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Estimating daily and diurnal variations of illicit drug use in Hong Kong: A pilot study of using wastewater analysis in an Asian metropolitan city

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Abstract

The measurement of illicit drug metabolites in raw wastewater is increasingly being adopted as an approach to objectively monitor population-level drug use, and is an effective complement to traditional epidemiological methods. As such, it has been widely applied in western countries. In this study, we utilised this approach to assess drug use patterns over nine days during April 2011 in Hong Kong. Raw wastewater samples were collected from the largest wastewater treatment plant serving a community of approximately 3.5 million people and analysed for excreted drug residues including cocaine, ketamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA) and key metabolites using liquid chromatography coupled with tandem mass spectrometry. The overall drug use pattern determined by wastewater analysis was consistent with that seen amongst people coming into contact with services in relation to substance use; among our target drugs, ketamine (estimated consumption: 1400–1600 mg/day/1000 people) was the predominant drug followed by methamphetamine (180–200 mg/day/1000 people), cocaine (160–180 mg/day/1000 people) and MDMA (not detected). The levels of these drugs were relatively steady throughout the monitoring period. Analysing samples at higher temporal resolution provided data on diurnal variations of drug residue loads. Elevated ratios of cocaine to benzoylecgonine were identified unexpectedly in three samples during the evening and night, providing evidence for potential dumping events of cocaine. This study provides the first application of wastewater analysis to quantitatively evaluate daily drug use in an Asian metropolitan community. Our data reinforces the benefit of wastewater monitoring to health and law enforcement authorities for strategic planning and evaluation of drug intervention strategies.

Keywords: cocaine, China, ketamine, MDMA, methamphetamine, substance consumption

1. Introduction

Illicit drug consumption is among the top 20 contributors to the global burden of disease and injury [1] and has a substantial negative economic impact [2]. As such, systematic surveillance of the extent of substance use and changes over time is important, particularly, to plan and to determine the success of law enforcement and health intervention strategies [3].

Hong Kong is one of the most densely populated cities in the world and its role as one of the key international financial centres draws a large number of international visitors each year. With such dynamic flow in people of different nationalities and high efficiencies in finance and transportation exchanges, Hong Kong is attractive for drug trafficking organisations [4]; for example, Hong Kong is found a key embarkation point for drugs to other Asian cities from China where illegal drug manufacturing appears often active [5].

The Narcotics Division of the Security Bureau in Hong Kong reports trends in substance use through its "Central Registry of Drug Abuse (CRDA)" reports. This report compiles data from law enforcement agencies (all arrests for substance use), drug rehabilitation and treatment centres, welfare and social work services (where substance use is suspected in clients) and hospitals (where withdrawal syndromes are present or individuals self-identify); and demographic and substance use information is collected [6]. The figures recorded in the CRDA are based on those drug consumers who have been identified with the agencies reporting in the system. While this dataset is the primary source for understanding drug use trends in Hong Kong, it is highly likely that many consumers may not be identified through this system. For example, for a population of seven million, just 12,400 consumers were identified for the 2010 CRDA report: <0.2% of the total population, which is extremely low by global standards (3.4-6.6% of adults) [3]. It is likely that infrequent consumers will not come into contact with the reporting agencies. The majority of consumers identified in CRDA were unemployed and had low education levels, suggesting that the consumers in other

demographics are not well captured by the system. To obtain more comprehensive information about substance use, multiple methods can help overcome the limitations of individual datasets [7].

An alternative method to estimate drug use is the quantification of drug metabolite residues in raw wastewater sampled at inlets of wastewater treatment plants. The feasibility of this approach – in this paper subsequently referred as *wastewater analysis* – to back-estimate drug consumption has been widely demonstrated [e.g. 8, 9, 10]. The basic concept of the approach is that excreted drug residues are collectively delivered from toilet systems to wastewater treatment plants in a catchment. Thus, a raw wastewater sample represents a pool of the excreted drug residues within a population and allows tracing back per capita consumption rates in the catchment. Daily composite samples are commonly collected for understanding day-to-day changes in population's drug use; higher consumption is typically identified in weekends than weekdays [e.g. 11, 12-16]. Analysing shorter time periods allows evaluating intra-daily variations in drug use [17, 18]. Such diurnal monitoring to date is less common in the literature.

Despite the fact that this approach cannot reveal patterns of individual drug use such as dose or the presence of poly-drug use, the final estimates from wastewater analysis are objective and maintain the anonymity of individual consumers. Hence, it produces less ethical issues compared to traditional epidemiological methods such as self-reporting surveys [19]. Another benefit of wastewater analysis is that it provides information about the use of chemically specified substances, which is particularly relevant to tablets sold as 'ecstasy', which may vary substantially in purity and content over time without the knowledge of the consumers [20, 21]. As such, wastewater analysis has been widely applied across different cities in western countries such as Australia, Canada, Europe and North America [e.g. 18, 22-28] but to date has not been conducted in any Asian communities.

In this study, we applied wastewater analysis to estimate the extent of use of ketamine, cocaine, methamphetamine and MDMA over nine days in the major urban community of Hong Kong. The data was then compared with that from the existing CRDA drug reporting system. Additionally, we examined diurnal variations of drug residue loads in the community through analysis of two-hourly composite wastewater samples.

2. Materials and methods

2.1 Wastewater sampling

Samples were collected at the inlet of the largest wastewater treatment plant (WWTP) in Hong Kong. It serves approximately 3.5 million people, which is about half of the local population living in the mainly urban catchment. The WWTP is fed by two main inlet pipes (channel A and channel B) receiving wastewater from seven preliminary treatment works (PTWs). These PTWs physically remove coarse particles and sediments (screening and de-gritting) and continuously pump the wastewater to the WWTP under study. The average overall hydraulic residence time of wastewater collected and pumped into the WWTP through channel A is approximately three hours and four hours for channel B. The sewer layout and hydraulic properties provide considerable mixing of wastewater and attenuation of short-term concentration variations facilitating the collection of representative samples. Samples were collected throughout the working week in 2011 on April 14th, 17th–21st and 24th–28th, representing the weekdays Sunday through Thursday. Unfortunately, samples from Fridays and Saturdays are missing since the WWTP does not conduct routine sampling on weekends and does not allow access for non-staff.

Hourly raw wastewater composite samples were collected at both inlet channels applying a time-proportional sampling mode, 250 mL every 15 minutes. With a few exceptions, intra-hour flow coefficient variations (CV) were relatively small: 3.6–53% (channel A) and 1.2–29% (channel B) (Fig. S1 and Table S1). Individual hourly samples were flow-proportionally mixed onsite in the laboratory of the WWTP to obtain representative daily composite samples for both channels. Additionally, to assess diurnal variations, the hourly samples from channel B were mixed flow-proportionally to two-hour composite samples on April 24th to 28th. Milli-Q water samples were prepared and put aside during the sample composition process as field blanks for quality control. Samples were preserved at pH 2 using 2M hydrochloride acid and frozen until analysis. The method of preservation has been widely applied and demonstrated

to stabilise target analytes in wastewater during storage [29-31].

2.2 Materials and chemical analysis

Reference materials, sample preparation and analytical measurement applied in this study have been previously reported [32]. Briefly, cocaine, benzoylecgonine, amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), ketamine and norketamine, together with their corresponding deuterated analogues, were purchased from Cerilliant (USA) (purities ≥ 99%). Methanol and acetonitrile (LC grade) were purchased from Merck (Germany) while hydrochloric acid (37%), formic acid and acetic acid were purchased from Sigma Aldrich (Australia).

Samples were filtered (0.45 μm, RC, Phenomenex) before spiking with deuterated standards (i.e. internal standards, 1–10 ng/mL) and then analysed together with seven calibration standards (0.05, 0.1, 0.5, 1, 5, 10, 50 ng/mL) using liquid chromatograph (Shimadzu Nexera UHPLC system, Kyoto, Japan) coupled with tandem mass-spectrometry (AB SCIEX QTRAP®5500, Ontario, Canada) (LC-MS/MS). Targeted analytes were chromatographically separated using a Luna C18 column, 3 μm, 150X2 mm, (Phenomenex, Torrance, CA). Scheduled multiple reaction monitoring with positive electrospray ionisation were operated to identify and quantify the masses of analytes (see Lai *et al.* [32] for details of analytical conditions).

For quality assurance and control of the analysis, duplicate samples and wastewater matrix spiked with native chemicals (1 ng/mL) were arranged for analysis. Also, blank samples of Milli-Q water were included to check for contamination in every batch of sample preparation and analysis. Milli-Q water samples were spiked with native chemicals as procedural recovery checks. The coefficient variation (CV) of duplicate samples was on average <6% (n=5). No target chemicals were quantified in the blank samples and field blank samples

(Table S1). Procedural and matrix spike recoveries were on average in a range of 97–110% (CV: 4–16%; n=3) and 89–104% (CV: 8–27%; n=5), respectively, and inter-day analytical variability (2 days; n=8) was in a CV range of 2–9% (Table S2). Average recoveries of individual internal standards in the samples were in a range of 62–120% (CV: 5–15%; n=77) (Table S3).

2.3 Targeted drug residues

Seven drug residues, including parent drugs and/or its major metabolites, were targeted. These are methamphetamine, amphetamine, cocaine, benzoylecgonine, ketamine, norketamine and MDMA. The drugs have been reported to be commonly consumed in Hong Kong [6] and are regulated under Schedule 1 of the Dangerous Drugs Ordinance in the Laws of Hong Kong [33], meaning that use is illegal without authorised licenses.

2.4 Back calculation of drug consumption

The back calculation method was based on the model previously proposed [11] and has been commonly applied in the literature [e.g. 23, 26, 28]. A mass load of a given chemical was estimated by multiplying concentrations by the wastewater flow. The figure is then multiplied with a correction factor which comprised of the average urinary excretion rate and molecular mass ratio of a parent drug to its metabolite. The correction factor of 3.14 (1.1/0.35) was used to back estimate cocaine consumption. This was derived from the average excretion rate of cocaine to benzoylecgonine (35%, covering administration routes of smoking, snorting and injection) [34-36] and the molecular weight ratio of cocaine to benzoylecgonine (1.1). Similarly, the average excretion of methamphetamine itself (33%, covering administration routes of oral, smoking, snorting and injection) [37, 38] was used to calculate the correction factor of 4.06 (1.0/0.33) for back estimating methamphetamine consumption. The correction factor of 65 (1.06/0.016) was used to estimate ketamine consumption based on its metabolite norketamine (1.6%, injection) [37, 39, 40]. Daily drug loads and consumption in the entire

204 catchment was estimated from the sum of measured drug residue loads in both channels. The
205 data was normalised to the total population (3.5 million people).
206

3. Results and discussion

With the collected samples representative of half the Hong Kong population, the results are adequate to provide an understanding of the illicit drug use profile in this metropolitan city. Additionally, the catchment area covers about 60% of the residential addresses of the reported drug consumers in the Central Registry of Drug Abuse (CRDA) report, which is the primary source for drug use trends in Hong Kong. Our results revealed patterns of inter- and intra-day variability in illicit drug residues through analysis of daily and two-hourly composite raw wastewater samples in Hong Kong. This contributes, in part, to addressing the paucity of literature describing wastewater analysis of illicit drug use in Asian communities.

3.1 Daily drug use patterns detected in wastewater samples

Five out of seven illicit drug residues were quantified in all the samples (Fig. 1). Among the drug residues, the daily load (average±standard deviation of the nine-day monitoring) of ketamine (290±27 mg/day/1000 people) was the greatest and about one order of magnitude higher than its metabolite, norketamine (23±4 mg/day/1000 people). The daily load of methamphetamine was the next highest (62±4 mg/day/1000 people). The load of cocaine (33±4 mg/day/1000 people) was approximately half that of its metabolite, benzoylecgonine (54±3 mg/day/1000 people). Amounts of amphetamine and MDMA were below the limit of detection (<10 mg/day/1000 people) in any of the samples. The load of each drug residue was steady from day to day during the monitoring period (coefficient of variations is relatively low: 5–17%). Thus, intra-week variations in drug use were not apparent. It should be noted that the weekly drug use pattern in this study comprised of four weekdays and only Sundays on the weekends, but still was inconsistent to a range of previous wastewater studies showing higher drug use during weekends than weekdays with a peak use particularly found on Sundays [e.g. 11, 13, 15]. This may suggest that regular and chronic users may be more predominant than infrequent consumers in this community.

234 *3.1.1 Comparison with the CRDA report*

235 The daily drug use pattern (ketamine > methamphetamine > cocaine > MDMA) detected by
236 wastewater analysis conformed to the CRDA report [6]. In 2011, the pattern of illicit
237 substance consumers identified in the CRDA was heroin (52% of cases) > ketamine (32%);
238 methamphetamine (14%) > benzodiazepines and related substances (11%) > cocaine (8%) >
239 cannabis (4%) > ecstasy (1%) [41]. While heroin is predominant (50% of consumers
240 identified in CRDA in 2010), reports of ketamine use have quickly escalated, doubling
241 between 2001 and 2010 to the point that one-third of consumers identified in the CRDA
242 report were ketamine consumers. Rates of ketamine use are substantially greater than that of
243 ecstasy, and rates of ecstasy use have been steadily declining since 2005 [6]. This high rate of
244 ketamine use among illicit substance consumers in Hong Kong is relatively unique
245 internationally [42]. Compared to ecstasy, ketamine is more readily available, less costly [5],
246 higher and more consistent in purity [43-45] and easy to sociably share with others due to its
247 distribution in powder form. This study found that mass loads of methamphetamine were
248 consistently greater than those of amphetamine in the samples. This is in agreement to the
249 finding in CRDA and also in United Nations Office on Drugs and Crime reporting that
250 methamphetamine is the most widely used amphetamine-related substance in East and
251 Southeast Asia, mainly due to its easy production process and high availability of the
252 precursors [46, 47].

253

254 *3.1.2 Comparison with other wastewater studies*

255 Estimated consumption of ketamine was predominated (1500±240 mg/day/1000 people),
256 followed by methamphetamine (190±11 mg/day/1000 people) and cocaine (170±11
257 mg/day/1000 people) (Fig. 2). Compared to the wastewater study across 19 European cities in
258 2011, the average methamphetamine consumption in Hong Kong was estimated at about two
259 to ten times higher than that in London (the U.K.), Stockholm (Sweden), Valencia (Spain)
260 and Milan (Italy), but at about three to five times lower than that in Oslo (Norway) and

Helsinki (Finland) [23]. The estimated consumption of methamphetamine in Hong Kong was on average similar to that in other wastewater studies in Australian communities [28, 48]. A different pattern of cocaine consumption among these countries was observed. The estimated consumption of cocaine in Hong Kong was three to ten times lower than the cities in the west and central of Europe and London but similar to the northern European cities, including Oslo, Stockholm and Helsinki [23]. Cocaine consumption was estimated to be two and six times more in Hong Kong than in the Australian urban communities of southeast Queensland [28] and Adelaide in South Australia [48], respectively. Such comparison of drug consumption across different major and urban cities worldwide demonstrates that wastewater analysis provides a standardised platform to equally gauge international drug use levels. This kind of data is rare in national and/or international drug monitoring systems but is valuable for any law enforcement authorities to estimate the rate of growth of the drug markets among various types of communities within a country or around the world.

3.2 Diurnal variations in drug residue loads

Drug residue concentrations and loads are plotted together in Figure 3 to facilitate the interpretation of diurnal variations: parent compounds and metabolites follow similar patterns throughout the four monitoring days (see Table S4 for total loads). The mass loads of the drug residues peaked in the mornings and at nights every day. The morning peak was generally apparent over two to four hours (7–9AM and/or 9–11AM), accounting for about 10–14% of the total mass load per two-hour period. The night peak extended four to six hours, starting in the evening (about 7PM) until midnight, reflecting approximately 10–15% of the total mass load per two-hour period. Similar wastewater studies with high resolution sampling was also conducted in Oslo, Norway (six-hour composite samples) [17] and the United States (one-hour composite samples) [18]. The variation of diurnal patterns among the international studies and this study broadly suggests that drug excretion rates were often higher during mornings and selectively during evenings. The daily mass loads of drug residues estimated

from physical daily composite sample and the sum of 12 two-hourly composite samples allow verifying the flow-proportional mixing process of individual samples. The deviations are within the expected range of analytical uncertainty and do not show any systematic deviations (Tables S5–6).

3.3 Ratio of a parent drug to its metabolite

The concentration ratio of the parent drug to its metabolite remained consistent in the analysed daily composite samples (ketamine/norketamine: 13±1.8; cocaine/benzoylecgonine: 0.61±0.08). However, three data points from the two-hourly samples were identified as outliers (Fig. 4): the cocaine/benzoylecgonine ratios were 1.05 and 1.52, rather than the usual value observed in this community. This may imply that part of the cocaine identified in these samples could be attributed to direct dumping events rather than human metabolism. These time points were between Monday midnight and Tuesday morning (April 25th-26th; 11PM–3AM) and on Tuesday night (April 26th; 7–9PM) (Fig. 3B). Such high resolution data of wastewater analysis could provide more information on drug use activities in the sewer catchment than daily composite samples. Direct dumping of cocaine can be due to different reasons, such as raids by police forces and/or hand-washing after handling cocaine.

3.4 Methodological limitations

While our study provides drug use data that complements the existing epidemiology reports, a few methodological constraints should be remarked for better interpretation of the results. Recent studies have proposed different human markers to estimate the number of people contributed in a wastewater sample for better estimation of per capita illicit drug use [18, 32, 49]; for example, our previous study suggested the use of a certain prescription pharmaceutical [32]. However, these kinds of pharmaceutical data are not readily available in Hong Kong for estimating the population that contributed to a sample. As such, we had to rely on a nominal figure for the population contributing to the wastewater treatment plant and

assumed that this population was consistent throughout the study period. Another issue, which also requires pharmaceutical data and thus limits this study, is to exclude potential contributions from legal sources of methamphetamine in wastewater samples as methamphetamine can be metabolised after prescribing selegiline for diagnosing Parkinson's disease [15, 28]. However, this may only produce a minor influence on the data presented here; studies showed that Parkinson's disease is less prevalent in Hong Kong than Australian communities [50]. Regarding the use of literature-based pharmacokinetic data for extrapolating drug use, there are two notable limitations: (a) the currently available studies reporting urinary excretion values were mainly conducted in Western countries, and thus cannot account for possible variations in metabolism due to different racial demographics (i.e. potential differences in people of Asian descent in comparison to Western samples); and (b) smaller urinary excretion fractions potentially increase uncertainty levels of estimations, particularly in the back-estimation of ketamine use from norketamine. Lastly, this study only monitored drug use across about two weeks and thus the results cannot be generalised to patterns of drug use over the whole year in Hong Kong.

4. Conclusions

This study for the first time applied wastewater analysis to quantitatively determine the level of drug use between and within days in an Asian metropolitan community. The overall pattern of drug use detected in daily wastewater samples was consistent with that in the current drug reporting system. Elevated concentration ratios of cocaine to benzoylecgonine were identified in three samples of the high-temporal resolution diurnal monitoring, suggesting possible dumping events of cocaine. Given that the current drug reporting system in Hong Kong only obtains limited data from drug users identified by health and law enforcement, setting up more sophisticated national monitoring systems with wastewater analysis as complementary means can provide more comprehensive assessments on drug use. These are valuable for health and law enforcement authorities to strategically plan and systematically evaluate the

effectiveness of drug use intervention programmes in the community.

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Figure 1

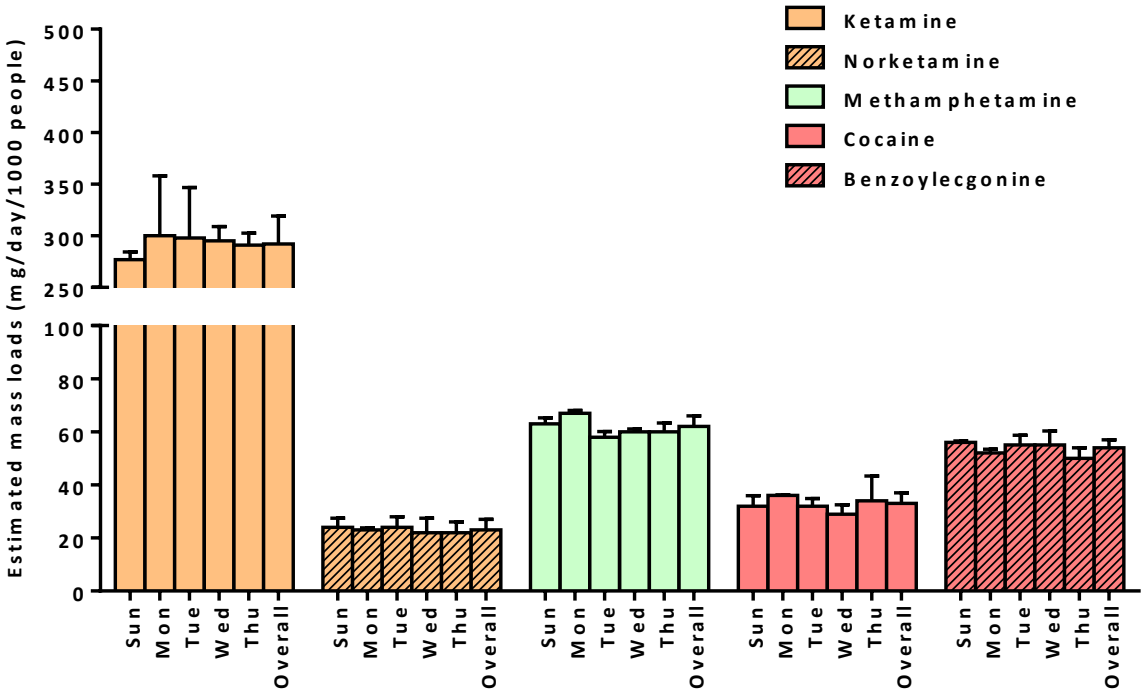


Figure 1: Comparison of weekly variation in daily mass loads (mg/day/1000 people) of the targeted drug residues. Concentrations of amphetamine and MDMA were below detection limits (< 10 mg/day/1000 people). Sampling dates included 14th, 17th–21st and 24th–28th April in 2011 (n=2 per weekday; the error bar indicates a single standard deviation of the two samples). Samples from Fridays and Saturdays are missing because the wastewater treatment plant does not carry out the routine sampling and does not allow access for non-staff on these two days.

Figure 2

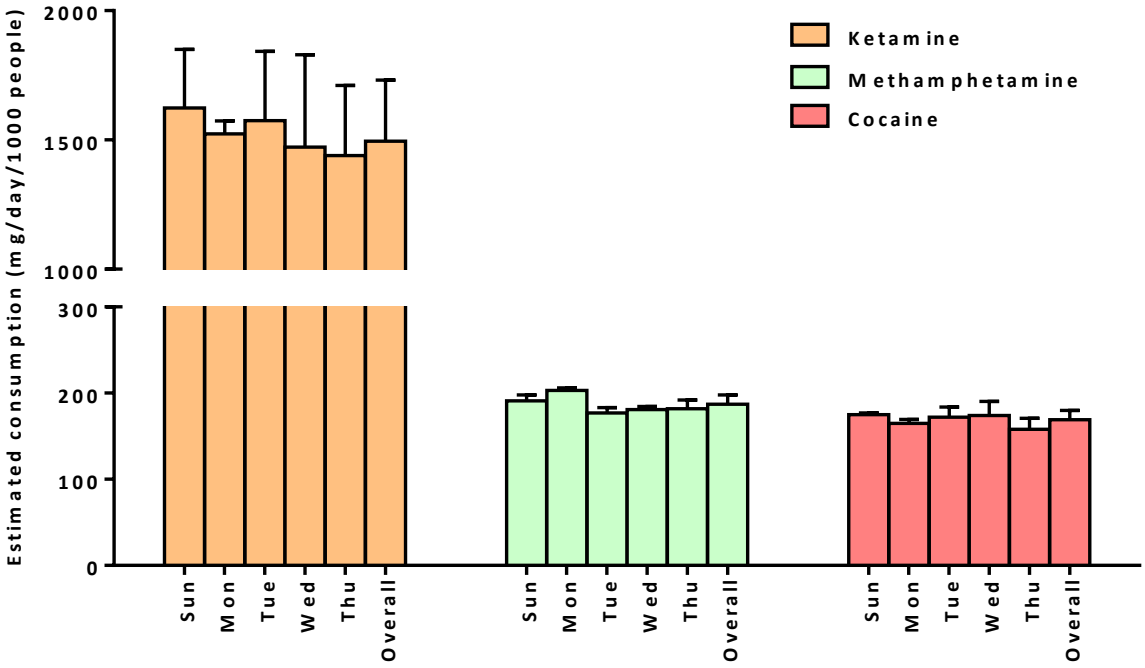
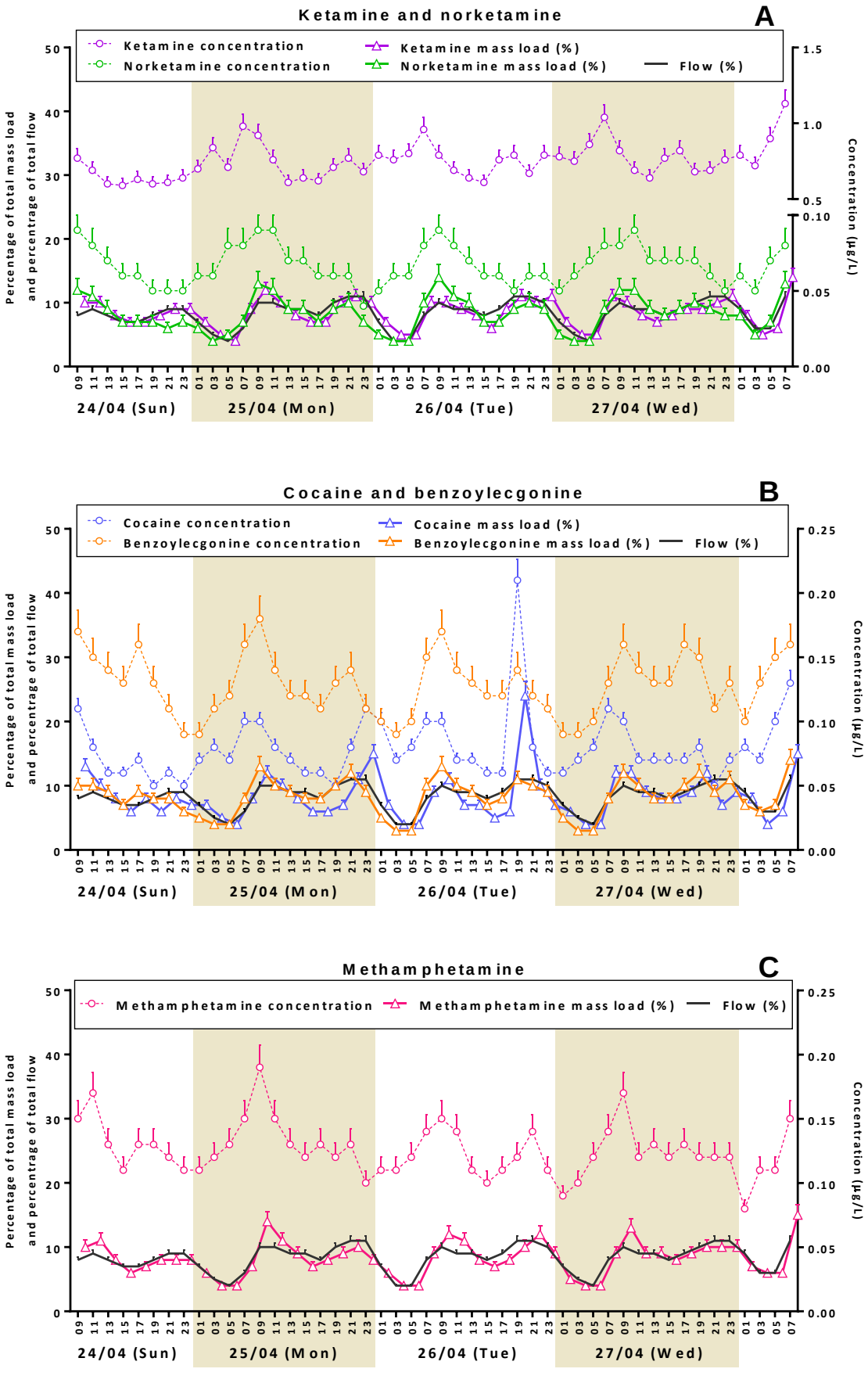


Figure 2: Estimated consumption (mg/day/1000 people) of ketamine, methamphetamine and cocaine in the studied community. Sampling dates included 14th, 17th–21st and 24th–28th April in 2011 (n=2 per weekday; the error bar indicates a single standard deviation of the two samples). Samples from Fridays and Saturdays are missing because the wastewater treatment plant does not carry out the routine sampling and does not allow access for non-staff on these two days.

520 **Figure 3**
521



522
523 **Figure 3:** Diurnal variations of drug residues (dt = 2 h). Right Y-axis: drug residue
524 concentrations (dashed lines). Left Y-axis: Percentage of total daily drug residue loads

(coloured solid lines) and percentage of the total wastewater flow (black solid line). Total wastewater flow and mass loads for each drug are reported in Table S4. An error bar included the uncertainty of chemical analysis, sampling and/or flow measurement (Table S6) [32].