routed through the drainage system. Assuming that the substance clouds are normally distributed, the mean velocity and average dispersion are the same for each single pulse (k), the mass flux patterns at the monitoring point ($q_{i,r}$), for a single user (i) and substance (r) is computed as the sum of all pulses. The predicted continuous total substance mass flux $q_r(t)$ is the superposition of $q_{i,r}(t)$ for all users (n) during the simulation period:

$$q_r(t) = \sum_{i=1}^{n} q_{i,r}(t) = \sum_{i=1}^{n} \sum_{k=1}^{n.pulses} m.pulse_{i,k}\left(1 - f_{leak}\right)\frac{1}{\sigma_{s,i}\sqrt{2\pi}}\exp\left(-\left(t - \left(Tv_{i,k} + \frac{s_i}{u}\right)\right)^2 \frac{1}{\sigma_{s,i}^{\;2}}\right) \qquad \text{eq. (2)}$$

with t= simulation time, $n.pulses$= number of pulses discharged by ith user, $m.pulse_{i,k}$= substance mass contained in kth pulse, f_{leak}= fraction that is lost with sewer leakage, u= mean velocity, $Tv_{i,k}$ = voiding time of kth pulse, s_i= flow distance,

$$\sigma_{s,i}^{\;2} = 2D_x \cdot \left(\frac{s_i}{u}\frac{1}{u^2}\right) + \sigma_{ini}^{\;2} \qquad \text{eq. (3)}$$

with $\sigma_{s,i}$= spread of substance cloud at monitoring station (σ of normal distribution), D_x= longitudinal dispersion coefficient, σ_{ini} = spread of cloud at house drain. Examples of output from the sewer transport sub-model are given in Figure 4 for different scnearios of drug users (*q.CO* not shown).

5) Sampling strategy: Once substance fluxes are computed, the desired sampling layout (U) is applied to compute average loads during the simulation period. First, samples are first taken with a defined certain sampling interval and then pooled into batches as specified in the sampling procedure.

As many influence factors (e.g., drug purity, pharmacokinetics, voiding numbers and times, sewer transport parameters) are considered as random variables in the model, simulation

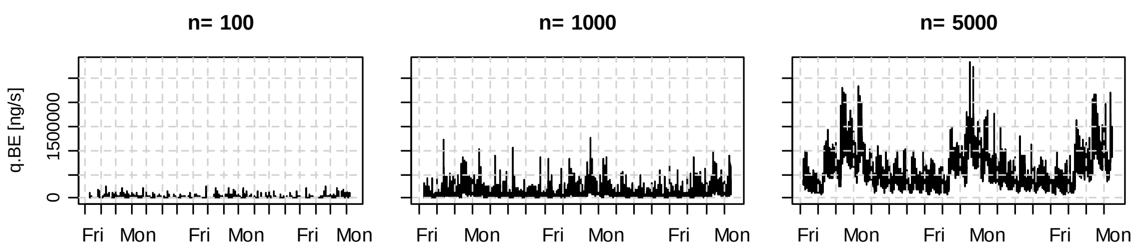

Figure 4 Exemplary time series of BE loads at the monitoring point for different number of users

are stochastic time series. Currently, formal methods of parameter estimation are lacking and the model is used to investigate different user scenarios instead. For each scenario, ranges of plausible values were considered for the model parameters and the results compared to measured substance loads. To this aim, 500 Monte Carlo Simulations were performed, using Latin Hypercube sampling. The associated sampling error was assessed as described in Ort *et al.* (2005b).

RESULTS

Steady state model

As detailed above, the steady state model (equation 2) assumes a fixed metabolism and a constant average consumption of cocaine. Applying it to sub-daily values requires to compensate for corresponding fraction of excretion rates, which are not constant over the day (Friedler *et al.*, 1996). Applying the model to the measured data, the average community consumption of cocaine differs from 55 to 187 doses per day per 1000 people (Table 1). Confidence intervals are not reported, because they would only include measurement uncertainty and not include sampling errors. Although sampling intervals were short (3 min), it is not clear what the resulting error might be. Conditional on the assumptions on average drug use, these doses would directly translate into 5.5% and 18.7% percent of the population, which is much higher than the survey result of 2.85%.

Integrated stochastic model

The results for three different scenarios of 500, 1300 and 2100 cocaine users are given in Figure 5. By visual comparison, it can be seen that the low and high numbers do not match

Table 1 Measured substance loads and steady state model results, f_{exc}= fraction of daily urinary excretion during monitoring interval, $n_{d,1000}$= number of average cocaine doses per 1000 people, which equals the number of average users given the underlying assumptions

Substance data							Modeled community CO consumption			
Date	Time	Q_{mean}	f_{exc}	q.CO	q.BE	q.NBE	CO_{1000}	$n_{lines,1000}$/ 4h	$n_{d,1000}$/ 4h	$n_{d,1000}$/ d
	[hrs]	[l/s]	[-]	[ng/s]	[ng/s]	[ng/s]	[g/4h]	[counts]	[counts]	[counts]
30-Nov-07	6-10	281.3	0.081	9748	155733	9569	0.151	6.0	24	74
1-Dec-07	6-10	204.9	0.059	14425	285260	17227	0.277	11.1	44	187
2-Dec-07	6-10	187.1	0.059	13141	222559	8865	0.216	8.6	35	146
3-Dec-07	6-10	272.5	0.081	11456	205536	11034	0.199	8.0	32	98
4-Dec-07	6-10	279.1	0.081	12528	131442	3373	0.127	5.1	20	63
5-Dec-07	6-10	266.6	0.081	6419	140901	7531	0.137	5.5	22	67
6-Dec-07	6-10	262.7	0.081	9368	148529	7423	0.144	5.8	23	71
7-Dec-07	6-10	268.6	0.081	21884	190642	9440	0.185	7.4	30	91
8-Dec-07	6-10	188.2	0.059	14132	206795	10662	0.201	8.0	32	136
9-Dec-07	6-10	164.2	0.059	17898	231787	11220	0.225	9.0	36	152
10-Dec-07	6-10	266.9	0.081	15206	157722	5252	0.153	6.1	24	75
11-Dec-07	6-10	255.0	0.081	6526	128208	4480	0.124	5.0	20	61
12-Dec-07	6-10	264.2	0.081	6587	115368	3406	0.112	4.5	18	55
13-Dec-07	6-10	267.3	0.081	7873	146467	7815	0.142	5.7	23	70
14-Dec-07	6-10	264.6	0.081	19669	161254	7662	0.156	6.3	25	77
15-Dec-07	6-10	193.5	0.059	16223	203873	8598	0.198	7.9	32	134
16-Dec-07	6-10	171.5	0.059	13533	206895	12325	0.201	8.0	32	136
17-Dec-07	6-10	246.3	0.081	15686	202203	10180	0.196	7.8	31	96

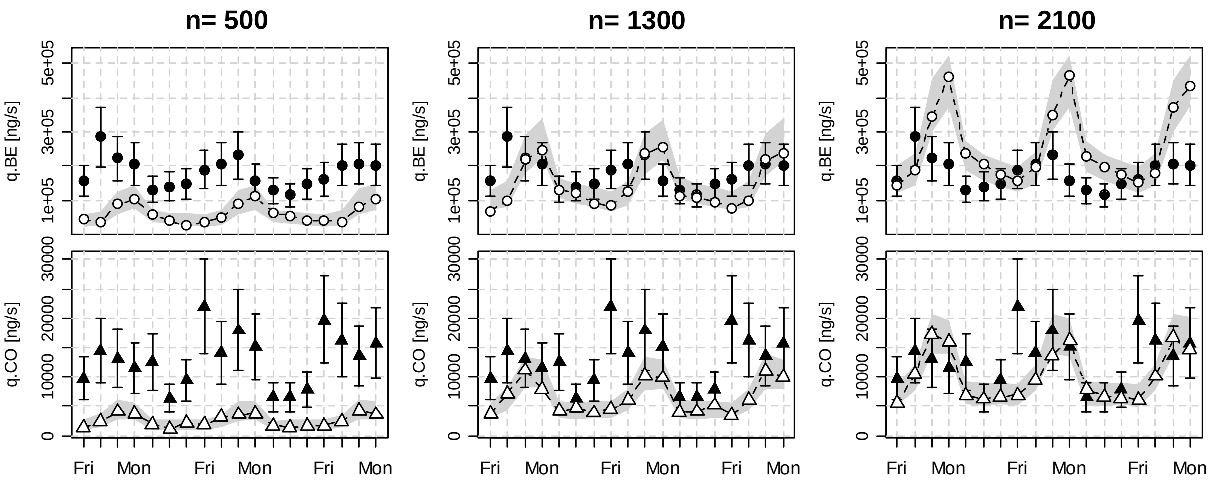

Figure 5 Model results for the integrated stochastic model for scenarios with 500, 1300 and 2100 drug users for a catchment of 52000 inhabitants.

BE loads (*q.BE*) and the best qualitative fit is obtained from the scenario with 1300 drug users in the catchment. The analysis further shows that the expected relative error due to the 3 min sampling interval is 2% (single std. dev.) for this scenario. However, even this best fit shows several discrepancies. First, although the overall magnitude of BE loads are well represented, loads on weekdays are rather underestimated. Second, measured loads on Friday mornings are always higher and loads on Monday mornings always lower than those predicted by the model. Third, even for the best matching scenario of 1300 users, measured parent drug loads are on average higher that modeled ones. This means that average estimated cocaine consumption could be in the range of survey results for this catchment (ca. 2.5% compared to 2.85%), but that some of the epidemiological assumptions (e.g., on weekend use patterns) need to be refined.

DISCUSSION

Monitoring drug loads in wastewater systems seems promising to assess community drug use, as it has excellent population coverage and does not suffer from the same biases as surveys. However, many challenges remain in this emerging field.

It has been shown that a dynamic model is needed to rigorously assess the uncertainty of the obtained results, including sampling errors. However, even with an integrated stochastic model, various scenarios lead to similar predictions, which makes an unanimous interpretation of monitoring results difficult. However, the application of the phenomenological model reveals interesting insight, e.g., weekend use does not necessarily happen on working weekend (SAT, SUN), but rather on party weekends (FRI, SAT) and is thus useful to formulate and test specific hypotheses. In this case, a better fit could possibly obtained by decreasing the number of recreational (weekend) users and increasing heavy users, which consume on a more regular basis. However, this is clearly beyond the expertise of engineers and requires close collaboration with epidemiologists.

To date, little is known on the behavior of illicit substances and transformation of compunds has only been investigated after three days (Castiglioni *et al.*, 2006), whereas sewer residence times are mostly in the order of several hours. In general, a degradation of CO should be expected, but cannot necessarily be confirmed with the current analysis.

Future work should investigate potential simplifications of the suggested model by means of sensitivity analysis. Also, the development of formal methods of parameter estimation would be important for the comparison of substance loads with survey results.

Absolute values of drug users might be very difficult to obtain from wastewater substance loads, due to the various assumptions and simplifications. Nevertheless, the relative comparison of various monitoring campaigns in time and over different regions would also be very valuable, as it provides epidemiologists with an indicator of drug use and could serve as a quantitiative surveillance system, e.g. for outbreak detection. However, one has to keep in mind that, even for relative comparisons, an accurate assessment of the involved uncertainties is mandatory. In this, the sampling error will always be an influence factor alongside measurement uncertainties and there are basically four strategies to address it: 1) ignore it, 2) guess it (presumably being safe assuming a large value), 3) spend large amounts of money monitoring empirical short-time load fluctuations, 4) assess it using an integrated stochastic model, as suggested in this study.

CONCLUSIONS

- The monitoring of illicit drugs in wastewaters is an appealing idea in an emerging field. Objective, evidence-based data on drug-use can be obtained from urban drainage systems in real-time and with different biases than population surveys. However, currently applied models are simplistic and miss potentially important aspects (e.g., transport and fate of substances in sewers, bias from inadequate sampling procedures).
- In a medium-sized catchment, observed hourly fluctuations of cocaine and benzoylecgonine cannot be explained with measurement uncertainty alone, which points to the fact that observed loads might be biased if sampling intervals are large.
- For this case study, community drug use was assessed to 55-187 typical doses per day using a steady state model. An integrated dynamic model suggests a population of approximately 1300 recreational, medium and heavy cocaine users. For this scenario, the sampling interval of 3 min would lead to a relative error of $\pm$2% (single std. dev.).
- Absolute values of community drug use might be difficult to obtain, and not very precise, due to various assumptions. Nevertheless, relative comparisons also require an analysis of uncertainty, which is incomplete if the sampling error is not regarded. Sampling uncertainty can either be assessed by expensive empirical investigations or by integrated modeling, as suggested here.
- The monitoring of illicit drugs in wastewater requires inter- and transdiciplinary research. Environmental engineers have a lot to contribute to this emerging field, e.g., their thorough understanding of drainage systems and wastewater, computational modeling of stochastic processes and a thorough assessment of uncertainty.

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REFERENCES

Batchelor, C. (2007) Wastewater sampling indicates significant cocaine usage amongst Dubliners - Something in the water. *Chemical Society Reviews*, **36**(6), C41-C41.

Boedker, A, Lendorf, A, Nielsen, AH and Glahn, B (1989) Micturition pattern assessed by the frequency/volume chart in a healthy population of men and women. *Neurourol Urodyn* 8), 4212.

Bones, J., Thomas, K. V. and Paull, B. (2007) Using environmental analytical data to estimate levels of community consumption of illicit drugs and abused pharmaceuticals. *Journal of Environmental Monitoring*, **9**(7), 701-707.

Castiglioni, S., Zuccato, E., Crisci, E., Chiabrando, C., Fanelli, R. and Bagnati, R. (2006) Identification and measurement of illicit drugs and their metabolites in urban wastewater by liquid chromatography-tandem mass spectrometry. *Analytical Chemistry*, **78**(24), 8421-8429.

Chiaia, A. and Field, J. (2007) Determination of illicit drugs and biomarkers in raw municipal wastewater influent as a tool for drug epidemiology. *In* “234th National Meeting of the American Chemical Society. Aug. 19-23. Boston.”

Chiaia, A. and Field, J. (2008) Large Volume (1,800 uL) Direct Injection (no SPE) HPLC/MS/MS for the Quantitative Determination of Illicit Drugs and Human Biomarkers in Municipal Wastewater. *in preparation*.

Chitwood, D.D. (1985). *In* “Cocaine use in America: Epidemiologic and clinical perspectives.” (N. a. A. Kozel, E. , ed.), Rockville, NIDA, 1985.

Cohen, Peter (1994) Cocaine use in Amsterdam in non deviant subcultures. *Addiction Research*, **2**(1), 71-94.

Cone, E. J., Sampson-Cone, A. H., Darwin, W. D., Huestis, M. A. and Oyler, J. M. (2003) Urine testing for cocaine abuse: Metabolic and excretion patterns following different routes of administration and methods for detection of false-negative results. *Journal of Analytical Toxicology*, **27**(7), 386-401.

Daughton, Christian G. and Jones-Lepp, Tammy L. (2001). “Pharmaceuticals and personal care products in the environment : scientific and regulatory issues”. American Chemical Society, Washington, D.C.

Friedler, E., Butler, D. and Brown, D. M. (1996) Domestic WC usage patterns. . *Build. Environ., 31(4), 385-392.*

Huerta-Fontela, M., Galceran, M. T. and Ventura, F. (2007) Ultraperformance liquid chromatography-tandem mass spectrometry analysis of stimulatory drugs of abuse in wastewater and surface waters. *Analytical Chemistry*, **79**(10), 3821-3829.

Hummel, D., Loffler, D., Fink, G. and Ternes, T. A. (2006) Simultaneous determination of psychoactive drugs and their metabolites in aqueous matrices by liquid chromatography mass spectrometry. *Environmental Science & Technology*, **40**(23), 7321-7328.

IBP (2006) First ever comparative multi-country study of cocaine use by a new measurement technique. Institute for Biomedical and pharmaceutical Research, Nürnberg.

Ort, C., Schaffner, C., Giger, W. and Gujer, W. (2005a) Modeling stochastic load variations in sewer systems. *Water Science and Technology*, **52**(5), 113-122.

Ort, C., Schaffner, C., Giger, W. and Gujer, W. (2005b) Sampling for Representative Micropollutant Loads in Sewer Systems. *In* “10th International Conference on Urban Drainage (ICUD), 21-26 August”, pp. 113-122, Copenhagen.

Peters, Irene , Brassel, Kai-H. and Spörri, Christian (2002) A Microsimulation Model for Assessing Urine Flows in Urban Wastewater Management. *In* “Proceedings of the 1st Biennial Meeting of the International Environmental Modelling and Software Society, pp.508-513.”

Postigo, Cristina, Alda, Maria J. Lopez de and Barceló, Damià (2008) Fully automated determination in the low ng/L level of different classes of drugs of abuse in sewage water by on-line solid phase extraction liquid chromatography-electrospray-tandem mass spectrometry. *Analytical Chemistry*, (accepted for publication).

Rauch, W., Brockmann, D., Peters, I., Larsen, T. A. and Gujer, W. (2003) Combining urine separation with waste design: an analysis using a stochastic model for urine production. *Water Research*, **37**(3), 681-689.

Rieckermann, J., Bareš, V., Kracht, O., Braun, D. and Gujer, W. (2007) Estimating sewer leakage from continuous tracer experiments. *doi:10.1016/j.watres.2007.01.024*.

Rieckermann, J., Chiaia, A., Ort, C. and Field, J. (2008) Learning from sewers - assessing community drug use from sewer monitoring and modelling. *In preparation*.

SAMHSA (2006) Results from the 2005 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-30, DHHS Publication No. SMA 06-4194). Rockville, MD.

Sloboda, Zili (2005). “Epidemiology of Drug Abuse”. Springer.

Zuccato, Ettore, Chiabrando, Chiara, Castiglioni, Sara, Calamari, Davide, Bagnati, Renzo, Schiarea, Silvia and Fanelli, Roberto. (2005) Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Environmental Health 4:14, 5. August 2005.