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European Monitoring Centre
for Drugs and Drug Addiction

EMCDDA
INSIGHTS

Assessing illicit drugs in wastewater

Potential and limitations of a new monitoring approach

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EMCDDA project leaders

Norbert Frost, Paul Griffiths

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European Monitoring Centre
for Drugs and Drug Addiction

Rua da Cruz de Santa Apolónia 23-25, 1149-045 Lisbon, Portugal
Tel. (351) 218 11 30 00 • Fax (351) 218 13 17 11
info@emcdda.europa.eu • http://www.emcdda.europa.eu

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Foreword

When talking about illicit drug use, it is important to remember that this term is a convenient 'shorthand' for a range of complex behaviours. Different drugs are used in different ways and in different combinations. And as patterns of drug use develop and change over time, so do the implications of drug use for public health. Successful prevention, treatment and harm-reduction interventions require a sound understanding of the nature and extent of the drug problem, as do interdiction and other supply reduction measures. Monitoring trends in drug use and accessing overall consumption levels is therefore a critical requirement for the development and targeting of effective interventions of every kind.

Although understanding patterns and trends in drug consumption is an important goal, it is also a methodologically challenging one. Drug use presents us with both a moving target and one that is difficult to observe. New patterns of drug use can become established in a short time, and sometimes develop into major problems before they have even been widely identified. The problems of measuring what is often a highly stigmatised and hidden behaviour are a key concern of the scientific literature in this area, and wrestling with these issues forms a central component of much of the work of the EMCDDA. In this area, no single measure provides a full picture of the drug situation, and the overall strategy has been to adopt a multi-indicator approach. Specific information sources have been developed to highlight particular aspects of the phenomenon, and by putting these together, a more comprehensive analysis can be built up. Surveys, for instance, provide an important window on some types of drug use, but need to be complemented with targeted studies and statistical modelling if a more comprehensive picture is to be produced. Considerable progress has been made in improving methods in all these areas, ranging from more sophisticated statistical models to the use of computer-aided interviews to reduce respondent bias. Nonetheless, sampling problems and response bias remain major problems for survey techniques, and indirect modelling of the unknown population from the observable population is both complicated to achieve and requires at least a proportion of the population of interest to be observable in some fashion. A common problem of all methods in this area is that, as they are often time-consuming and complex, they often require considerable resources to be invested if they are to produce satisfactory results.

In this report, we explore both the potential use and the likely limitations of a new and novel approach to monitoring the use of illicit drugs. This approach has

been made possible by recent improvements that have increased the sensitivity of analytical laboratory equipment. Developments in chromatographic and mass-spectrometric analysis have made it possible to identify urinary excretion of illicit drugs and their main metabolites in wastewater at very low concentrations. The initial focus of work in this area was on the monitoring of environmental contamination caused by the excretion of prescription medicines. However, it was quickly realised that these approaches might lead to the possibility of assessing levels of illicit drug use by detecting their residues in the environment.

While work in this area is in its infancy, the approach itself appears increasingly promising. It is becoming clear that new developments in our ability to detect drugs and their metabolites in wastewater are likely to have important implications for the approaches we adopt to monitoring drug consumption trends over time. On a practical level, this approach raises a number of important technical and ethical issues. With these considerations in mind, in April 2007, the EMCDDA hosted a technical meeting to stimulate a dialogue between drug epidemiologists and those working in this new field on how best to integrate this new approach into current research thinking. The results of this meeting are summarised in this edition of the EMCDDA Insights series, which I feel will make an important contribution to the debate on future approaches to drug use monitoring in Europe.

Wolfgang Götz
Director of the EMCDDA

Acknowledgements

This report is based on the presentations made at an experts' meeting held at the EMCDDA in Lisbon in 2007, organised by Norbert Frost. The EMCDDA would like to thank all those who attended the meeting and those who contributed to the discussion and to this publication. The agency thankfully acknowledges the invaluable role played by Professor Michael Gossop in reviewing and improving the text. The volume was edited by PrePress Projects and staff of the EMCDDA.

Chapter 1: Introduction to sewage epidemiology and the wastewater system

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Norbert Frost and Paul Griffiths

Wastewater analysis

Human societies produce many kinds of waste products. Even where relatively sophisticated methods of disposal are available, there always remain some residues, which in one way or another are returned to the environment. At a time when there is a growing awareness of what our societies introduce into the environment, the reliable detection of potential ecological threats or health damage due to environmental agents has become an important issue. Measures to detect such potential threats are being included in the continuous monitoring of the environment that is becoming increasingly common in many Member States.

The environmental fate of therapeutic drugs has been increasingly recognised worldwide as an important issue. Concern about this issue was one of the factors that provided an initial impetus to work in the area of wastewater analysis through the monitoring of environmental contamination caused by prescribed drugs, and the related question of the effectiveness of water treatment plants. An example of this is the work conducted in Germany during the 1990s in which investigations were carried out into the extent that therapeutic drugs were detectable in rivers and wastewater systems (Ternes, 1998; Ternes et al., 1999). The main concern of this environmental monitoring was the extent to which a known level of drug prescription was likely to produce residues that were excreted into the environment.

Following on from the earlier work to monitor for the presence of therapeutic drugs in wastewater samples, it became clear that it might also be possible to use the same methodology to assess levels of illicit drug use by detecting their residues in the environment. One of the first suggestions that it might be possible to use the results of analyses conducted on wastewater samples taken from sewage treatment facilities to determine illicit drug use within communities was made by Daughton (2001). Illicit drug use is, by its nature, a covert and hidden activity, and traditional survey methods (such as population or household surveys) can

be inefficient and sometimes ineffective ways of estimating levels of at least some types of illicit drug use.

The possibility that a new technique for estimating illicit drug use might be added to the existing repertoire of research methods was, therefore, an exciting prospect.

As the sensitivity and accuracy of analytical equipment and methods have improved during the past 30 years, so have the capacities for the detection of substance use. Recent technological advances have increased the sensitivity of chromatographic and mass-spectrometric analysis. These developments have made it possible to identify urinary excretion of illicit drugs and their main metabolites in wastewater at very low concentrations (Castiglioni et al., 2006). This is comparable to taking a much diluted urine sample from an entire community (rather than from an individual user). When monitoring for drugs, wastewater analysis depends on the mass flow of the substance detected. Using wastewater as a matrix, the residues of therapeutic drugs or illicit drugs that have been released into the sewage system can be separated in chromatograms. This may include the possibility of computing the mass balances of substances in order to back-calculate levels of overall drug consumption.

When making back-calculations of drug consumption based upon the mass flow of metabolites, surface water samples cannot be considered to be a matrix of choice due to their vulnerability to confounding influences from large numbers of unpredictable variables. Surface water analysis in the neighbourhood of a wastewater treatment plant's outlet (effluent) may, however, provide a means to assess the effectiveness of the treatment plant. For drug monitoring purposes, sampling in the main proximal influent to the wastewater treatment plant may be both opportune and recommended.

A crucial component in the management of communal waste is the wastewater system in general, and the wastewater treatment plant in particular. Wastewater systems differ from each other, as do the communities they serve. Beyond knowing what may happen to drug residues while they are in the wastewater, interpretation of the analytical data will depend on the answer to the key question 'what is happening to drug residues in this wastewater system?' It is clear that developing an approach to monitoring community drug use based on wastewater analysis will be a multidisciplinary endeavour involving fields as diverse as system theory, non-linear dynamics and spatial epidemiology.

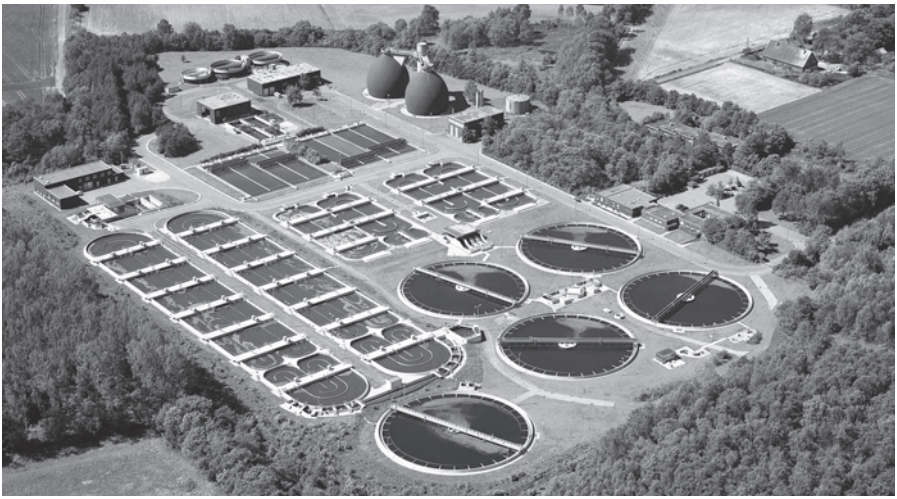

Figure 1: Wastewater treatment plant Münster (North Rhine-Westphalia), Germany, provided by Stadt Münster, Städt. Tiefbauamt.

The content of this publication

This document presents a number of contributions that relate to what is becoming known as 'wastewater sampling for drugs', 'drug wastewater analysis', or 'drug sewage epidemiology'. This area of work is developing in a multidisciplinary fashion, and contributions to our understanding of the topic are being made by scientists working in different research areas. For this reason, the contributions to this document come from a variety of different perspectives. Analytical chemistry has traditionally been the science most closely involved in this type of work. More recently, within environmental toxicology, a specialty has developed that is concerned with the surveillance, detection and quantification of drug residues whether these were legally or illegally introduced into the environment. In the present document there are important contributions from the perspectives of analytical chemistry, physiology and biochemistry, sewage engineering, spatial epidemiology and statistics, and conventional drug epidemiology.

The chapter on estimating community drug use by Ettore Zuccato and colleagues at the Istituto di Ricerche Farmacologiche 'Mario Negri', in Milan, provides an overview of the procedures used to estimate drug consumption rates in communities by analysis of wastewater. The method is based on the measurement of the breakdown

products of illicit substances collectively excreted with the urine by consumers and conveyed to the treatment plants with the wastewater. When pharmacokinetic and metabolic factors and the environmental fate of excretion products are taken into account, the environmental loads of a drug and its metabolites can be used as indicators of consumption.

This 'sewage epidemiology' approach investigates mass flows of the urinary breakdown products of illicit drugs to estimate epidemiological data, i.e. drug consumption rates in the population. However, among the important points made by Zuccato and colleagues are that the 'sewage epidemiology' approach may be able to provide objective data of drug consumption in real time, but it also carries with it several potential sources of uncertainty that may compromise the accuracy of subsequent consumption estimates. Despite its limitations, the authors conclude that this approach may have specific value in profiling drug consumption in real time, where official methods are lacking, and in monitoring changing trends (see Zuccato, in press, for a discussion on this topic).

The chapter by Teresa Summavielle presents an overview of the metabolic pathways of two different substances and their intracorporal degradation before reaching the wastewater system. The chapter considers some of the factors that may occur at the individual level, prior to the excretion of drug residues into the wastewater system.

For example, different routes of drug administration produce different blood levels of the drug and different peak times. Although plasma concentrations are generally proportional to the dose of the ingested drug, the ratio between ingestion and blood level will depend on the route used. This chapter also draws attention to uncertainties surrounding possible individual variations in the response to a set dose of drugs. These may be affected, for example, by the age and sex of the user, by body mass, kidney and liver function, by interaction with other drugs, previous drug use history and genetic variability.

Jörg Rieckermann's chapter discusses current knowledge on the transport and fate of illicit drugs in urban drainage systems. Typically, a drainage system includes house connections, manholes, main sewers, and retention tanks, and the system itself is normally complemented with a wastewater treatment plant. Sewer systems are themselves complex: mostly they have evolved over time and few of them have been planned from scratch. The chapter considers the discharge patterns of drugs to sewers, and a description is provided of in-sewer processes, and the relevance of

these processes to making accurate back-calculations of usage figures is discussed. Finally, the chapter looks at issues regarding the monitoring of drug loads over time. As in other chapters, these issues are considered mostly in relation to cocaine, since this is the substance for which most information is available.

The chapter by Fátima Pina considers how maps can be used by health scientists as an important tool to understand the complex interrelationships that exist between humans, diseases, and the environment. Maps can be used to complement other tools of spatial statistical analysis, epidemiology and public health in order to increase our understanding of the occurrence and localisation of health events. Geographical information systems provide options for spatial analysis by allowing the overlay of different maps to determine topological relationships of connectivity, proximity and adjacency. This has particular relevance to sewage epidemiology. For example, maps of the sewage network can be overlaid with maps containing population distribution. Wastewater samples are taken at specific locations (exact geographical coordinates) and can be geo-referenced. The relationships between the sampling point, the sample itself, and its final analytical description become more meaningful when combined with contextual information such as population density in the catchment areas, and demographic or socio-economic variables.

Lucas Wiessing and colleagues consider how data from wastewater studies might be integrated with estimates of illicit drug use from conventional approaches. The chapter briefly reviews current methods for monitoring and estimating illicit drug use and discusses issues that arise with regard to future work linking wastewater measurements with prevalence estimates.

In the final chapter, Roberto Fanelli and Norbert Frost bring together the various contributions, and sketch out some final conclusions and recommendations.

There is no doubt that the prospect of estimating drug loads from wastewater measurements presents an attractive proposition. In the various chapters, it becomes clear that this interesting new approach is accompanied by a number of uncertainties. There are various factors that may have important, but currently, poorly understood effects upon the findings and their interpretation. These issues are themselves interesting and further research will undoubtedly be required to enable a better understanding of the utility of this approach and of the best interpretation of the results.

Areas of uncertainty

Undoubtedly, there are difficulties in using wastewater measures of drugs to make inferences about the prevalence of users. The approach may, for example, be subject to limitations in the accuracy of estimates regarding collective consumption parameters, and these levels of uncertainty might be further increased by potential sources of error and variability related to the assumptions that are required for the calculations.

Uncertainties surrounding the analysis of wastewater samples may include, for example, issues concerning epidemiological questions, such as the phenotypes of users or behavioural variations in patterns of drug taking. Uncertainties may be related to individual differences in drug metabolism, such as the levels of drug metabolites in the blood. Information on human excretion rates for different substances is important for calculating the original amount of drugs consumed, but the data that is available on this topic is very limited. In the case of cocaine, the correction factors that are applied to metabolism and excretion rates tend to be based upon average values of the percentage of cocaine dose that is excreted as its metabolite, benzoylecgonine, and in the absence of other data, these correction factors are applied to other types of drugs. Little evidence is available to support or question the validity of these assumptions. Also, these values have generally been obtained from rather small samples of healthy volunteers, and they may not be representative of the metabolic responses of chronic drug users.

Similarly, a more precise interpretation of the results of wastewater analysis will require further information about the mobility of the introducing population. Closed water systems may serve transient human populations, and as a result, it may be difficult to characterise the population served by a given wastewater treatment system because of various sorts of changes that may occur in the resident populations of a given area (for instance, due to people congregating at inner-city venues during weekends). This may lead to problems in determining whether an apparent rise in observed drug use measures are due to an increase in consumption by the resident population, or to an increase in the number of the consumers because of changes of the resident population.

In addition, information will be required about excretion patterns and other factors relating to the introduction of drugs and their metabolites into the wastewater system. Variations in patterns of lavatory usage combined with the low percentages

of users of illicit drugs (e.g. cocaine or heroin) mean that marked fluctuations would be expected in the load patterns for these illicit drugs and their metabolites.

From an environmental engineering standpoint, the back-calculation of use figures and the monitoring of trends from illicit substance loads require an understanding of the wastewater system and its processes. The samples obtained from a wastewater system will be affected by leakage or heavy rainfalls. The greatest loss of drug residues is likely to occur during storm events. The analysis of wastewater samples may also be confounded by the sudden or unexpected introduction of high concentrations of chemical agents. Information should be available about significant potential confounders such as the clinical use of different drugs and the influence of introduced products from the pharmaceutical industry or veterinary medicine (Heberer, 2002). Such information is required to avoid erroneous interpretations concerning 'illegal' consumption.

Finally, information is required about substance transport or degradation in wastewater systems. The physical, chemical and biological transformation processes of solutes may have an important effect upon the ability to make meaningful estimates, and knowledge about such processes is incomplete, even for conventional pollutants. A number of complex chemical and biological interactions occur within sewer systems. Very little is known about how drugs and their metabolites in wastewater systems may be affected by biotransformation or sorption in sewer biofilms and sediments. Drug loads may also be affected by natural processes such as changes in wastewater temperature.

The analysis of wastewater is based upon samples drawn from the total liquid waste produced by a society. The mass flow of the analytes contains information about overall consumption. The results do not provide specific information about who has consumed which drugs, or what specific doses of drugs may have been taken. It is not possible to determine directly whether the observed variation in wastewater samples is reflective of changes in the number of active users (prevalence), or whether it relates to changes in levels of use (patterns of use, dosage) among users. It is possible that wastewater measurements may be more readily applicable for continuous monitoring of the amounts of a drug in the wastewater system. This sort of consumption index might be used as an index of drug use for specified closed systems (e.g. at the city level).

An interesting possibility is that wastewater analysis at the community level might offer an innovative method for obtaining information about whether interventions

targeting drug supply or drug demand (for instance interventions directed against drug distributors, identification and blocking of drug distribution, or public health campaigns) might have achieved any effect. Again, the utility of the method for such purposes is unproven and requires empirical investigation.

Ethical and legal aspects of wastewater sampling

In addition to the theoretical and scientific limitations, the work in this area also raises some interesting but challenging ethical and legal questions in relation to wastewater sampling.

Unlike surface waters, which are generally accessible to everybody and therefore do not create any obstacle in obtaining fluid samples, access to wastewater systems is likely to be subject to certain restrictions. Often, this will be for obvious reasons of safety and security. Generally, access to wastewater systems is restricted to the staff that are involved in maintenance. These processing systems are usually operated by public institutions such as community municipalities, or private enterprises as contractors. In practice, when an external agency wants to obtain wastewater samples, it will be necessary to obtain some form of permission from the responsible authorities. The decision to provide or deny access will often be taken by the operator, in accordance with the day-to-day operating rules of the service or the municipality and any relevant national legislation or codes of practice.

It is likely that a primary purpose of wastewater monitoring for residues of drugs will often be to obtain an area-level profile regarding concentrations of drugs. In this case, the focus will be upon mass flow and the choice of location for sample collection is likely to be the main proximal influent to the wastewater treatment plant. This would avoid conflicts with data protection issues, since the results would be aggregated and would relate to a population and not to identifiable individuals. In the case of several joint systems, one could also consider the main collectors as sampling points, where each community discharges into the jointly used collector sewer.

Nonetheless, an important feature of the wastewater system is that the house connection provides the last 'private point' before the individual household's waste products are mixed with all other input. The waste products that are carried through house-linked sewers can, therefore, be clearly identified in relation to specific households. Individual waste from a single household, when subject to wastewater

analysis, would allow for the identification of illicit drug use and for the construction of a specific, identifiable profile of consumption patterns.

The nature of closed wastewater systems permits the selection of a specific location as a unit of analysis. This could be, for example, the wastewater that comes directly from a particular building, a university campus, a military establishment, a local neighbourhood, or even a parliamentary chamber. Wastewater analysis does not require individual consent, and may be viewed by some as representing an unacceptable form of intrusion. There are clearly a number of potential ethical and privacy issues that are raised by this kind of surveillance approach.

It is not difficult to see that various individuals and agencies might take an interest in being able to identify the emission of illicit drugs (or other substances) from identified households. Information of this sort might be of interest to police, journalists or blackmailers. At present, other than the normal operating procedures regarding restricted access, there is little or no legal safeguard against private or state agencies obtaining access to household waste. Taking samples directly at the level of house connections goes beyond the scope of system monitoring and, from an ethical perspective, cannot be recommended.

A clear distinction should be made about the purposes and extent of investigations involving wastewater sampling: in particular, clarity is needed about whether the findings are to be used in the interests of public health or as a part of law enforcement or political control measures. While a monitoring programme of main wastewater streams or wastewater treatment plant influents seeks to establish community-wide average values, the specific sampling of public institutions or private households will not provide public-health relevant information and therefore cannot be recommended.

From an ethical and legal perspective, many of the apparent difficulties arise if this new approach is applied for purposes other than scientific inquiry. From a purely research perspective, ensuring the anonymity of individuals is a familiar issue that applies to any study that generates collective data; though in this case, the issue of informed consent may be more problematic. Standard research procedures are generally required to provide guarantees of anonymity. The same ethical understanding should apply to sampling in wastewater systems. However, a crucial difference is that wastewater sampling can take place without informed consent and users may not be given the option of not 'participating'. It should be noted, however, that this issue also applies to sampling for environmental monitoring purposes.

It would be prudent, therefore, if the ethical and data protection issues could be formally clarified, and a clear political and legal statement should be made about the circumstances under which samples may or may not be taken without violating the rights of individuals against the risk of illegal surveillance. The European directive on the protection of individuals with regard to the processing of personal data (European Parliament, 1995) is of relevance in this context. Such issues should be taken into consideration in the conduct of field trials.

Greater clarity is needed regarding current and required legislation concerning sampling procedures. It is recommended that all involved stakeholders should contribute to a full and open discussion of the ethical and legal issues that are involved in the application of wastewater analysis.

Concluding comments

The application of wastewater analysis to the investigation of illicit drug use represents an innovative approach to the monitoring of this problem. This method is most useful for drug surveillance at the community level. It could be used as a drug surveillance tool to assist public health and law enforcement officials in identifying patterns of drug use across municipalities of all sizes. And because wastewater sampling and analysis can be conducted on a daily, weekly or monthly basis, the data can be used to give a real-time measure that provides communities with more opportunity for monitoring the impact and effectiveness of prevention and intervention activities.

As with any new approach, wastewater analysis may be expected to generate a polarised response. Both the advantages and the disadvantages can be overstated. There remain many issues for which existing empirical data are either missing or very limited. Also, it can undoubtedly be expected that concerns will be expressed about the possible risks associated with this method. The currently available technologies for wastewater analysis increasingly provide opportunities for the investigation and interpretation of matters which touch upon issues of political or social sensitivity. In this case, there are potentially sensitive issues relating to intrusion and potential loss of privacy, and these matters may form the basis for potentially controversial discussions. It is to be hoped that a clear-headed assessment will be made of the advantages and implications of the developing science.

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Chapter 2: Estimating community drug use

Chapter 2: Estimating community drug use

Ettore Zuccato, Chiara Chiabrando, Sara Castiglioni, Renzo Bagnati and Roberto Fanelli

Introduction

The aim of this chapter is to provide an overview of the procedure we have developed to estimate drugs consumption in communities by analysing wastewater from treatment plants. The method involves measuring the levels of breakdown products of illicit substances excreted in the urine of consumers. The levels of breakdown products measured in wastewater are then scaled up to calculate consumption of the parent drugs among the population. Although this 'sewage epidemiology' approach provides objective consumption data in real time, some potential sources of uncertainty need to be addressed. Although measurements of levels in wastewater utilise specific and reproducible analytical methods, such as mass spectrometry, back-calculation is based on assumptions that might introduce some bias. This chapter therefore intends to give an overview of the procedure and to discuss potential drawbacks and margins of improvement of this method.

Sewage epidemiology

The 'sewage epidemiology' approach attempts to estimate epidemiological data regarding substance consumption from measurements of urinary breakdown products in pooled wastewater, e.g. in an urban sewage treatment plant. For example, measurements of the residues and by-products of drugs may be used to estimate the total consumption of these substances in a population (Dove, 2006).

The prevalence of drug use is currently estimated by subjective methods, such as population surveys (EMCDDA, 2005), which rely on self-reporting of socially undesirable behaviour and are thus likely to underestimate the true figure (EMCDDA, 1997). Here, we describe and discuss an alternative approach to estimate, objectively, consumption of illicit drugs in large communities. This approach is particularly suitable for monitoring consumption in real time, enabling prompt identification of changing trends, which is pivotal to the identification of problems, the planning of selective countermeasures and the assessment of the effectiveness of treatments.

Combining findings from these methods with those from classical population surveys would provide an integrated and potent tool to study drug use trends in the general population and would enable the phenomenon to be continuously reviewed.

The possibility of using 'non-intrusive drug monitoring at sewage treatment facilities to determine collective drug usage parameters at community level' was first proposed by Daughton (2001). Subsequently, we implemented this idea by measuring the level of benzoylecgonine (BEG), a metabolite of cocaine, in the sewage water of some Italian cities, and from these measurements we estimated the levels of consumption of this drug in those localities (Zuccato et al., 2005). We have now extended this procedure to other illicit drugs, such as opioids, amphetamine-type stimulants and cannabis, which we have identified in the wastewater of treatment plants (Castiglioni et al., 2006).

This chapter aims to provide an overview of the 'sewage epidemiology' approach and to discuss potential sources of variability and possibilities for improvement.

Sample collection and analysis

Several studies have reported that therapeutic and veterinary drugs excreted by humans and animals end up in the aquatic environment via the sewage system (Ternes, 1998; Zuccato et al., 2000; Kummerer, 2001; Heberer, 2002; Kolpin et al., 2002). We found published evidence that environmental levels of widely used therapeutic drugs approximately reflect the total amounts consumed by the local population, as calculated from prescription figures (Calamari et al., 2003; Castiglioni et al., 2004; Heberer and Feldmann, 2005). It appears that local wastewater and the receiving surface waters can be viewed as a sort of transient 'depository' for any sufficiently stable compound excreted by the local population.

Thus, provided factors such as pharmacokinetics and metabolism and the environmental fate of excretion products are appropriately taken into account, the environmental load (i.e. the amounts entering the environment over time) of a drug or its major metabolites or both, whether therapeutic or illicit, can be used as an indicator of consumption of that drug by the local population.

Although it is theoretically possible to sample both wastewater and surface waters, it is clear that only sampling of untreated water (influents) at the wastewater treatment plant (WWTP) level can be recommended for population studies because the concentration of the target substance in the receiving surface waters is determined

by the amounts persisting in the effluent of the WWTP following degradation or removal of the substance, at a rate that is variable and sometimes unpredictable. Moreover, in the case of a river, the degree of dilution and the size of the contributing population can be difficult to be estimated accurately, and sampling is also affected by several variables. The representativeness of the samples may therefore be inadequate, and analysis might provide unreliable results. In contrast, in a WWTP, the influent (untreated water) can be adequately sampled by an automatic sampling device, and flow rates and the size of the contributing population can be reliably determined.

In theory, estimates of drug consumption obtained in this way should fall within the range of the official figures. In practice, the method of collecting samples and the assumptions made in the calculations mean that the true consumption is only likely to be underestimated. For example, of the drug excretion products entering a sewage system, an unknown fraction may be lost or degraded before reaching the sampling site. In addition, the only source of drug metabolites present in wastewater is likely to be human excretion and, as these substances cannot accumulate in flowing waters, this method can again only underestimate the true value.

The starting point of our procedure is the selection of the molecules for analysis. We chose a range of illicit drugs that are among the most used worldwide, i.e. cocaine, opioids, cannabis and amphetamine-type stimulants. We then selected relevant excretion products of these drugs as analytical targets for wastewater monitoring (drug target residues, DTRs), after having considered the available knowledge on the metabolic fate of each active drug. The chosen DTRs were the main urinary metabolites in the case of cocaine, heroin and cannabis, and the unchanged parent drug in the case of amphetamine-type stimulants (Ambre, 1985; Smith et al., 2001; Baselt, 2004; Maurer et al., 2006), as detailed below.

Cocaine: Both cocaine and BEG were measured. In humans, cocaine is mainly excreted in the urine as BEG and only a small percentage is excreted as the unchanged drug. BEG levels were used to back-calculate cocaine consumption, as the only plausible source of BEG in wastewater is the urine of cocaine consumers. However, evaluating the presence of both cocaine and BEG can be useful to distinguish consumption from disposal by traffickers or users.

Opioids: Morphine was selected as a DTR. As several sources may account for the presence of morphine in wastewater, such as illicit use of heroin and therapeutic use of morphine and codeine, we also measured 6-acetylmorphine, a specific metabolite

Table 1: Stability of drug target residues in wastewater

Drug target residue	Amount spiked (ng/l)	Difference after 3 days (%) ± SD (%)
Benzoylecgonine	5 000	+13.9 ± 0.37
Cocaine	2 000	–36.1 ± 2.19
Morphine	2 000	+25.6 ± 1.45
6-Acetylmorphine	500	–4.0 ± 0.53
Morphine-3β-D-glucuronide	500	–96.3 ± 6.28
Amphetamine	500	+4.9 ± 0.04
Methamphetamine	500	+0.3 ± 0.01
MDA	500	–4.4 ± 0.15
MDMA	500	+0.8 ± 0.02
MDEA	500	–2.5 ± 0.05
11-Nor-9-carboxy-Δ9-THC	2 000	–7.8 ± 0.17

Note: The results are expressed as percentage differences between initial and final concentrations of each substance after three days' storage at 4°C (Castiglioni et al., 2006). SD = standard deviation.

of heroin. Morphine is excreted mainly as a glucuronide conjugate. However, we measured free morphine only, as glucuronides are hydrolysed to morphine by the beta-glucuronidases of faecal bacteria present in untreated wastewater (D'Ascenzo et al., 2003) and during wastewater treatment (Ternes et al., 1999).

This was confirmed by stability studies (Table 1) and by the detection of morphine-3β-D-glucuronide in random samples.

Amphetamine-type stimulants: We chose to monitor the parent compounds of amphetamine, methamphetamine and MDMA (ecstasy), as they are reported to be excreted mainly unchanged.

Cannabis derivatives: We measured 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH), the major urinary metabolite of Δ9-tetrahydrocannabinol (THC), the primary active constituent of cannabis. THC-COOH can be excreted as the glucuronide conjugate, but we monitored only the free compound for the reasons explained above for morphine.

A fraction of the drugs could theoretically be degraded before reaching the sampling site, and this would result in consumption levels being underestimated. Controlling for this factor involves experimental determination of the chemical and biological stability of the drug's excretion products. This was achieved by spiking a sample of wastewater with a known concentration of the target molecules and measuring the concentration after three days' storage at 4 °C (Table 1). Corrections for degradation can then be introduced in calculations.

The second step is to establish a suitable method for analysis of the selected DTRs. Samples of urban wastewater were enriched with internal standards labelled with a stable isotope and subjected to solid-phase extraction. Analysis requires highly selective and thoroughly validated methods, such as liquid chromatography–tandem mass spectrometry (Castiglioni et al., 2006). In our opinion, the inaccuracy in estimating consumption that may derive from the analytical variability is of little importance as this potential source of error can be adequately controlled by using analogues of the DTRs labelled with suitable stable isotopes as internal standards.

Back-calculation and assumptions

The concentrations of DTRs in wastewater conveyed to the treatment plant, reflecting the amounts collectively excreted in urine, can be used to estimate consumption of the parent drugs. For instance, as about half of a dose of cocaine is excreted in the urine as BEG, and only a small fraction as the unchanged drug (Zuccato et al., 2005), we used the concentrations of BEG in wastewater to estimate the amounts of cocaine consumed in a locality. However, we also measured cocaine concentrations to verify that the BEG/cocaine ratio was stable and in the expected range, which would confirm that the source of these substances was human consumption. If a sampling site were to be contaminated by the accidental or intentional disposal of a significant amount of cocaine, then the normal BEG/cocaine ratio would be altered in favour of cocaine. BEG loads (g/day) at each sampling site — calculated from the BEG concentration in water (ng/l) and water flow rate (m^3/day) — were multiplied by a factor of 2.33 to estimate the load of parent cocaine. This factor was derived from the BEG/cocaine molar mass ratio (0.954) and the average molar fraction (45%) of a cocaine dose that is excreted as BEG according to different studies (Ambre, 1985; Baselt, 2004). Cocaine loads were then related to the local population equivalents (i.e. the number of people served by a WWTP). The estimated consumption (g per day per 1 000 people) at each site was referred both to the

general population and to young adults (15–34 years), a group that reportedly accounts for almost all consumers (Ministero del Lavoro, 2001). The data were also expressed as the number of doses per day per 1 000 people, assuming 100 mg as an average dose (UNODC, 2004).

We have now extended this procedure to the other illicit drugs, such as opioids, amphetamine-type stimulants and cannabis, which we have identified in the wastewater of treatment plants (Castiglioni et al., 2006).

In the case of amphetamine, methamphetamine and ecstasy, calculation of consumption assumed that the proportion of an oral dose excreted unchanged in the urine was 30%, 43% and 65%, respectively (Baselt, 2004).

As the major metabolic product recovered in the urine after consumption of both morphine and heroin is morphine, estimates of heroin consumption were calculated after subtracting the amount of morphine attributable to consumption of therapeutic morphine based on known morphine consumption in Italy. Our calculations assumed that 42.5% of a dose of intravenous heroin and 85% of an oral therapeutic dose of morphine is excreted in the urine as morphine (Baselt, 2004) and that the heroin–morphine molar mass ratio is 1.29 (Baselt, 2004). Levels of 6-acetylmorphine, a specific but minor metabolite of heroin, could be also used to refine calculations. However, our preliminary analysis found higher than expected concentrations of 6-acetylmorphine in wastewater, revealing a need for further studies.

Estimates of THC consumption, based on THC-COOH loads in wastewater, took account of previous findings in volunteers that, for each milligram of THC smoked as resin or herbal cannabis, 6 micrograms of THC-COOH is excreted in the urine (Huestis et al., 1996) and that the THC/THC-COOH molar ratio is 0.91.

The number of doses consumed by a population can be estimated by dividing the total consumption in milligrams by the size of a 'typical consumption unit': 100 mg for cocaine, 30 mg for amphetamine and methamphetamine, 100 mg for ecstasy and 30 mg for intravenous heroin (UNODC, 2004). For therapeutic oral morphine, we used a defined daily dose (DDD) of 100 mg (WHO, 2007). For cannabis, we based our calculations on evidence that the concentration of THC in street resin or herbal cannabis in Italy has recently increased to an average of 15%, or 125 mg per dose (Camera dei Deputati, 2007) (Table 2).

The procedure described here has certain limitations in that the accuracy of the calculated consumption estimates is subject to potential sources of error and

Table 2: Selection of drug target residues (DTRs) for illicit drug monitoring in wastewater

Drug	DTR	Relation of DTR to parent drug	Drug dose excreted as DTR (%)	Molar mass ratio	Correction factor
Cocaine	Benzoylecgonine	Major metabolite	45	1.05	2.33
	Cocaine	Parent drug (minor excretion product)			
Heroin	Morphine	Major but non-exclusive metabolite	42	1.29	3.08
	6-Acetylmorphine	Minor but exclusive metabolite			
Amphetamine	Amphetamine	Major excretion product	30	1.0	3.3
Methamphetamine	Methamphetamine	Major excretion product	43	1.0	2.3
Ecstasy	Ecstasy (MDMA)	Major excretion product	65	1.0	1.5
Cannabis	THC-COOH	Major metabolite of THC	0.6	0.91	152

Note: The correction factor takes into account the percentage of parent drug excreted as the chosen DTR and the parent drug-to-DTR molar mass ratio. Morphine can derive from illicit heroin use, but also from consumption of therapeutic morphine and codeine (see text).

variability related to some of the assumptions. For instance, the values used to correct for the metabolism and percentage excretion of unchanged drug are based on published average values generally experimentally measured in healthy volunteers, who might not be representative of the whole population, and sample sizes are sometimes rather small. The accuracy could be improved by using an average drug-to-metabolite fractional conversion factor obtained from multiple

thorough studies. In addition, studies providing new, updated and accurate data on the metabolism of drugs in consumers would increase the precision of the estimates.

Another potential source of uncertainty is based on the difficulty of characterising the population served by a given WWTP at any particular time. Although the size of the population can be estimated, for instance by measuring organic carbon in wastewater, or simply by considering the wastewater flow rates during days with no rain, it is difficult to identify changes in the resident populations, e.g. at weekends. So, for example, it is not possible to determine whether an apparent increase in cocaine consumption on Saturdays (Figure 1) is due to an increase in consumption by residents or to an increase in the number of consumers resulting from an increase in the resident population at the weekend. Resolving this issue would require parallel surveys of the target population.

Reproducibility of the results

As discussed above, this method of determining collective consumption has some intrinsic limitations. Nevertheless, we believed that it was worth testing whether or not this analytical method offers any improvement over existing indirect methods or provides any valuable additional information.

The results of a repeated survey of the Nosedo WWTP in Milan (sampling was carried out daily during three non-consecutive weeks) gave us some useful information for discussion. The variation in average daily excretion rates for benzoylecgonine, THC-COOH and morphine were generally low, both between different days and between different weeks (relative standard deviation < 16% over seven days and < 19% over three weeks). When replicate data grouped according to the day of the week were analysed, we found that BEG concentration (indicating cocaine consumption) peaked on Saturdays and was significantly higher than on Mondays ($P < 0.01$), Tuesdays and Wednesdays ($P < 0.02$ vs. one-way analysis of variance and Dunnet's test) (Figure 1). Cocaine and amphetamine-type stimulants also exhibited an increasing but non-significant trend over the weekend, whereas morphine and THC-COOH consumption remained constant throughout the week, suggesting a rather steady use of heroin and cannabis in Milan.

Overall, there is evidence from the weekly surveys in Milan that the average daily excretion rates for major DTRs appear to be reproducible both on different week days and between different weeks.

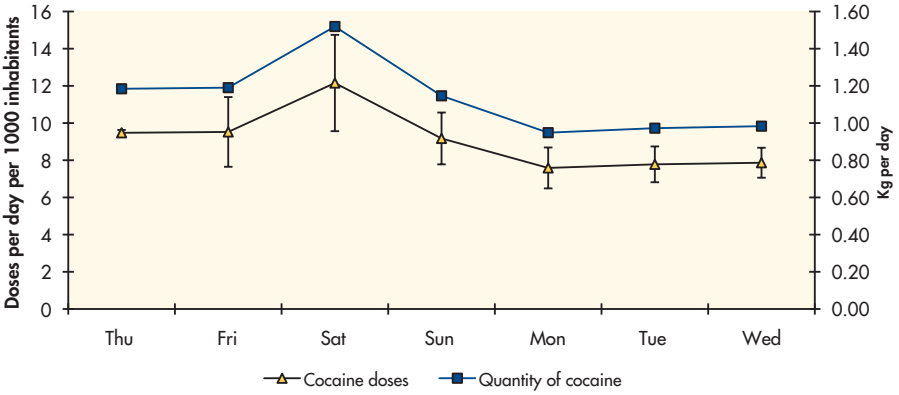

Figure 1: Day-by-day monitoring of cocaine equivalents in sewage water entering Milan's wastewater treatment plant, which serves 1.25 million people. Cocaine equivalents were estimated from benzoylecgonine levels (see text) (Fanelli et al., 2006).

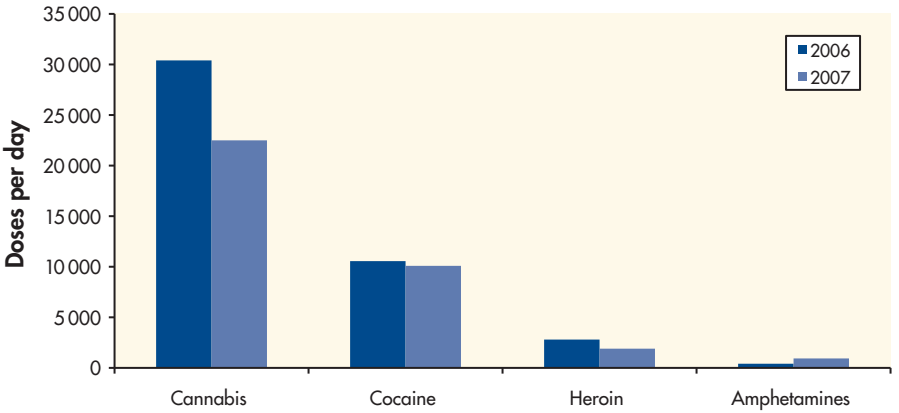

Figure 2: Profile of illicit drug use in Milan based on analysis of wastewater entering the Nosedo treatment plant (serving 1.25 million inhabitants). Comparison of the results obtained in 2006 and 2007. Doses per day were back-calculated from excretion rates of drug target residues after correction, as detailed in the text. Estimates of heroin consumption were back-calculated after subtracting the fraction of morphine probably excreted as a by-product of therapeutic morphine, as determined from known morphine consumption in Italy. The 'amphetamine-type stimulants' bar represents the total number of doses of MDMA (ecstasy), methamphetamine and amphetamine.

As previously discussed, estimating drug consumption by this method could be a useful tool to profile and monitor the drug use habits of the consumers and to promptly identify changes in trends. A comparison of the results obtained in 2006 with those of a survey carried out in March 2007 (five days' sampling at the Milan WWTP) gives an example of this potential (Figure 2). Our preliminary results indicate that consumption of cannabis and heroin in Milan decreased between 2006 and 2007 (by 26 % and 32 %, respectively) and that consumption of cocaine remained relatively stable, whereas consumption of amphetamine-type stimulants (ecstasy, methamphetamine and amphetamine) increased substantially (+127 %). Overall, these results would suggest that the behaviour of consumers changed between the two sampling dates: an increase in the consumption of amphetamine-type stimulants was offset by reduced consumption of cannabis, and the known decreasing trend in heroin was confirmed. However, before drawing any conclusion, we must take into account the fact that these data were obtained over a short time span only, and should be confirmed by long-term monitoring data.

Conclusion and perspectives

Surveys of the general population are useful for determining patterns of drug use, but they are expensive to carry out and are too slow to detect changing trends promptly (EMCDDA, 1997). Here, we propose and describe a new objective approach to estimate consumption of illicit drugs.

Clearly, this method still requires validation. This could be done indirectly, i.e. by comparing consumption estimates obtained in field trials with local prescription figures for a pharmaceutical drug, for instance methadone or other drugs with chronic indications, such as atenolol or carbamazepine; in fact, this has been already done, at least partially (Heberer and Feldman, 2005; Lindberg et al., 2005). However, we believe that a proper validation will require direct comparison of field trial results with findings regarding drug use from parallel local population surveys.

Once properly validated, patterns and trends of drug use in large communities could be monitored by this method, which will provide a useful complement to current official tools. This approach would seem to be particularly suitable for profiling consumption in real time, for which other methods are lacking, and for the prompt identification of changes in trends and habits, which is essential for planning and prioritising countermeasures. Combining findings from this method with those from population surveys would offer an integrated tool to monitor drug use.

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Chapter 3: Drug metabolism

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Teresa Summavielle

Introduction

As a precondition for quantifying drug consumption based on the measurement of drug breakdown products in wastewater samples, it is necessary to determine the metabolic pathways of specific substances and the extent to which they are degraded in the body before reaching the wastewater system. One of the outcomes of the first multidisciplinary meeting on this subject, held in Lisbon in April 2007, was the conclusion that cocaine and methadone should be used as test substances. Cocaine was chosen because its distribution in Europe has been reported to be increasing and thus there is a need for careful monitoring. Methadone was chosen because it is a prescribed licit drug, used in heroin substitution programmes, and as a powerful painkiller in cancer patients, as well as in veterinary anaesthesia. Cross-matching methadone concentrations in wastewater with dispensing figures from pharmacies may provide a better understanding of mass flow in wastewater systems in the context of potential field trials. The wide range of sources of methadone means that back-calculation must be carried out with particular care.

Cocaine

Cocaine is metabolised in the human body either by spontaneous hydrolysis or by the action of hepatic esterases and plasma cholinesterase (Figure 1). The major metabolites are usually benzoylecgonine (BEG) and ecgonine methyl ester (EME). In the presence of ethanol, cocaine is preferentially converted into cocaethylene (CE) by a transesterification reaction in the liver, with CE being further transformed into norcocaethylene (NorCE) and ecgonine ethyl ester (EEE). The presence of ethanol also increases cocaine demethylation to norcocaine (NC), the most toxic of cocaine metabolites. Heating of cocaine, as occurs when crack cocaine is smoked, results in the production of anhydroecgonine methyl ester (AEME), which is hydrolysed to anhydroecgonine (AE).

Significant toxicity arising from the use of cocaine was not considered a problem until purified cocaine became available for recreational use in the 1970s. Investigations into the metabolism of cocaine also began in the early 1970s. Human metabolism of cocaine seems to be largely dependent on the previous levels of

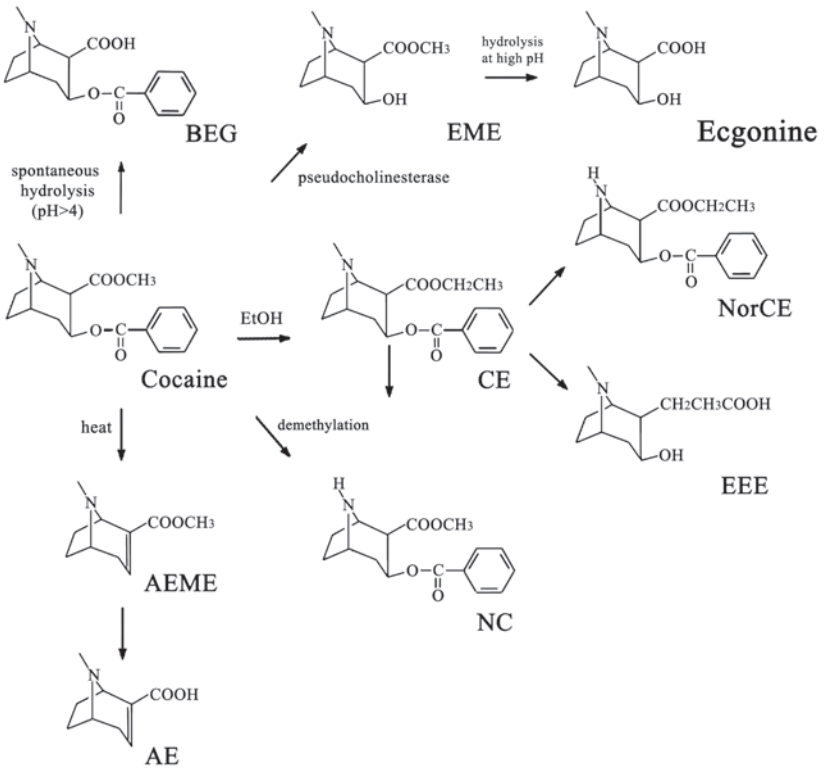

Figure 1: Metabolism of cocaine.

exposure to this drug. Initially, most findings were limited by serious methodological problems, such as the absence of a control group, unreliable identification of cocaine users and non-users, and inadequate control of confounding variables (Lester et al., 1995). Consequently, published results are often contradictory and the mechanisms of action of cocaine are still not fully understood. The use of consistent criteria and of research animal models in which major confounding factors, such as polydrug use, environment and lifestyle (Neuspiel, 1995) are well controlled is clearly necessary (Dow-Edwards, 1991; Vorhees, 1995; Spear et al., 1998; Frank et al., 2001; Henck, 2002). Here, we address the metabolism of cocaine, aiming to show which are the main human metabolites and how individual variability and environment and social

behaviour can influence the course of cocaine biotransformation. The metabolism of methadone is also described in a simplistic way. Although the methadone found in the sewage system may come from different sources, there are reliable sources of data sources on its availability, prescription and use. Therefore, potentially, methadone could provide a good control for back-calculation in sewage systems.

Blood concentrations

Different routes of administration will result in different blood levels of cocaine, and these will peak at different intervals after administration. Although plasma concentrations are generally proportional to the dose of cocaine ingested, the exact relationship will depend on the route of administration. This is because the potent vasoconstrictive properties of cocaine (Knuepfer et al., 1994) mean that cocaine inhibits its own absorption, increasing the time for maximum blood concentration to be achieved compared with intravenous administration. Thus, in the case of cocaine consumed by snorting, leaf chewing or even smoking, the higher the dose, the slower the absorption.

On average, chewing 12–15 g of leaves (with an alkaloid content of usually less than 0.5%) results in ingestion of around 75 mg of cocaine. In a novice chewer, who may spit out saliva, blood concentration will peak at around 38 ng/ml after 1 hour; however, in experienced users, who swallow saliva, peak blood concentration averages 249 ng/ml (individual variation can range from 130 to 859 ng/ml) (Holmstedt et al., 1979; Paly et al., 1982).

Previous studies have shown that intranasal application of cocaine, which mimics the effect of snorting, in doses of 1.5 mg/kg, i.e. 90 mg in an average 60-kg man, (equivalent to two to three 'lines' of cocaine), results, on average, in blood peaks of 120 ng/ml at 15 minutes and 470 ng/ml at 30 minutes (Brogan et al., 1992). Cocaine persists on the nasal mucosa for at least three hours after exposure, probably because of its vasoconstrictive properties (Van Dyke et al., 1976). These levels are similar to those observed in an experienced cocaine chewer for a similar dose of the drug.

Intravenous cocaine use, on the other hand, will result in much higher levels of the drug in the blood. Injection of 100 mg will result in a peak blood concentration of 700–1 000 ng/ml in five minutes, which implies the need for multiple injections to maintain persistent high levels of the drug (Barnett et al., 1981).

Benzoylecgonine

At pH values above 4, cocaine is rapidly hydrolysed to benzoylecgonine (BEG), its main metabolite. BEG has a urinary excretion half-life of 6–8 hours (Ambre, 1985) and, in general, can still be detected in the urine 48 hours after cocaine administration (Saxon et al., 1988). Although BEG was originally believed to be pharmacologically inactive, it was later shown to be able to cause vasospasm. As BEG has no adrenergic properties, it probably acts by altering calcium influx and calcium channel regulation (Madden et al., 1995). Although results obtained in animal models support a possible role for BEG in the genesis of stroke and myocardial infarction, which sometimes occur hours after cocaine ingestion, there are no clinical data to support this hypothesis.

No studies have shown any psychoactive properties of BEG. Nevertheless, *in vitro* studies have demonstrated that BEG is inherently cytotoxic (Lin and Leskawa, 1994). Although most BEG is formed from spontaneous hydrolysis, human carboxylesterase 1 (hCE-1), a microsomal serine hydrolase found in the liver, intestine, kidneys, lungs, heart and plasma, is capable of catalysing the conversion of cocaine to BEG (Bencharit et al., 2003).

Ecgonine methyl ester

The other major metabolite of cocaine is ecgonine methyl ester (EME) (Stewart et al., 1979; Matsubara et al., 1984; Cone et al., 1998; Kolbrich et al., 2006). Cocaine is metabolised to EME by pseudocholinesterase and hCE-2. EME is very stable at pH values between 3 and 5, but as pH increases, EME is hydrolysed to ecgonine. Above pH 9, EME is no longer detectable (Vasiliades, 1993). Thus, circulating EME is rapidly converted into ecgonine.

After death, as a result of anaerobic metabolism, acidity increases and spontaneous hydrolysis ceases, although enzymatic synthesis of EME persists and it accumulates, altering the BEG/EME ratio (Karch, 1996).

The rate of metabolism of cocaine to BEG or EME varies between individuals, a finding that has been attributed to phenotypic variations in pseudocholinesterase, which binds to cocaine with different efficiencies (Xie et al., 1999). EME is considered to be the least toxic of all cocaine metabolites. Although some authors have suggested that it may afford some protection from cocaine toxicity (Hoffman

et al., 2004), recent reports suggest that EME is involved in vasodilation processes (Madden and Powers, 1990; Pane et al., 1997; Hollander and Henry, 2006).

Cocaethylene

In the presence of ethanol, cocaine undergoes transesterification to cocaethylene, a reaction that is catalysed by hCE-1 in the liver or by ethyl ester synthetase (widely distributed in the body) (Hearn et al., 1991; de la Torre et al., 1995; Farre et al., 1997; Harris et al., 2003). Several studies have found that cocaethylene is more toxic than cocaine and that it readily crosses the blood–brain barrier and has similar affinity for the dopamine transporter protein (DAT) (McCance et al., 1995; McCance-Katz et al., 1998; Pennings et al., 2002; Goldstein et al., 2004).

Alcohol intensifies the psychotropic effects of cocaine and increases the incidence of violent behaviour (Pennings et al., 2002). Cocaethylene has a longer elimination half-life than cocaine (Laizure et al., 2003), and can be further metabolised to BEG, norcaethylene and EME (Cone et al., 1994). The presence of alcohol has also been shown to increase peak levels of cocaine, which is probably associated with alcohol-induced pH shifts that reduce spontaneous hydrolysis to BEG (Farre et al., 1997).

Norcocaine

Hepatic necrosis due to cocaine metabolism results from the conversion of cocaine to norcocaine, the most toxic metabolite of cocaine. It has been shown that P450 enzymes participate in this process; cocaine being first demethylated to norcocaine and then metabolised to N-hydroxynorcocaine by brain FAD-containing mono-oxygenases (Kloss et al., 1984a,b). Further enzymatic breakdown in brain microsomes results in norcocaine hydroxide, which, although itself stable, can be oxidised to the norcococaine nitrosodium ion, a highly reactive compound that reduces glutathione levels and increases lipid peroxidation and protein carbonylation (Evans, 1983; Shuster et al., 1983; Kloss et al., 1984b). Additionally, norcocaine can be hydrolysed to benzoylnorecgonine.

Anhydroecgonine methyl ester

Anhydroecgonine methyl ester (AEME) is a pyrolysis product of cocaine that is excreted solely in the urine of crack smokers. AEME is converted to ecgonidine, probably through enzymatic hydrolysis (Scheidweiler et al., 2000, 2003). AEME chemically resembles other compounds that have cholinergic properties and may

therefore be responsible for the decrease in air flow observed in crack smokers (Chen et al., 1995; Kleerup et al., 2002).

Excretion

Cocaine is eliminated almost entirely by renal clearance (Chow et al., 1985). Disposition of cocaine has been characterised by one- and two-compartment open kinetic models (e.g. Ambre, 1985; Cone, 1995) and by non-compartmental models (Kolbrich et al., 2006). Despite the justifications presented in most papers, none of the current models fully explains the disposition of cocaine. A detailed study investigating the large number of variables that can significantly affect the rate of cocaine metabolism and the formation of its various metabolites is needed.

Conclusion

The assumption that 30–50 % of ingested cocaine is usually converted to BEG is clearly insufficient. The use of BEG quantification to estimate levels of cocaine consumption should, therefore, take account of the fact that the metabolism of a fixed dose of cocaine ingested by the same route will vary between individuals depending on sex (Dhossche, 2000; Visalli et al., 2005), age (Sandberg et al., 1995), body mass (brown fat tissue avidly retains cocaine) (Som et al., 1994), kidney and liver function, interaction with other drugs (such as alcohol), previous drug use history and genetic variability, including variation in receptors, transporters and enzyme polymorphism (Evans, 2003; Maurer et al., 2006).

Methadone

The main metabolites of methadone are 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyraline (EDMP) (Figure 2). Methadone undergoes pharmacological inactivation by mono- and di-N-demethylation, followed by spontaneous cyclisation to EDDP catalysed by cytochrome P450 3A4 (CYP3A4). Methadone may also be metabolised to a much smaller extent to methadol and normethadol; however, these metabolites can also originate from the deacetylation of acetyl methadone (LAAM).

Methadone is a diphenylpropylamine derivative (6-dimethylamino-4,4-diphenyl-3-heptanone) that contains the same basic structures as other opioids. Its high oral bioavailability and a long elimination time make it suitable for the treatment of heroin addiction and for analgesia in cancer patients. Methadone is available

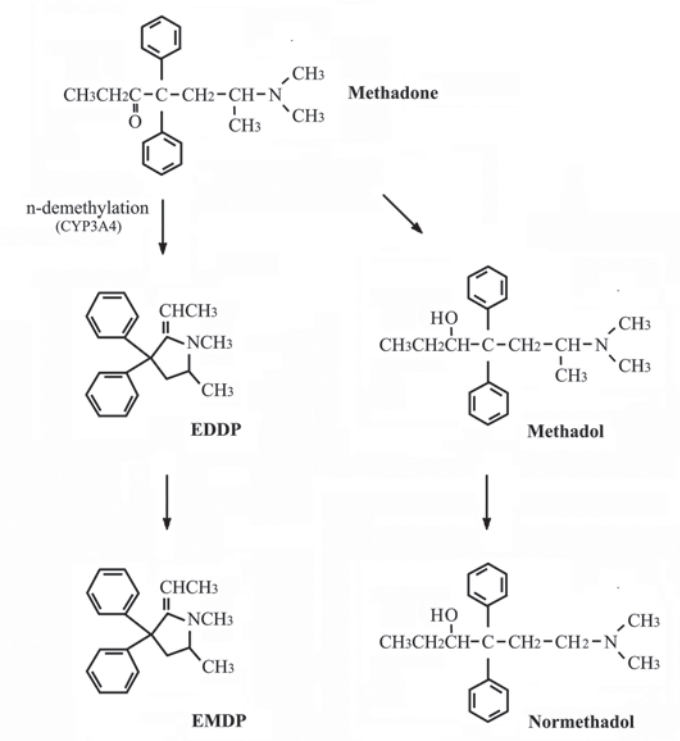

Figure 2: Metabolism of methadone.

on the market as a racemic mixture of two enantiomers. (*R*)-methadone has a 10-fold higher affinity for opioid receptors, and therefore is much more pharmacologically active (Olsen et al., 1977; Kristensen et al., 1995; Eap et al., 2000). Methadone taken orally is detectable in the plasma about 30 minutes after administration (Inturrisi and Verebely, 1972). All oral formulations of methadone — solid tablets, dispersible tablets and liquid concentrate — are intrinsically equal in terms of their absorption and metabolism (Gourevitch et al., 1999).

Plasma concentrations

Previous kinetic studies have found a strong relation between a given dose of methadone and the resultant plasma levels. For example, Wolff et al. (1991a) reported a linear correlation between oral dose of methadone and plasma

concentration over the range 3–100 mg per kilogram body weight, with each mg/kg dose increase resulting in an increase in plasma methadone concentration of 263 ng/ml. Despite this, inter-individual variability in absorption and metabolism is now believed to be the main factor responsible for the unpredictability of plasma levels and clinical effect at different doses.

According to recent data, the plasma concentration of methadone follows a bi-exponential curve, with a rapid β-phase, corresponding to the transfer of methadone from the central compartment to the tissue, and a slow β-phase that represents the elimination stage (Verebely et al., 1975; Nilsson et al., 1982a; Wolff et al., 1991a,b; Rostami-Hodjegan et al., 1999; Ferrari et al., 2004). The maximum plasma concentration is reached between one and six hours (average 2.5–4.4 hours). The greatest inter-individual variation appears to occur during the elimination phase. Transfer to tissues such as liver, kidneys, lungs and brain occurs rapidly because methadone is very lipophilic (Dole and Kreek, 1973). The methadone that remains in the blood (1–2%) is in equilibrium with methadone bound to plasma globulins and can be altered by factors such as stress and addiction (Olsen, 1972). According to some authors, plasma levels and excretion rates may vary during prolonged exposure (Verebely et al., 1975; Holmstrand et al., 1978).

After administration, methadone is converted via N-demethylation into several metabolites that are apparently inactive. The elimination of methadone occurs through urine and faeces (20–50% unchanged) (Nilsson et al., 1982b). The proportion of methadone excreted unchanged depends on the pH of the urine, increasing with increasing acidity; at pH values lower than 6, levels of unmodified methadone can be 3–8 times higher compared to those at higher pH values (Baselt and Casarett, 1972a,b; Nilsson et al., 1982b). The most important enzymes in methadone metabolism are cytochrome P450 proteins known as CYP enzymes (Leavitt et al., 2000; Shinderman et al., 2003; Crettol et al., 2005). These enzymes are found mainly in the liver but can also be found in other organs. CYP3A4 and CYP2B6 are the major CYP isoforms involved in methadone metabolism, with CYP2D6 contributing to a minor extent (Crettol et al., 2006). CYP polymorphisms also add to the inter-individual variability of methadone kinetics.

Another metabolically important protein is P-glycoprotein, which is found mainly in the intestine and along the blood–brain barrier (Wang et al., 2004; Nanovskaya et al., 2005; Ortega et al., 2007), and which functions as a pump, transporting methadone out of cells lining the intestinal wall and back into the lumen. Therefore,

some of the methadone ingested and absorbed by the intestine is pumped back and never reaches the blood circulation. Thus, differences in the expression of P-glycoprotein also account for inter-individual variation in methadone metabolism (Leavitt et al., 2000).

Excretion

Methadone is primarily eliminated from the body by metabolism in the liver. Among the nine metabolites of methadone that have been identified in human urine, the main breakdown products of methadone are 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyraline (EDMP). Methadone undergoes pharmacological inactivation by mono- and di-N-demethylation, followed by spontaneous cyclisation to the EDDP catalysed by intestinal, hepatic and expressed cytochrome P450 3A4 (CYP3A4) (Eap et al., 2001; Shinderman et al., 2003; Ferrari et al., 2004; Crettol et al., 2005). It has been shown that the process of N-demethylation is not markedly stereoselective, although CYP2D6 may be involved in other oxidative pathways involving the (*R*)-methadone form. EDDP accounts for 3–25% of the dose excreted in the urine over the first 24 hours. However, excretion of EDDP is relatively slow and it may still be present in the urine 2 days after the last ingestion of methadone. Urinary excretion of EDPM accounts for less than 1% of the ingested dose. Methadone, EDDP and EDMP also undergo hydroxylation in the para-position of one of the phenyl rings and glucuronide conjugation.

Methadone is also metabolised to two minor pharmacologically active metabolites: methadol and normethadol. However, these metabolites can also be originated by the deacetylation of acetyl methadone (LAAM) (Kaiko et al., 1975; Kreek, 2000).

Other drugs that compete for the same binding sites in the plasma, or which are metabolised by the same enzymes in the liver, can modify the action of methadone, increasing or decreasing the amount of unaltered methadone that is excreted and the rate of excretion (for review, see Stout and Farrell, 2003). Nevertheless, if both methadone and EDDP are monitored in the urine, it is still possible to estimate the ingested dose.

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Chapter 4: On the occurrence and fate of illicit substances in sewer systems

Chapter 4: On the occurrence and fate of illicit substances in sewer systems

Jörg Rieckermann

Introduction

This chapter provides an overview of current knowledge regarding the transport and fate of illicit drugs in drainage systems. The representativeness of measured data can be evaluated completely only when the load pattern of a substance at the monitoring point is known, which in turn requires a detailed understanding of wastewater systems. The chapter is structured as follows. First, the patterns of discharge of drugs to sewers, e.g. in urine, are addressed briefly. Then, in-sewer processes are described and their relevance for accurate back-calculations of usage figures is discussed. Finally, issues regarding the monitoring of drug loads over time are presented. From an environmental engineering perspective, the evaluation and prediction of drug loads in wastewater systems is a complex and challenging topic that requires a level of knowledge of the processes involved (either as models or experimental data) that is beyond the scope of this chapter. Therefore, references are given where possible. Again, cocaine serves as a model substance, as it is the illicit substance for which the greatest amount of information is available.

Assessing cocaine loads in sewers

Urination patterns

As described in Chapter 3, cocaine and its metabolites are excreted mainly in urine. The spatiotemporal pattern of urination (also called voiding or micturition in medical literature) in a catchment depends on where, when and how much is voided. While voiding patterns are clearly stochastic, they are not uniformly distributed over time or the catchment area, with certain factors, e.g. work schedules, tending to result in peaks and troughs. Voiding patterns have been mainly investigated in medical research (Larsson and Victor, 1988; Boedker et al., 1998; Schick et al., 2003; Pfisterer et al., 2006), and it has been found that people use the lavatory approximately 4–6 times per day (Boedker et al., 1998; interquartile range). In addition, recent studies have found that lavatory use generally occurs mostly during the morning hours and in the evenings, and that this

pattern is different at weekends (Friedler et al., 1996; Hellström and Kärrman, 1996; Rauch et al., 2003).

Taking these findings into account, and given that drug users constitute only a few per cent of the population, one would expect the load pattern of illicit substances and their metabolites at any particular monitoring station to fluctuate wildly, even those serving medium or large catchments. As stated above, although the dynamics of a drug load pattern at a monitoring point is not particularly interesting per se, it can be critical for the correct interpretation of measured data (see further below). Therefore, it is also important to know whether: (1) cocaine in urine could come from sources other than drug consumption; and (2) what other sources of cocaine might be discharged to the sewer system.

Discharge of cocaine from sources other than illicit drugs

Some studies have reported that cocaine and/or its metabolites are produced following consumption of tea made from coca leaves (Jenkins et al., 1996; Hammett-Stablers et al., 2003; Perrone et al., 2005; Turner et al., 2005). Although coca tea is consumed frequently in some Latin American countries, it is less common in other regions. Usage figures are not readily available, and it is not clear whether cocaine is destroyed during tea preparation. Cumulative benzoylecgonine excretion is reported to be approximately 3 mg per coca tea bag consumed (Jenkins et al., 1996). If one assumes that a typical dose of 100 mg of cocaine leads to an excretion of approximately 30–50 mg of benzoylecgonine, the population-wide consumption of coca tea (e.g. in Bolivia) might lead to an overestimation of illegal drug use. A brief literature review on cocaine use in industrial processes and on possible industrial discharges to municipal sewers did not produce evidence that these might be significant. The influence of residues resulting from the use of cocaine in clinical trials or animal studies (e.g. laboratory mice) is not considered here.

Little is known about the occurrence of cocaine residues in groundwater, which often infiltrate sewer systems through cracks and fissures. In some studies, drinking water analysis has revealed traces of pharmaceuticals (Hummel et al., 2006; Zuccato et al., 2006), but the concentrations of cocaine and its metabolites were always below the detection limit. It is speculated that this is because chlorine residues in drinking water have the potential to oxidise these compounds. In summary, current evidence suggests that additional sources can generally be ignored in estimates of illicit cocaine consumption, with the potential exception of a contribution from residues of coca tea.

Modelling urine flows in sewers

As urine is the major pathway for the excretion of not only drugs, but also of nutrients, recent investigations in environmental engineering have modelled urine flows in sewers to assess the potential impact of nutrient control strategies on wastewater treatment plants (WWTPs). In the literature, specifically tailored stochastic models are used to predict ammonium loads and to evaluate the impact of control strategies (Peters et al., 2002; Rauch et al., 2003). These models vary in complexity, but generally incorporate variables such as urine volume, population mobility and sewage transport. Generally, transport processes are considered in a simple fashion and transformation is usually ignored on the assumption that the substance of interest is not altered or degraded in the drainage system (e.g. ammonium).

To evaluate the applicability of such models, current knowledge regarding sewage transport and transformation processes is summarised below. As environmental analysis of illicit substances is a recently emerging field, few experimental data regarding the fate of illicit substances in wastewater systems have been reported. Much more work has been done on pharmaceuticals and personal care products (PPCPs), which will be used for comparison where appropriate.

Transport and transformation processes in sewer systems

The urban drainage system

Sewers are a key part of urban drainage systems because they transport polluted and unpolluted water from settlements. This is necessary to maintain hygiene and to provide flood protection. A drainage system usually has the following elements: (1) house connections; (2) manholes; (3) main sewers; and (4) retention tanks. The system (Figure 1) is normally complemented by a WWTP, which generally removes suspended solids and nutrients through various physical, chemical and biological processes (Gujer, 2002).

Drainage systems are designed as combined or separate systems. In 'separate systems', two complementary pipe systems are installed. Sanitary sewers (also known as foul sewers) specifically collect the domestic and industrial wastewater that is discharged from the house connections. Storm drains, which are independent of sanitary sewers, carry the runoff of rain and other water that washes into city streets. In the 'combined system', both sewage (from homes and businesses) and rainwater drain into the same pipe network.

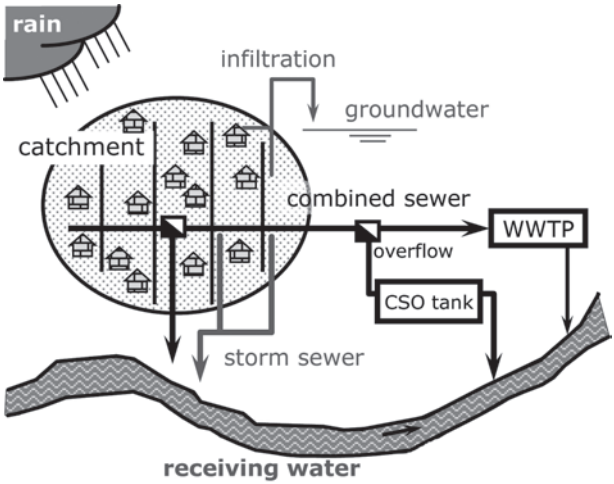

Figure 1: General representation of an urban drainage system (after Gujer, 2002).

Where possible, sewers are generally constructed as gravity sewers, enabling free surface flow, which has a number of advantages (Gujer, 2002). However, most urban drainage systems evolve over time to meet changing needs; few are designed from scratch. Thus, most urban sewage systems are a combination of different separate systems and may include a number of pumping stations and alternative systems (e.g. vacuum assisted or pressurised systems) that influence the propagation of substances and the residence time of the wastewater. Decentralised systems (Otterpohl et al., 1997) or systems that enable urine separation for nutrient recovery (Henze, 1997; Larsen et al., 2004) are perceived as promising alternatives to existing designs; but as these systems have not been widely implemented, they can currently be ignored in the assessment of illicit drug loads.

Substance losses during storm events

As urban drainage systems capable of handling the maximum load during wet weather are very expensive, it is generally accepted that sewerage systems will overflow at some tolerable frequency, e.g. once every 10 years (Verworn, 2002). To alleviate flooding problems in both the catchment and the receiving waters, combined sewer overflows (CSOs) and retention tanks, in which combined rain and wastewater is stored temporarily and later routed to the WWTP, have

been introduced. During heavy storms, if the capacity of the tank is exceeded, stormwater (with sewage) spills into the receiving waters, preventing back-up into streets and homes. From the point of view of monitoring consumption of illicit substances, this means that an amount of substance that is very difficult to quantify may be lost during heavy rain events. Analysis of long-term CSO data in Germany and Switzerland has shown that sewer overflow occurs roughly 2% of the time (Gujer, 2002; Weiss et al., 2006). As a rule of thumb, it can be assumed that 50% of the diluted water is discharged (Krejci et al., 2000), which means that the long-term substance loss would amount, on average, to approximately 1%. As losses during individual events might be much larger, it is recommended that monitoring campaigns should be restricted to periods of dry weather to avoid biased results.

Regarding transport and transformation, the sewer system can be subdivided into four compartments: (1) sewer atmosphere; (2) bulk wastewater; (3) biofilm (sewer slime); and (4) sediments. The interactions between these compartments are affected by: (1) physical properties (e.g. slope and roughness); (2) hydrodynamic conditions (e.g. discharge dynamics); (3) environmental conditions (e.g. temperature, pressure); and (4) physical, chemical and biological processes (Huisman, 2001; Huisman et al., 2003; Vollertsen et al., 2005a).

The next section describes the processes that affect the discharge of illicit drugs into the sewer system. Only transport in gravity sewers under dry weather conditions is considered, because it is much more difficult to determine transport during rainy weather when flow is highly irregular owing to the utilisation of surcharged manholes and tanks. In addition, only solute transport is discussed and sediment deposition and resuspension processes are ignored, as these are still not understood completely (Ashley et al., 2005).

Sewage transport during dry weather

To estimate drug loads in sewers, it is preferable to monitor substances at a certain distance from the source (i.e. in the so-called 'far field'), where the impact of the impulse of the discharge process on substance mixing is negligible. Transport in the far field is dominated by advection, dispersion (stretching of the substance cloud due to non-uniform velocity profiles) and transformation processes, e.g. degradation, that may eliminate the contaminant (Fischer et al., 1979).

Advective transport and solute mixing

The effect of advection (solute transport with the bulk water) and dispersion (stretching effect due to the three dimensional, non-uniform velocity field) is illustrated in Figure 2, which shows the results of a tracer experiment. A salt tracer was injected instantaneously (at point 0) and the tracer curve monitored at two points further downstream (1 and 2). It can be seen that advection transports the tracer cloud from point 1 to point 2 in about 2 800 s. In addition, the tracer curve is being stretched and the peak concentration is reduced substantially. For most sewers, transport is considered one-dimensional, because solute concentrations are usually vertically and laterally well mixed in the wastewater (Huisman et al., 2000; Rieckermann et al., 2005a).

Longitudinal mixing in sewers is usually modelled by a dispersion coefficient that depends on the velocity distribution. An analysis of a large number of sewer tracer experiments has shown that dispersion coefficients in gravity sewers are generally small in comparison with those of rivers and do not differ much from system to system. Furthermore, it was found that in the absence of tracer data, prediction of dispersion from sewer geometry and flow data is limited. For details on suggested models and the magnitude of dispersion coefficients, see Rieckermann et al. (2005a).

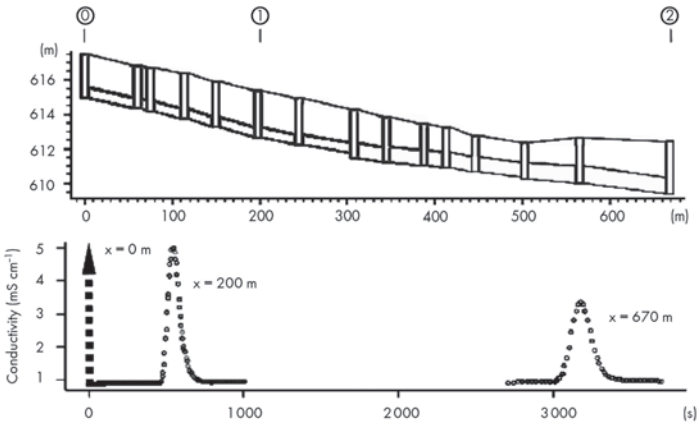

Figure 2: (Top) Longitudinal profile of a sewer section. ⓪ = dosing point of tracer (slug injection), ① = first monitoring point (outside the initial zone), ② = second measuring point at the end of the reach. (Bottom) Tracer curves at dosing and monitoring stations. From Rieckermann et al. (2005a).

Transport in house connections

Wastewater flow in house connections is usually intermittent and arises mostly from periodic use of household utilities such as the lavatory, dishwashers or showers. To the author's knowledge, very little is known about how a dissolved substance is propagated through household utilities and house connections, there apparently being only one study of solute transport from the lavatory to the main sewer reported in the literature (Ort, 2006). The findings revealed a skewed tracer distribution with long tails (not shown). It was posited that this pattern was caused by backwater effects and dead zones resulting from deposits in the house connection, which seems highly plausible as house connections are normally not included in regular sewer inspections and are often in a structurally poor state. In addition, house connections are often incorrectly linked to the sewer system and are sometimes regarded a major source of wastewater losses (Barrett et al., 1997; Ballweg, 2002; Ternes and Joss, 2006). When quantifying drug residues, significant losses of wastewater would lead to an underestimation of drug consumption. Currently, no established leakage estimates are available for house connections; partly because appropriate monitoring techniques are lacking (Rutsch et al., 2006).

Sewer leakage

Wastewater leakage occurs not only via dilapidated house connections, but also through ageing main sewers, which may not be completely watertight (Rutsch et al., 2006). Despite many years of research, little is known about the magnitude of water loss through sewer leakage, because it is difficult to observe *in situ* and experimental methods have been lacking (Rieckermann et al., 2005a; Rutsch et al., 2006). Our current understanding of the processes is incomplete, and contradictory results have been reported in case studies. Some authors have suggested that leaks in sewers undergo self-sealing as a result of particle clogging and bacterial growth, with the result that reported losses amount to less than one per mille of the average dry weather flow (DWF) (Wolf et al., 2006). However, in experimental studies, concentrations of wastewater-borne substances found in the groundwater have ranged from 0 to 20% of DWF or more (Heberer, 2002; Reynolds and Barrett, 2003; Webb et al., 2003; Fenz et al., 2005; Wolf et al., 2007). It can only be speculated as to whether these substances have entered the groundwater via a large number of unobserved small leaks, leaky house connections or a few extreme leaks in the system. One particular problem is that inter-study comparability is difficult due to different measurement methods and procedures (Rutsch et al., 2006).

In general, we can conclude that excellent tools are available to describe the hydrodynamics of sewers during dry and rainy weather. Also, apart from sewer leakage, the transport processes of solutes such as cocaine and its metabolites in main, are reasonably well understood. However, wastewater in sewer systems is subject to important physical, chemical and biological changes, and the transformation of substances in sewers, which is not normally taken into account, might be critical for the back-calculation of consumption estimation.

Transformation processes in sewers

The conversion of wastewater in sewers has traditionally received little attention, but recent research has confirmed the importance of chemical and biological sewer processes that have complex interdependencies (Nielsen et al., 1992; Hvitved-Jacobsen et al., 1998; Huisman, 2001; Vollertsen et al., 2005a).

The schematic transformation of organic matter in the gas phase, the wastewater and the biofilm is shown in Figure 3 (the sediment compartment is omitted for simplicity). The sewer biofilm mainly consists of rapidly growing heterotrophic microorganisms that degrade organic matter under aerobic conditions. However, nitrifying bacteria and others, such as methanogenic or sulphur-reducing species, are also present. In addition, sewer biofilms also contain a large amount of inorganic material, such as sand and zeolite, as well as fats. It is known that sewer biofilms are constantly eroded during dry weather flow, but most biomass is lost during storm events, which cause increased shear forces (Huisman, 2001).

Several attempts have been made to describe the conversion processes in sewers, and some models have been suggested to describe transformation of organic matter, nitrogen and sulphur under aerobic, anoxic and anaerobic conditions (Huisman et al., 2003; Vollertsen et al., 2005b). Although there seems to be evidence that cocaine and its metabolites undergo significant changes (see further below), no detailed information is currently available regarding the transformation of cocaine and its metabolites. However, to illustrate their potential impact, the processes involved in the removal of PPCPs in WWTPs, which are much better understood, will be described. Ternes and Joss (2006) give a detailed description of the most important removal mechanisms for PPCPs in wastewater: (1) stripping; (2) sorption; and (3) biotransformation.

In sewer systems, stripping of cocaine, i.e. its removal in the gas phase, can probably be ignored. According to Ternes and Joss (2006), even in an aeration

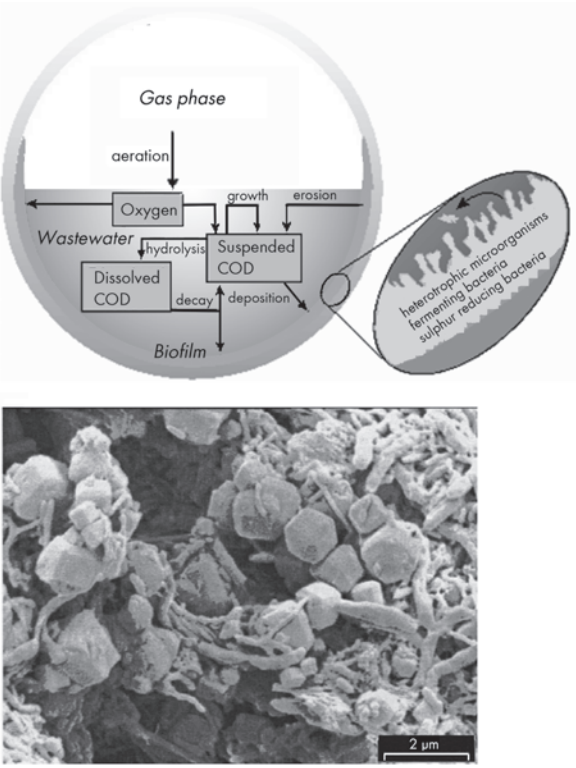

Figure 3: (Top) Interactions and processes involved in the conversion of organic matter, expressed as chemical oxygen demand (COD), in the sewer system. The enlargement shows the structure and composition of sewer biofilm schematically. (Bottom) Scanning electron micrograph of a sewer biofilm showing filamentous bacteria and entrapped sand and zeolite particles. From J. Huisman (2001), 'Transport and transformation processes in combined sewers', Ph.D. thesis No 13989, ETH Zürich. Reproduced with permission.

tank, where air input (e.g. because of re-aeration at drops) is much higher than in sewers, a Henry coefficient (K_H) > 3 × 10^{-3} is necessary to observe an effect, whereas pharmaceuticals are rather hydrophilic and have low K_H values, of the order of less than 10^{-5}.

The sorption of pharmaceuticals in sewers attenuates the load pattern and removes substance due to biofilm erosion, which can be substantial during rain events. According to Ternes and Joss (2006), sorption in WWTP processes can be predicted

by using solid–water distribution coefficients (K_d values) (Schwarzenbach et al., 2002). Their experimental findings suggest that, in WWTPs, sorption is less than 10% when K_d < 0.3 l/g suspended solids, but currently no experimental information is available on K_d values of cocaine. It can only be speculated that the sorption of cocaine is rather small and will depend on the particle concentration of the wastewater (T.A. Ternes, 2007, personal communication). Interestingly, the sorption behaviour was found to be different in primary and activated sludge, and the transferability of these results to sewer biofilm and sediments has yet to be proved. In a computational experiment, Ort and Gujer (2007) model the sorption of different PPCPs to sewer solids and biofilm. They found that load pattern is attenuated in the same order as from dispersion, but only for medium and high K_d values. Currently, no experimental data on sorption of cocaine or its metabolites in sewers are available, and K_d has most probably to be determined experimentally in batch experiments (Ternes et al., 2004).

As expected, no detailed information is currently available on the biotransformation of illicit substances in sewers or WWTPs, which might also include the conversion of metabolites back to the parent drug. Ternes and Joss (2006) assume that, owing to the very low concentrations involved, biotransformation of PPCPs (and, by analogy, illicit substances) does not contribute significantly to microbial growth. Rather, it is speculated that some PPCPs are being degraded by enzymes that are produced for other purposes (co-metabolism). The transformation rates apparently depend on many factors such as: (1) the biodegradability of each substance; (2) the biodiversity of the sludge; (3) sludge production; (4) wastewater temperature (i.e. transformation rates correlate positively with temperature); and (5) wastewater composition (availability of co-substrate and proportion of inert matter).

Although current knowledge regarding the transformation of cocaine and its metabolites is very poor, there is some preliminary evidence that this aspect cannot be ignored. Heltsley et al. (2007) compared the molar fraction profile of cocaine and its major metabolites in a wastewater sample with profiles reported for urine, and concluded that cocaine undergoes significant transformation processes within the sewer system. Castiglioni et al. (2006) spiked batches of wastewater with different drugs and compared the initial concentration with the final concentrations after three days' storage. Although they found that the concentrations of cocaine, norcocaine and cocaethylene decreased during storage (by 36%, 15% and 13% respectively), an increase in the metabolites benzoylecgonine and norbenzoylecgonine (14% and

13 %) was observed. Currently, experimental data allowing even an approximate computation of the transformation of illicit substances in sewers are lacking. For a quantitative assessment, e.g. in predictive models, more detailed experiments are clearly needed to establish rate constants for the individual processes.

This section has described how transport processes attenuate and stretch solute concentrations and how transformation processes might reduce or alter cocaine loads, which is critical for both back-calculation and monitoring of use trends. Another important aspect that contributes to uncertainty in drug load estimates, and is often overlooked, is the sampling procedure.

Sampling for representative substance loads

Unfortunately, we must accept that no measurement is ever exact. Flowmeters are inaccurate, automatic sampling devices have individual characteristics and uncertainties linked to sampling time and spatial scales influence the result. In addition to validating mass spectrometry techniques, it is necessary to investigate the representativeness of the measured wastewater pollutant loads.

In urban drainage, discharge is usually measured by an area–velocity method, which determines the water level (or cross-sectional area) and mean velocity in the cross-section. Experiments show that, even under optimal conditions, relative uncertainties are about 20 % for flow rates in sewers and 6–10 % for wastewater volumes (Bertrand-Krajewski et al., 2003). For conventional pollutant loads, which combine flow and concentration measurements, (particles and organic matter), random uncertainty estimates can be in the order of 25–50 % (Gromaire and Chebbo, 2001; Bertrand-Krajewski et al., 2003), depending on the temporal occurrence of the substance. More problematic are systematic deviations of discharge measurement devices. Unfortunately, these are often not detected in WWTPs, as costly control studies would be necessary. However, such control studies have been carried out in Germany (Port, 1994) and Switzerland (Thomann, 2002). These studies revealed that systematic under- or overestimations of flow rates of about 20 % occurred in about 30 % of the plants investigated.

To investigate the representativeness of sampling for micropollutant loads in sewers, Ort and Gujer (2006) presented a concept that makes it possible to quantify the expected uncertainty for a given combination of substance pattern and sampling scheme. Substances tested included benzotriazole, a component of dishwasher powders, and ammonia. As expected, the error was largest for substances that occur

in only a low number of wastewater discharges (e.g. from dishwashers) and which are sampled at low frequency. In addition, the authors estimated the extent to which error could be reduced by using composite sampling rather than grab sampling. As the pollutant pattern depends not only on human activity, but also on the sewer transport characteristics, the impact of the sampling scheme has to be evaluated for each sampling station individually. Rieckermann and Christakos (2007) adapted this framework to investigate the sampling error for cocaine loads in a catchment of 4 000 inhabitants, where the average flow distance was 2.5 km (Figure 4). Using a stochastic simulation model, they estimated that the relative error (ratio of sampled load to true load) was as high as 7 % (single standard deviation) for a 24-hour composite sample that was based on a 5-minute sampling interval. For a 24-hour composite sample based on a 20-minute sampling interval, the relative error increased to 26 %.

In the case of larger catchments including a larger number of drug users and increased dispersion due to longer travel times, the error is expected to be lower, but currently no rule of thumb is available and stochastic simulations are recommended to assess the uncertainty on a case-by-case basis.

One important characteristic of sewer systems is that they are buried in the ground. This not only makes the monitoring of illicit drugs very costly, but also has other unpleasant repercussions. First, because sewers are a hazardous environment and, as is the case with all confined spaces, must be tested before entry, experimentation is relatively difficult (see below) and monitoring studies are not readily performed.

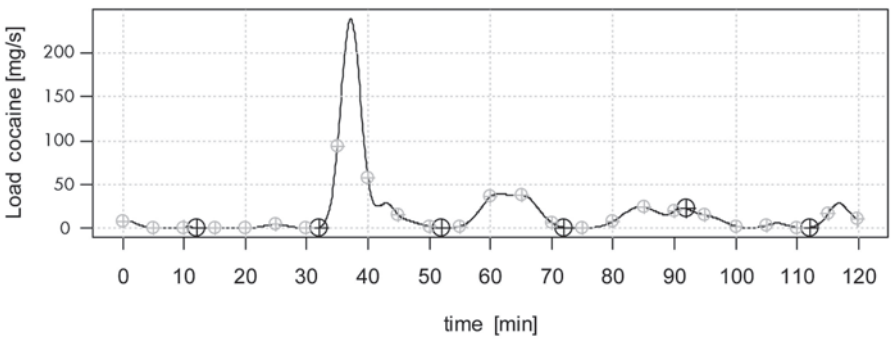

Figure 4: Modelled section of cocaine loads and sampling intervals of 5 minutes (grey) and 20 minutes (black) (from Rieckermann and Christakos, 2007).

Furthermore, manholes are often located in roadways, which makes them difficult to access, and a power supply for monitoring devices is usually not available. Ideally, measuring would be carried out on influents to WWTPs; however, sampling performed at the WWTP after initial clarification would have the advantage that short-term fluctuations in illicit substances would be largely attenuated by mixing in the tank and thus the error attributable to sampling frequency would be less critical. However, as described above, sorption to primary sludge might have to be taken into account.

Conclusions

Estimating drug loads from wastewater measurements seems a very attractive concept. However, from an environmental engineering standpoint, both the back-calculation of consumption figures and the monitoring of trends from illicit substance loads have several pitfalls: they require not only information on drug metabolism and socio-economic usage characteristics, but also an understanding of the wastewater system and the processes involved. This chapter provided a broad overview over the urban drainage system and the processes involved, and presented available knowledge regarding the monitoring and modelling of illicit drug loads in sewers. As this is an emerging field and no experimental data are available, findings from comparable studies of pharmaceuticals, which are also present in wastewater at trace concentrations and have similar characteristics, e.g. hydrophilicity, and are metabolised over similar time scales, were reported, where appropriate.

Sewer systems are complex and are composed of many different elements. They have usually evolved over time and are rarely planned from scratch.

As flood protection is mandatory, there is generally a good understanding of volume flows and substance transport. Critical aspects are the loss of wastewater due to sewer leakage and the fact that the processes involved are not currently well understood. Current estimates of loss range from 0 to 20% of dry weather flow or more, but no generally valid estimates are available.

The interplay of physical, chemical and biological transformation processes of solutes is not trivial and their understanding is still incomplete, even in the case of conventional pollutants. There is some evidence for transformation of illicit drugs in sewers, but very few experimental data have as yet been published. Research on pharmaceuticals and personal care products suggests that the processes that might affect cocaine and its metabolites are biotransformation and (to a lesser extent)

sorption in sewer biofilms and sediments. However, little experimental evidence of the magnitude of these processes in WWTPs is available and to date there are no experimental data are available regarding these processes in sewers. It has still to be proven whether drug loads are influenced by natural processes (e.g. seasonal variations due to changes in wastewater temperature).

The back-calculation of prevalence levels requires accurate analytical measurements with reliable estimates of uncertainty. In addition to analytical uncertainty, the sampling uncertainty also has to be taken into account. To date, no rule of thumb is available for this task, and stochastic simulations are recommended to evaluate the representativeness on a case-by-case basis.

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Chapter 5: Georeferenced wastewater sampling and applied spatial statistics

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Maria de Fátima de Pina

Disease mapping

Maps have been used in medical geography for almost 300 years, although disease mapping did not become widespread until the nineteenth century, when health data became available, accompanied by the desire to evaluate geographical patterns of diseases and to identify risk factors that might affect such patterns. Maps were used by statisticians, medical doctors and geographers to test many theories of causation. The most famous map at the time was that made by John Snow in 1854 to study the distribution of cholera in England. His map was an important step in determining the causal relationship between disease and place and strongly influenced subsequent mapping of diseases and health. For many years, the main purpose of maps was to depict features of the real world or to present the results of statistical analysis, but they also acted as a communication tool for disseminating information.

Since the development of new geotechnologies, especially geographical information systems (GIS), in the last three decades of the twentieth century, maps have become much more than just a means of transmitting knowledge; rather they are now a means of generating new knowledge. Maps are now viewed by health scientists as an important tool to better understand the relation between humans, disease and the environment. Mapping ranks with other tools of spatial statistical analysis, epidemiology and public health in helping to further our understanding of the nature of health events (Koch, 2005).

Geographical information systems

GIS provides a set of sophisticated options for spatial analysis. Within a GIS it is possible to overlay different maps to visualise complex topological relationships such as connectivity, proximity and adjacency and to identify influencing factors or how these change between different areas. This can be of particular use in the context of sewage epidemiology. First, it is possible to overlay maps of the sewage network on maps showing population distribution derived from census data, enabling the demographic characteristics of the population to be linked to the

wastewater system. Census data include the number of people of each gender and in different age groups as well as some types of socio-economic information. This background information will improve estimates of consumption based on drug loads in wastewater. The data link allows estimates to be broken down by sex, age or socio-economic conditions.

In addition, by considering each wastewater system as a discrete unit, the use of socio-economic information will enable comparisons between geographic regions. The geographical unit of analysis, in this context, is the area served by the wastewater system, which can be an entire city, part of a city or a city plus some area extending beyond the city limits. In practice, it is quite common for several municipalities to share complex wastewater systems.

As population data obtained from censuses are associated with administrative areas [census tracts, municipalities, districts or NUTS (nomenclature of territorial units for statistics) regions], rather than the area served by a sewage system, GIS are a useful means of interpolating the population of the area of interest with the area served by the wastewater system.

Besides the precise identification of the population linked to the sewage system, it is also possible to model the concentrations of certain drugs coming from specified treatment facilities within the geographical region under focus and, if monitored continuously, to detect any reduction in drug use resulting from a specific intervention programme. Ideally, samples should be collected from more than one site in the sewage system, in order to identify differences in consumption, while at all times maintaining confidentiality. By mapping the sources of high concentrations of specific drugs and relating these to the population at risk, it is possible to suggest hypotheses for further investigation. The use of GIS enables environmental, socio-economic and health data to be combined, improving analytical output and inferential statistical methods.

Mapping and statistics

In the context of analysing the spatial distribution of an event, maps should be used in conjunction with statistical tools to describe, compare and interpret results. Descriptive or inferential statistics help to make explicit what is implicit in maps. Statistics add precision to a qualitative description, facilitate comparisons between different populations in time or space and reveal details that are not apparent in more qualitative analyses.

Applied statistics have three important advantages:

- they enable spatial data to be collected systematically;
- they enable analysis and visualisation of data in the form of maps or summary measures;
- they enable conclusions about the generation of data to be extracted from probabilistic models (Assunção, 2001).

Statistical tools can be used to draw inferences about drug consumption based on observed data from samples. The classic approach aims to determine what generalisations (if any) can be made about a population based on samples collected from that population. The Bayesian approach considers that spatial correlation or other 'random effects' may be modelled using prior distributions. Prior distributions can be constructed from the knowledge of specialists or empirically from the data (Paulino et al., 2003). The spatial statistics approach can be defined as the set of scientific methods that are used to collect, describe, visualise and analyse data in a geographic context. In broad terms, 'spatial statistical analysis is the quantitative study of phenomena that are located in space' (Bailey and Gatrell, 1995). The main difference from non-spatial analysis is that the place where the event occurs is, in an explicit way, present in the analysis (Assunção, 2001). Spatial analyses are based on the first law of geography, defined by Waldo Tobler in 1970, who stated, that 'everything is related to everything else, but near things are more related than distant things'.

Data categories

There are four categories of geographic data, and in each case a set of statistical techniques is available to perform analyses.

A point data set consists of a series of point locations with coordinates that represent the exact site of events. In the case of sewage epidemiology, each point is the location of one sample captured in the wastewater system. Point pattern analysis focuses on observed random patterns or some form of regularity (Bailey, 2001). Analyses include kernel estimation or smoothing, distance methods, K-functions, multiple types of events, bivariate K-functions and space–time clustering.

Spatially continuous data include a set of point locations in the region of study. However, these data are different, in so far as the focus is not on the exact location,

but seeks to explain observed variation in an attribute value over the region (Bailey and Gatrell, 1995). Thus, the focus of this method is centred on the surface of the phenomenon under study, rather than the location (Assunção, 2001). Analyses of this type include trend surface, variograms and covariograms, spatial regression, spatial prediction and Kriging.

Area data consist of variables associated to polygons and are commonly used to find spatial trends in attributes, trying to 'explain' spatial variation within the attributes of the variable of interest in terms of covariates measured (Bailey and Gatrell, 1995). In addition, the technique aims to detect subareas, where the values are higher than expected, according to an applied statistical method. These objectives are particularly important in demographic studies and those analysing health, political or economical activities. The focus of this process is in the spatial distribution of the attributes through the areas. This would include smoothing methods, kernel regression, spatial correlation, correlograms and spatial regression.

Spatial interaction data are of particular relevance to the study of emerging diseases. Spatial interaction models analyse and predict the movements of people, information and goods from place to place. Spatial modelling and mapping of geographical interactions is best represented by flow patterns, e.g. the flow of the number of people, goods or services between their origin and their destination (Assunção, 2001). The resulting maps are called flux maps. The use of this kind of data in the context of this approach enables the analysis of distribution patterns of substances in a wastewater system as well as the creation of flux maps in a greater geographical context when monitoring various plants within a country.

These four categories of spatial data allow a variety of spatial problems to be solved. Although area data are the most widely used in health studies, they are not always the best analytical approach to visualise a geographic phenomenon. When aggregating data into areas, it is assumed that each area is homogeneous and that differences between areas occur discretely at the borders. This is not true either for diseases or for any other geographical variable that is non-linearly distributed.

Populations tend to concentrate in certain areas and demographic density changes smoothly from one neighbourhood to another. Surfaces are considered a more natural way to analyse and represent the underlying distribution of population data. There are many methods to construct such surfaces, all of them being based on the construction of a grid of regular cells, each of which has an associated value. The value of each cell is interpolated from the sample points (for instance, one point

localised in the centroid of a NUT3 ([1]) area, with the value of a variable for the entire area artificially associated with that point). The closer the sample points are to a cell, the greater their contribution of the final value of that cell.

There are several mathematical algorithms that can be used for interpolation, but all of them are based on this basic principle of spatial analyses — the closer, the more likely. The value of each cell is calculated as a function of the closest sample points. How many and which points contribute to each cell depend on a moving window (called bandwidth) that is based on each sample point, and with a radius of search for sample points that is defined by the user. This parameter determines the amount of smoothing, because it defines the region of influence. A very large bandwidth will produce a flat surface and local features may be obscured; in contrast, a very small bandwidth will produce a very spiky surface, with 'peaks' in every sample point.

A method that is often used to generate surfaces is kernel estimation, which is an estimate of the intensity at events per unit area (Bailey and Gatrell, 1995). Another problem when dealing with data associated with areas in health studies is the well-known 'problem of small numbers', which occurs when calculating rates in areas with small populations. A small increase in the numerator results in a large increase in the rates that does not represent a real increase in risk. As a consequence of this statistical instability, the rates may not be reliable and may merely reflect random fluctuation. Such problems are common when working with political administrative areas in which the range of population at risk varies widely.

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([1]) Nomenclature of territorial units for statistics: a statistical geographical categorisation system applied throughout Europe, within which 3 denotes regional level.

Chapter 6: Integrating wastewater analysis with conventional approaches to measuring drug use

Chapter 6: Integrating wastewater analysis with conventional approaches to measuring drug use

Lucas Wiessing, Julian Vicente and Matthew Hickman

Drug use monitoring

Accurate estimates of drug consumption in a population and of how consumption has changed over time would be a pillar of evidence-based drug policy and inform public health, social science and economic models (Reuter and Stevens, 2007; Thomas et al., 2007). For example, one could monitor whether drug consumption has fallen or increased in response to a change in the delivery or coverage of interventions. In the United Kingdom and other European countries, there have been substantial increases in the number of people in opioid substitution therapy, yet despite clear evidence of effectiveness at the individual level it is unclear what impact this has had on heroin consumption in the population at large.

Currently, accurate estimates of drug consumption are unavailable, as a consequence of the usually stigmatised nature of drug use, which often leads drug users to hide their habits. This influences data quality to a potentially large extent. Drug monitoring systems rely heavily on unknown rates of willingness to self-report use and to participate in general population studies, or to become 'visible' in routine statistics as a result of contact with services and institutions such as drug treatment services, police, hospitals and other medical or social services.

However, the joint interpretation of the available prevalence and incidence indicators, in combination with other drug-related indicators such as drug treatment demand, drug-related infectious diseases, drug-related mortality and drug supply data, has so far permitted a relatively global but broad monitoring of prevalence and incidence, patterns of use and trends over time in the European Union (EMCDDA, 2007).

In this chapter, we give a brief description of current methods for monitoring and estimating drug use as well as a discussion on some aspects that may need further review for linking prevalence estimates based on wastewater with those based on established methods.

Prevalence estimation methods

There are two principal methods of prevalence estimation: 'direct' estimation through general population surveys, including more targeted surveys such as school surveys, and 'indirect' estimation methods that are based on extrapolating from the observed parts (e.g. problem drug users in treatment) of the target group to be estimated (e.g. problem drug users).

Direct methods

General population surveys directly measure the prevalence of drug use in a sample that is assumed to be representative of the general population, as prevalence is directly inferred from the proportion in the sample giving a positive answer, with or without some correction for staged or stratified sampling. Although the methods are easy to understand and often appealing because of their conceptual simplicity, estimating the prevalence of drug use patterns adopted by very small proportions of the general population or estimating prevalence of very severe patterns of use, such as heavy use, injecting drug use or problem drug use (PDU), may be highly problematic.

This is first a problem of precision (reliability). In the case of drug use patterns that affect only a few individuals per 1 000 population, very large sample sizes are required to gather sufficient cases for reliable prevalence estimation. Second, there are problems around the potential bias (validity) of the method arising from the fact that the inclusion of homeless or otherwise deviant people in the sampling frame is likely to be insufficient. For example, if a sizeable proportion of heroin users are homeless or unable or unwilling to respond to a request to participate in a general population survey, then even very large samples will fail to provide reliable data. A third problem with general population surveys is caused by the already mentioned stigma and prejudice associated with heavy patterns of use in many societies, causing potential participants to choose not to disclose their heavier drug use patterns. It is not possible without supplementary studies to know the extent to which those who are interviewed are not telling the truth for fear of stigma or other consequences or, conversely, perhaps overstating drug consumption in order to fit with social norms in their peer group (e.g. male schoolchildren).

For example, in a randomised general population survey experiment in the USA, respondents were more likely to report the recent use of 'harder' drugs in a

telephone-based audio-computerised interview (T-ACASI) than to admit this to human interviewers. T-ACASI respondents were more likely to report cannabis use in the past month (10.0% vs. 5.7%, crude odds ratio (OR) = 1.9, $P < 0.001$), cocaine use in the past month (2.1% vs. 0.7%, crude OR 3.2, $P < 0.001$) and injection drug use in the past five years (1.6% vs. 0.3%, crude OR = 4.8, $P < 0.01$) (Turner et al., 2005). In another general population survey in the USA, in which respondents were asked to give a hair, saliva and urine sample immediately after a computer-assisted interview in their home, under-reporting appeared to depend both on the drugs reported and on race (probably as an indicator for social factors): '… higher rates of cannabis use were generated from survey reports than from drug testing. Drug testing generated higher prevalence rates than survey reports for recent use of cocaine and heroin. Under-reporting of recent drug use was apparent for all three substances. Sensitivity was particularly low for cocaine and heroin. Race was related to under-reporting, with African Americans less likely to report cannabis use despite a positive test result' (Fendrich et al., 2004).

The problems with general population surveys are probably less severe when looking at drugs whose use is more prevalent, for example, cannabis or ecstasy and in some countries perhaps also powder cocaine, if one assumes that heavy users missed by the general population survey constitute a relatively smaller proportion of the total owing to the generally higher overall prevalence (as a result of larger numbers of 'light' users). However, the problem of relying on general population surveys alone can be severe in the case of drugs or drug use patterns that usually involve only a very small proportion of the general population, typically opioid use or injection and crack use, and in some countries also the heavy use of amphetamine, methamphetamine or powder cocaine.

Indirect methods

Thus, in drug monitoring systems, the use of general population surveys needs to be complemented by 'indirect methods' for estimating the prevalence of heavier patterns of drug use such as heroin use, crack cocaine use, amphetamine use, injecting drug use or more in general 'problem drug use' (PDU). Of these indirect methods or PDU estimation methods, some have been used more consistently in several countries, following the initial development of consensus guidelines in the EU (EMCDDA, 1999, 2004; Kraus et al., 2003) that have subsequently been adopted for use in other parts of the world (UNAIDS/WHO, 2003; UNODC, 2003).

The indirect methods include:

- multiplier-benchmark methods that basically multiply observed cases by a simple, independently obtained, multiplier value;
- capture–recapture methods, which estimate prevalence from observed double-counts between multiple datasets and which can in the best case adjust for some of the dependencies between those datasets;
- the multivariate indicator method, which extrapolates from existing local prevalence estimates to a larger (national) geographical level;
- some less commonly used approaches that may require more assumptions but have in some cases been successfully applied (e.g. demographic method, truncated Poisson method).

In general, these methods estimate the total number of drug users that are comparable, in terms of likelihood of being observed in the different statistics, to the actually observed cases in routine statistics or samples. They are called 'indirect' methods because, rather than estimating prevalence 'directly' in a general population sample (prevalence is simply the observed percentage of cases in the sample) and then accounting for the known 'sampling intensity' of the study (proportion of the sample among the total population) to estimate the absolute number of cases in the population, they first estimate the sampling intensity of the observed cases (estimate what is the proportion of observed versus non-observed cases), after which a population prevalence is obtained by dividing the estimated total existing cases by the size of the general population in the same area.

The fact that drug users have to be comparable to those observed in routine statistics means that drug users who have not developed the type of behaviour that would lead them to come into contact with the sources of those statistics (e.g. police, hospitals, drug treatment centres) are not estimated and remain hidden, even from the final (PDU) estimates. This is not a problem in so far as these individuals can be assumed not to be problem drug users. However, problem drug users who have a lower probability of being 'caught' by routine statistics (for example, women whose partners buy drugs for them and who are thus less likely to be caught by the police) can be accounted for only by assuming that these users are few, such as is probably the case for the drugs included in the EMCDDA definition of PDU (opioids, cocaine or amphetamines). For example, if one assumes that a heavy user is very likely to come in contact with these institutions, then it follows logically that what is not being

estimated is mostly non-heavy (non-dependent, non-problematic) use. The non-heavy users are then either users who will develop problem use in the future (as part of their drug-using 'career', these users will possibly be counted in future estimates) or users who will never do so and will always remain hidden from PDU estimates (and are best estimated using general population survey given their likely higher numbers and likely less problematic or deviant lifestyles).

The EMCDDA uses a rather global definition for problem drug use ('injecting drug use or long duration/regular use of opioids, cocaine and/or amphetamines') that is not directly related to existing classifications of abuse and dependence (DSM) or harmful use and dependence (ICD), which require exact diagnosis by an experienced physician. The EMCDDA definition of PDU rather follows from the indirect methods used to estimate PDU, i.e. by selecting data sources for using the indirect methods that probably contain the target group of problem drug users and by selecting according to the agreed drugs within those sources (e.g. excluding cannabis users from drug treatment data) it is assumed that the resulting PDU estimate reflects reasonably well the group of users who are 'problematic'. Note also that the definition of PDU does not mention 'problems'; rather, it assumes that a harmful route of administration ('injecting') and 'long duration/regular' use of certain drugs are the categories most likely to include the most problematic users and to exclude non-problem users, although empirical data regarding the sensitivity and specificity of the definition are not available due to the lack of a gold standard for comparison. In practice, the EMCDDA's definition of PDU has worked well to describe PDU prevalence and incidence at the population level, in the context of a general lack of precision of PDU estimates and a lack of exact information on the patterns of use of the target population that can be obtained through these methods.

As is the case for general population surveys, PDU estimates have important limitations that often preclude deriving very exact or valid information on the prevalence of PDU. Indirect estimates often depend on a number of assumptions that are difficult to verify. The assumptions for capture–recapture for example include: (1) independence of lists; (2) homogeneity of capture probabilities; (3) error-free matching across lists; (4) no in- or out-migration; (5) no duplicates within a list; and (6) lists are random samples (Asher, 2002). Similarly, most indirect (and direct) methods assume that the population is closed (no in- or out-migration) during the period of assessment (usually several months but often up to one calendar year) and the effect of in- and out-migration on the final estimate is not always clear or even

discussed, although in some situations violation of this assumption may result not in bias but only in loss of precision (Kendall, 1999).

The final estimates are as good as the data that they are based on, which is often not as good as would be liked. Problems related to the above assumptions often follow from the quality of the data available from routine statistics; although this can be improved by prospective designs (Bello and Chêne, 1997), perhaps even by using a specifically designed community-wide recruitment study as one of the data sources for the estimation. Problems may also stem from geographical and other sources of heterogeneity in the available data, which prohibit straightforward interpretation of resulting estimates (validity problems) as well as large uncertainty intervals around estimates (reliability problems) or the impossibility of producing confidence intervals at all. For example, the multivariate indicator (MIM) method is based on an imputation using regression analysis from existing local estimates and the methodology to incorporate the uncertainty of the local estimates into the overall MIM estimate is still in development (Frischer et al., 2001; Smit et al., 2006).

In practice, given the nature of the indirect methods and the sometimes low quality of the routine statistics they use, it may be difficult to know exactly what types of drug use the problem drug use estimates refer to. For example, consider capture–recapture estimates based on data obtained from drug treatment, police and hospital sources. The data from drug treatment and hospitals may be accurate in terms of the main drugs used, but police data are often not very precise (being limited to the recording of suspects as 'drug users'). It is usually unclear to what extent the resulting final estimate of PDU based on these three sources is affected by the lack of precision on drug use patterns in the police data, and it is likely that the definition of PDU of the final estimate is as good as the broadest (least precise) definition in the original data sources.

As general population surveys and PDU estimates adopt complementary approaches, they should be used as complementary elements within an overarching drug monitoring system. Either of the approaches is likely to miss an important part of the population using a given drug. This implies that both approaches should be used to estimate total drug consumption, ideally implemented at the same time and in the same geographic area, compared and checked for consistency. To then make the next comparison of central interest to this report, that between prevalence estimates from direct and indirect methods and those based on wastewater measurements, information on per capita consumption is needed.

Drug use patterns and the influence on total consumption

Drug consumption estimates are often based on a combination of the estimated prevalence of opioid, cocaine or cannabis use and estimates of the pattern and frequency of drug use by drug users. Consumption is sometimes differentiated into 'heavy or dependent' and 'light or recreational', based on the average frequency of drug use. These separate estimates of prevalence and mean use are generated through a mixture of direct and indirect methods and behavioural surveys — each with its own uncertainty. These uncertainties will be propagated and may well be increased through combination.

Information on per capita consumption (including patterns, frequency of use, average dose) is probably best obtained by targeted surveys directed to recent users of the drugs in question. This can be done in convenience samples from settings where these users can be found (e.g. drug treatment centres or low-threshold centres), but a better approach would be to sample users by chain referral methods (snowball sampling) (Taylor et al., 2005). One chain referral method much discussed recently is respondent-driven sampling, in which each respondent is paid to recruit another respondent (Abdul-Quader et al., 2006a,b).

What remains unknown, and probably varies between countries, is the proportion of the population using a certain drug who can be classified as light or recreational ('infrequent') users or heavy ('intensive') or 'problem drug users' ([1]). It should be noted that such a classification is still in development at the EMCDDA, although systems exist in the USA (DSM IV) and at international level (ICD-10) (Hasin et al., 2006; Saunders, 2006). Also, it is important to note that the possible classifications used in Europe (and other regions) are not necessarily one-dimensional, focusing on time since last use, frequency of use, dependence (SDS or CAST scales, DSM) or harmful use (IDC-10) or the non-clinical but epidemiologically useful EMCDDA definition of problem drug use given above, which is applied to the PDU estimates resulting from the indirect methods.

For the purpose of this report, a simple division into 'light' and 'heavy' users would be useful. This could perhaps be based on frequency of use with a cut-off point of, for example, 'using two days per week or less' for the first category and without necessarily looking at other dimensions such as dependence, harms or problem use.

([1]) See the EMCDDA definition above, broadly covering abuse or harmful use of, or dependence on, opioids, cocaine or amphetamines.

As the most interesting parameter for comparing with wastewater measurements is the total amount used, and given the difficulty of determining average dosage or dosage distribution and patterns (e.g. by day of the week and time of the day), frequency of use perhaps comes closest to approximating the central parameter of interest: 'total amount used over a given time period'. However, an additional difficulty in using this measure is that frequency of use may be quite irregular, for example it is known that 'binge' use of stimulants such as cocaine or amphetamine is relatively common ([2]).

The adoption of a simple binary categorisation into light and heavy users raises the question of whether it is legitimate to estimate the prevalence of both groups in a study area, to multiply these by a calculated 'average dose' and to take the total as an estimate of total amount consumed in the study area over a given period of time. As discussed above, it is likely that general population surveys are more powerful in estimating the prevalence of the light users, whereas indirect methods are probably needed to estimate the number of heavy users. It is difficult to estimate the proportion of the total consumption accounted for by light and heavy users, but this is important to enable the sensitivity of total estimated drug consumption to direct or indirect methods used. Such knowledge would perhaps enable the calculation of a confidence interval taking account of uncertainties in data obtained by both the general population survey and indirect methods, and perhaps resulting in one of the estimation methods being omitted because its contribution to total use would be too small to be of interest. However, it is not easy to determine in advance if the total amount used is influenced more by a larger group of light users or by a smaller group of heavy users.

To combine these different types of information, a conceptual and/or mathematical model should be constructed. There is often a lack of an appropriate framework to combine multiple information sources and test their consistency in order to validate their output. Indirect prevalence estimates, for example, are often unreliable and open to bias because they rely on numerous, potentially erroneous, assumptions (as discussed above). Equally, estimates of drug use frequency and dosage are open to bias arising from the difficulty of generating representative samples of drug users. Evidence synthesis methods utilising Bayes's theorem offer the opportunity of testing the consistency of information (Ades and Sutton, 2006). Specific examples

([2]) Not using for long periods and then suddenly using at very high frequency over several consecutive days and nights.

in the drugs field include estimates of the prevalence and number of HIV and HCV infections, which have been used to derive and test estimates of the prevalence of current and former intravenous drug use and the prevalence of HIV or HCV by risk group based on multiple information sources (Goubar et al. 2006; Sweeting et al., 2008). Information on drug consumption derived from metabolite testing within an 'evidence synthesis' framework would allow improved estimation of the prevalence of different types of drug use and frequency of use.

The problem with this type of estimation of drug consumption is twofold. First, information that would enable testing the reliability or consistency of estimates of total consumption, drug use prevalence and frequency are not available. In theory, estimates of drug seizures or drug importations and production could be used to produce a model of consumption against which consumption and use estimates could be validated. However, the relationship between these data and the true level of consumption is also uncertain, influenced as it is by changes in policing and interdiction policy, and is therefore unlikely to be informative. In contrast, it is likely that metabolite testing, as outlined in the case study and discussion below, could provide an accurate measure of overall drug consumption and thus constitute a data source that could inform and test the consistency of combined information on drug prevalence and frequency of use, within an appropriate framework model.

Can prevalence be estimated and compared using wastewater data?

As mentioned elsewhere in this document, a number of additional uncertainties complicate matters when comparing prevalence estimates using 'wastewater data'. First, it is difficult to determine whether a change in, for example, cocaine flow through the system is the result of a change in the number of inhabitants using cocaine or could be explained by people entering or leaving the city. Second, even assuming a 'closed city', it would still be difficult to determine the extent to which the measured variation reflects variation in levels of use (patterns of use, dosage) or variation in the number of active users (prevalence). Targeted surveys of users could shed some light on average dose used and patterns of use (e.g. over different days and hours in the week) at a certain point in time. However, these surveys could not be used to continuously adjust the measured quantities and thus continuously adjust the prevalence estimates.

Perhaps a more sound position is to use wastewater measurements not for continuous prevalence monitoring, but rather for continuously monitoring the

amounts of a drug in the wastewater system. In this case, the main outcome variable at city level would be a 'consumption index' based on a 'standard dose' (an internationally agreed definition/amount) and the number of 'standard users' (assuming that further research confirms that binary classification into light and heavy users can be omitted). However, it seems unlikely that changes in drug residue concentrations in wastewater will necessarily be directly correlated with changes in prevalence estimates in any simple way.

Another option is to regard wastewater data as an additional 'indirect indicator' of drug use. Although the main part of this contribution has discussed the two general methods of estimating drug use prevalence, another way to use drugs data for monitoring is to follow trends over time in so-called indirect indicators, without generating explicit prevalence estimates, as mentioned in the introduction of this chapter. Indirect indicators are any statistics that are probably related to drug use prevalence. Among these would be drug overdose deaths and drug-related cases of HIV or hepatitis B/C — all likely to be mostly related to injecting drug use; drug treatment demands — probably related to drug problems in general; drug-related emergencies — reflecting acute problems such as overdose, and police drug seizures. Although there have been attempts to relate different combinations of indirect drug indicators to prevalence, no generally accepted model has yet been developed, mainly because of the lack of comparability of available datasets between countries and over time (EMCDDA, 2001). Wastewater data might provide a unique and comparable set of data, as an additional indicator, for improving this situation. It is thus imperative to invest in the development of better models that can utilise this important data source in order to test and validate the consistency of estimates.

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Overall conclusions

Roberto Fanelli and Norbert Frost

Health benchmarking data are often used in epidemiological studies. Public health surveillance methods are currently used for the systematic collection of data that can be used for the planning, implementation and evaluation of public health programmes. Similarly, the collection and analysis of data in relation to specific locations are already used with regard to, for example, unemployment rates, road traffic accidents, air pollution and the quality of bathing water.

Wastewater analysis offers an interesting and new opportunity to provide a comparable picture of the distribution of illicit drug consumption, which could also help to inform a more precisely tailored preventive response or other appropriate interventions. In view of a proposed European agreement to monitor wastewater for environmental purposes, it may be feasible to consider the possibility of extending this approach to include monitoring of illicit drugs.

The analysis of illicit drugs in wastewater samples represents a new field of study; one that until recently has not attracted much attention. However, case studies are now being conducted, and scientific research in this newly emerging field is progressing quickly. Studies of specific urban areas with known elevated prevalence and good quality background data (demographic, socio-economic) could be particularly interesting and fruitful for further research investigation.

A wastewater system contains information about the society that it serves, and it can reflect the behaviours of that population with regard to its discharge of liquid waste. Wastewater sampling for drugs in any given area has the potential to provide what might be regarded as a drug consumption index. This method is most suited for the purposes of drug surveillance at the community level, where it may be used to help public health and law enforcement activities.

Table 1 summarises the system of wastewater analysis and how information may be derived from it. The basic data are the measured concentrations of drug residues in the wastewater point of sampling (for example, at the inflow to the sewage treatment plant). These data, combined with information on the mass flow of sewage at the sampling point, enable estimation of the daily amounts of drug residue entering the wastewater system. At this level, a number of assumptions are required regarding the processes and events that occur prior to the analysis. The data may, for

Table 1: Overview of the types of information relating to community drug use that may be provided by analysis of drug residues in wastewater systems

Information provided	Data requirements	Notes
Drug residue load (the amount of drug passing through the system in a given time) **(Estimate 1)**	Concentration of a drug residue in wastewater Flow rate of wastewater at sampling point — from which mass flow of water can be calculated	These are the initial measurements Assumptions: No significant loss in the sewage system
Excretion rates of target drug residue at population level Standardised daily amounts (g/day/1 000 people) **(Estimate 2)**	Estimate 1 (drug residues over time) Population served by system Migration activities within population	Allows tracking of variation over time in the case of continuous measurement Assumptions: No considerable variation in population during measurement intervals Exclusion of potential confounders
Total amount of target drug consumed by population Consumption rates for target population and variation over time **(Estimate 3)**	Estimate 2 (total drug excretion rates for the population) Typical excretion rates	Assumptions: Excretion rates 'typical' and stable for target population
Total number of doses of target drug consumed (over monitoring period) **(Estimate 4)**	Estimate 3 (total amount of drugs consumed by target population) Information on typical doses (purity, size etc.) for target population	Knowledge about typical doses at street level including purity is often limited

example, be affected by leakage from sewers, heavy rainfall or the introduction of pharmaceutical or chemical agents into the system.

Assuming that there are no losses from the sewage system, the drug residue load in the wastewater is identical to the amount of drug residue excreted. In a second stage of the model, the estimate of total drug residue excretion can be translated into an average daily amount per head of population. The interpretation of this data will also be affected by the assumptions that are made about the stability of the population within the catchment area, and whether large events or temporary changes in population are known to have occurred. A third stage permits a rapid calculation to be made of the index of drug consumption. At this stage of the analysis, further interpretation of the results may require assumptions about the metabolism of the drug in question — and especially about the percentage of target drug residues that are excreted in relation to the amount of the drug that was consumed. On the basis of such assumptions, the results may be interpreted in terms of estimates of the daily amounts of drugs consumed ([1]).

Assuming that the prior stages of the model have been met, a fourth stage might allow for estimates to be made that number the doses of the target drug that are being consumed, or alternatively, of variations in patterns of drug use over time. Again, interpretation of the data at this stage requires certain assumptions, for instance, knowledge of typical daily doses of drugs used by recreational or problematic users, and knowledge about the purity levels of illicit drugs.

It is clear that wastewater sampling as a monitoring tool is still far from being able to identify drug consumption patterns or categories of users. Instead, it provides a screening tool for communities. The assessment of illicit drugs that have been introduced into wastewater systems is not intended (nor very likely to succeed) in targeting individual drug users. The assessment yields average values of 'output' that allow the characterisation of a relatively well-defined entity within a given geographical area. Any further extrapolation towards prevalence estimation of drug use will require additional demographic, epidemiological and other information.

The usefulness of the index of drug consumption obtained by monitoring drug residues in wastewater systems will be greatly increased when this is cross-matched

([1]) These areas of uncertainty and the need to make different types of assumptions have been discussed throughout the text. Some of them are also identified later in this concluding chapter as issues for further research investigation.

with other data sources. As with other indirect estimation methods, the utility of the results are enhanced by combining them with multiple data sources so that the additional information can be used to provide greater specificity and accuracy of the results. This sort of supplementary information is usually derived by other methodologies from other sources. Particular attention should be paid to the potential for using multiple data sources to link the results of wastewater analysis with findings from other studies about the characteristics of the target populations and on geographical issues to enhance the interpretation and application of the results.

It can be seen from the various chapters and discussions in this volume that work in this area is still at a very early stage. Advances will require further theoretical development of the key concepts of sewage epidemiology as well as improvements to the current rudimentary model. In addition, there are undoubtedly many opportunities to support the development of this approach through well-conducted empirical research studies. Although the informed reader will be able to propose many such topics, the following are suggested as providing a basis for further theoretical, conceptual and empirical investigation:

- internal dynamics of wastewater systems;
- factors relating to possible degradation of substances from origin to sampling point;
- development of methodologies and reasonable strategies for sampling;
- variations in patterns of illicit drug consumption;
- purity of samples of illicit drugs available at the point of sale to users;
- individual differences in pharmacokinetics and excretion rates;
- potential confounding effects due to multiple drug use;
- prospective long-term monitoring in several wastewater systems;
- ethical and privacy issues.

With regard to the last of these suggested topics for further investigation, it is clear that both the approach and the procedures of wastewater sampling raise a number of challenging ethical and legal issues. It would be timely to conduct a thorough review of current and required legislation concerning sampling procedures for this new approach to illicit drug monitoring. And it is recommended that a full and open discussion of the ethical and legal issues should be conducted with all stakeholders.

The detection and analysis of drugs and their metabolites in wastewater is a challenge, but all new methodologies need time for development. Wastewater analysis for the monitoring of illicit drugs is still at the earliest stage and requires a great deal of additional information to support the results and the applicability of this new and promising approach.

Contact details

Renzo Bagnati
Department of Environmental Health Sciences,
'Mario Negri' Institute for Pharmacological Research, Via La Masa 19,
I-20156 Milan, Italy
Tel. (39) 239 01 43 98
Fax (39) 239 01 47 35
E-mail: bagnati@marionegri.it

Sara Castiglioni
Department of Environmental Health Sciences,
'Mario Negri' Institute for Pharmacological Research, Via La Masa 19,
I-20156 Milan
Tel. (39) 239 01 47 76
Fax (39) 239 01 47 35
E-mail: castiglioni@marionegri.it

Chiara Chiabrando
Department of Environmental Health Sciences,
'Mario Negri' Institute for Pharmacological Research, Via La Masa 19,
I-20156 Milan
Tel. (39) 239 01 44 97
Fax (39) 239 01 47 35
E-mail: chiabrando@marionegri.it

Roberto Fanelli
Department of Environmental Health Sciences,
'Mario Negri' institute for Pharmacological Research, Via La Masa 19,
I-20156 Milan
Tel. (39) 239 01 44 98
Fax (39) 239 01 47 35
E-mail: fanelli@marionegri.it

Norbert Frost
European Monitoring Centre for Drugs and Drug Addiction,
Rua da Cruz de Santa Apolónia, 23–25,
P-1149-045 Lisbon
Tel. (351) 218 11 30 53
Fax (351) 213 58 44 42
E-mail: norbert.frost@emcdda.europa.eu

Paul Griffiths
European Monitoring Centre for Drugs and Drug Addiction,
Rua da Cruz de Santa Apolónia, 23–25,
P-1149-045 Lisbon
Tel. (351) 218 11 30 06
Fax (351) 213 58 44 41
E-mail: paul.griffiths@emcdda.europa.eu

Matt Hickman
Department of Social Medicine,
Canynge Hall,
University of Bristol
Whiteladies Road
Bristol BS8 2PR
United Kingdom
Tel. (44) 117 928 72 52
E-mail: matthew.hickman@bristol.ac.uk

Maria de Fátima de Pina
Faculdade de Medicina,
Serviço de Higiene e Epidemiologia,
Laboratório de Biomateriais, INEB — Instituto de Engenharia Biomédica,
Universidade do Porto
Alameda Prof. Hernâni Monteiro,
4200-319 Porto,
Portugal
Tel. (351) 225 51 36 52
Fax (351) 225 57 39 71
E-mail: fpina@med.up

Jörg Rieckermann
Department of Geography,
San Diego State University,
5500 Campanile Dr.,
San Diego, CA 92182-4493
United States of America
Tel. (1-619) 594 80 36
GSM: (1-619) 947 20 47
E-mail: jriecker@mail.sdsu.edu

Teresa Summavielle
Neuroprotection Laboratory, Molecular Neurobiology Group,
Instituto de Biologia Molecular e Celular (IBMC),
Universidade do Porto
Rua do Campo Alegre, 823
4150-180 Porto
Portugal
Tel. (351) 226 07 49 00
Fax (351) 226 09 91 57
E-mail: tsummavi@ibmc.up.pt

Julian Vicente
European Monitoring Centre for Drugs and Drug Addiction,
Rua da Cruz de Santa Apolónia, 23–25,
P-1149-045 Lisbon
Tel. (351) 218 11 30 23
Fax (351) 213 58 44 41
E-mail: julian.vicente@emcdda.europa.eu

Lucas Wiessing
European Monitoring Centre for Drugs and Drug Addiction,
Rua da Cruz de Santa Apolónia, 23–25,
P-1149-045 Lisbon
Tel. (351) 218 11 30 16
Fax (351) 213 58 44 41
E-mail: lucas.wiessing@emcdda.europa.eu

Ettore Zuccato
Department of Environmental Health Sciences,
'Mario Negri' Institute for Pharmacological Research, Via La Masa 19,
I-20156 Milan
Tel. (39) 239 01 45 44
Fax (39) 239 01 47 35
E-mail: zuccato@marionegri.it

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