Use of legal and illegal substances in Malé (Republic of Maldives) assessed by wastewater analysis

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Abstract

This study used wastewater-based epidemiology (WBE) to investigate the lifestyle of the inhabitants of Malé, the capital of the Republic of Maldives. Raw wastewater 12-h composite samples, collected from nine pumping stations serving the city area - thus representative of the whole Malé population - were collected and analysed for residues of illicit drugs, alcohol, coffee, nicotine and pharmaceuticals, to estimate the consumption of these substances. The illicit drugs identified were mainly cannabis (THC) and heroin, with low consumption of cocaine and amphetamines. It is important to note that the consumption of THC in Malé was comparable to that measured in other countries, while the consumption of heroin was much higher. Among cathinones, mephedrone was also detected at a level of concern. Consumption of alcohol, which is not allowed in Maldives, was found at a medium-low level, while the consumption of coffee and cigarettes was generally in line with reports from other countries. WBE provided valuable information complementary to traditional epidemiological approaches, which may be useful for national and international agencies to understand population lifestyles better, including illicit drug issues, and for planning and evaluation of drug prevention programs in Malé.

Keywords

Urban wastewater, illicit drugs, alcohol, nicotine, pharmaceuticals, Republic of Maldives

1. Introduction

Wastewater-based epidemiology (WBE) is a novel approach capable of providing valuable information complementary to traditional epidemiological methods. WBE can be used for instance to study population's lifestyle, by investigating the consumption of various substances, particularly illicit drugs but also alcohol, tobacco and coffee. The use of illicit drugs is a global phenomenon involving millions of individuals with tremendous implications for public health and social behavior (United Nations Office on Drugs and Crime - UNODC, 2012). According to the World Drug Report 2016 (UNODC, 2016) a quarter of a billion people aged 15-64 years used at least one drug in 2014 and almost 12% of the total number of people who use drugs (more than 29 million) are estimated to suffer from drug use disorders. Countries in the South Asian region have not been immune. Substance abuse was first reported in Nepal in 1976, Sri Lanka in 1981, India in 1986 and Maldives in the mid - 1970's (Ageel, 2006).

Epidemiologic studies on drug use in Maldives are scarce. The most recent survey (2011-2012) from UNODC (UNODC, 2013) estimates the number of drug users at 4,342 in Malé and 3,154 in all the other islands of the archipelago. The statistical yearbook of the Maldives (2011) reported that in 2006 and 2007 a total of 1970 persons, most of them aged 16-24, were detained by the Maldives Police Service in relation to drug use offenses (UNODC, 2013). The only "situation assessment" of the Maldives available (United Nations Economic and Social Commission for Asia and the Pacific, 2003) found that drug users were mainly males (97%) and the most commonly used drugs were opioids (76%) and cannabinoids (12%). The remaining 12% reported the use of alcohol, cola water, inhalants/solvents and sedative/hypnotics, with rare cases of cocaine and 3,4-methylenedioxymethamphetamine (MDMA).

Currently in the Republic of Maldives drug use is described by passive surveys that do not objectively catch the full extent of the problem because the data collected are far from accurate. Other common indicators are seizure statistics, but in the Maldives these are largely subject to randomness, providing limited information that can at best reflect the overall drug use trend (Li et al., 2014).

WBE offers a reliable method to provide more realistic drug consumption data (Zuccato et al., 2008, 2011) by measuring drug metabolites in urban wastewater and back-calculating the consumption in the population served by the treatment plant. WBE has been applied worldwide, such as in Europe (Zuccato et al., 2008; van Nuijs et al., 2009; Nefau et al., 2013; Zuccato et al., 2016), including multi-city monitoring campaigns (Thomas et al., 2012; Ort et al., 2014), USA (Banta-Green et al., 2009), Canada (Yargeau et al., 2014), Australia (Lai et al., 2016), Hong Kong (Lai et al., 2013), Martinique (Devault et al., 2014), and China (Li et al., 2014; Khan et al., 2014). The benefits of estimating illicit drug use based on WBE are the objective and updated estimates and a non-intrusive tool providing information for an entire population, thus not suffering survey problems such as the subjective results, and the limited number of subjects (Zuccato et al., 2008).

The aim of this study was to use WBE to estimate, for the first time in South Asia, lifestyle habits in a defined population living on an island. The use of illicit drugs, alcohol, caffeine, nicotine and pharmaceuticals was assessed in Malé, the capital of the Republic of Maldives. Wastewater from all the nine sewage collectors of the city was collected and analysed, covering the entire population living in Malé.

2. Materials and Methods

2.1 Area Investigated

Malé is the capital of the Republic of Maldives. The city is on an island, with a surface area of less than two km^2, on the southern part of the Kaafu Atoll. With the growth of tourism, the population of the capital has increased from 62,519 in 1995 (https://goo.gl/Xftpm7) to 153,940 in 2016 (https://goo.gl/N8ZGZo). In 2015 almost half the population of the Maldives (344,025) lived in Malé (https://data.worldbank.org/indicator/SP.POP.TOTL?locations=MV), making it the only real city in the archipelago, comparable to other South Asian cities (Scheyvens, 2011) not so much for the number of inhabitants as for the population density. The majority of inhabitants come from the other inhabited islands to work in the administrative and tourism offices of the capital (Fallati et al., 2017).

The sewage network of the city was established in the 1980s. It is divided into nine zones flowing into nine pumping stations (PSs) (Figure 1/a). From these all the untreated wastewater is discharged directly into the ocean. The PSs are essentially a pit covered by a metal grid, easily accessible for sampling (Figure 1/c).

2.2 Samples Collection

Composite 12-hour samples, representative of the “day” and “night” periods, of untreated urban wastewater were collected from the inlet of the nine PSs in Malé. Samples were collected every 30-60 min with an automatic computer-controlled sampling device (Sigma 900 Standard, Hach Company, USA) (Figure 1/b). Composite samples were taken daily from each PS for nine consecutive days, one PS a day, from Thursday March 12, 2015 to Friday March 20, 2015. Two

125 samples were collected each day, one during the day and the other during the night. Samples
126 were collected in 500-mL inert plastic bottles, immediately frozen at -20°C, and stored frozen until
127 analysis.
128
129 **2.3 Selection of target residues**
130
131 *Illicit drugs (IDs).* Consumption of the major IDs, i.e. cocaine, heroin, cannabis (it was
132 measured the active principle tetrahydrocannabinol - THC), amphetamine, methamphetamine and
133 MDMA - ecstasy, was estimated by analysing selected drug excretion residues (target residues) in
134 wastewater (Zuccato et al., 2008). Briefly, the target residues were selected according to current
135 knowledge of the metabolic fate of each active drug (Huestis et al., 1996; Baselt, 2008) and the
136 stability of the candidate residues in wastewater (Castiglioni et al., 2013). The main urinary
137 metabolites of cocaine (benzoylecgonine), heroin (morphine and 6-acetylmorphine), THC (11-nor-
138 9-carboxy-delta9-tetrahydrocannabinol - THC-COOH), and the unchanged parent drug of
139 amphetamine, methamphetamine, and MDMA were measured.
140 *Synthetic cathinones (CAT).* The presence of new psychoactive substances (NPS) was also
141 investigated by including a panel of CAT, which are one of the most used classes (EMCDDA, 2015).
142 Since information about human metabolism of these substances is scant, only the parent
143 compounds were measured in wastewater (Gonzalez-Marino et al., 2016).
144 *Alcohol.* Ethyl sulphate (EtS), a minor phase-II metabolite of alcohol, was measured in
145 wastewater as a target residue of alcohol consumption, as previously reported (Reid et al., 2011;
146 Rodriguez-Alvarez et al., 2015).
147 *Nicotine and caffeine.* We measured nicotine, caffeine and their human metabolites to
148 estimate respectively tobacco and caffeine consumption, as previously described (Castiglioni et al.,

2015; Senta et al., 2015). For nicotine, the two urinary metabolites, cotinine and trans-3'-hydroxycotinine, were selected as target residues, while for caffeine, paraxanthine (1,7-dimethylxanthine), 1-methylxanthine, 7-methylxanthine, 1,7-dimethyluric acid, and 1-methyluric acid were measured.

Pharmaceuticals (PHARM). A set of *PHARM* belonging to different therapeutic categories such as antibiotics, anti-cancer, anti-inflammatory, bronchodilator, cardiovascular, central nervous system (CNS) drugs, diuretics, estrogens, gastrointestinal and lipid regulators were selected. They were chosen according to their patterns of use, persistence and toxicity in the environment, as detailed elsewhere (Riva et al., 2015). For *PHARM*, we mostly considered the parent substances, except for a few metabolites.

2.4 Analysis of target residues in wastewater

Because of the high heterogeneity of the substances analysed, different highly selective multi-residue methods previously developed and validated in our laboratory were used. First, the samples were filtered on glass microfiber filters GF/A 1.2 µm (Whatman, Kent, UK) and on a mixed cellulose ester microfiber filter ME25 0.45 µm (Whatman, Kent, UK); then they were spiked with deuterated internal standards and solid-phase extracted using Oasis MCX and HLB 60 mg cartridges (Waters Corp., Milford, MA, USA). Eluates were dried under a gentle nitrogen stream and dissolved following the specific procedure for each class of analytes.

Liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) in the selected reaction monitoring mode (SRM) was used for analysis and the isotopic dilution method for quantification. Briefly, samples for *IDs*, *CAT* and *PHARM* target residues were acidified and solid-phase extracted on mixed reversed-phase/cation-exchange cartridges (Oasis MCX). Detailed information on

analytical methods is given elsewhere for *IDs* (Castiglioni et al., 2006; Zuccato et al., 2016), *PHARM* (Castiglioni et al., 2005; Riva et al., 2015) and *CAT* (Gonzalez-Marino et al., 2016). Samples for nicotine, caffeine and their metabolites were checked for pH around 7 and were extracted on reversed-phase cartridges (Oasis HLB) as detailed elsewhere (Castiglioni et al., 2015; Senta et al., 2015).

EtS was analysed by direct injection slightly modifying a method previously published (Rodriguez-Alvarez et al., 2015). Briefly, 1 mL of the sample was centrifuged, 200 µL were spiked with the internal standard EtS-d_5 (10 ng) and transferred into a vial for analysis. Chromatographic separation was done with an Atlantis T3 2.1x150 mm column (Waters Corp., Milford, MA, USA), using acetic acid 0.1% and acetonitrile as mobile phases. The flow rate was 180 µL/min and the injection volume was 4 µL. The method was validated in-house and run as previously described (Rodriguez-Alvarez et al., 2015).

2.5 Back calculation of consumption

Concentrations (ng/L) of target residues in wastewater were multiplied by the wastewater flow rate (L/day) to estimate the loads of the different classes. Given the proven stability of the chosen target residues in wastewater (Castiglioni et al., 2013), mass loads reasonably reflect the collective excretion rates (g/day). The mass loads of the target residues were used to extrapolate the loads of the parent substance by taking into account: 1) the average percentage of the parent drug excreted as target residue in urine, and 2) the parent drug-to-target residue molar mass ratio (Zuccato et al., 2008). The loads of each parent substance indicate its consumption in the population producing the wastewater. The method described for *IDs* (Zuccato et al., 2008) was adapted to the other substances, as indicated below. The main parameters used to estimate

consumption of the different substances is reported in the Supplementary Material (SM) (Table S1).

IDs. The consumption of cocaine, amphetamine, methamphetamine, MDMA and cannabis was calculated as previously described (Zuccato et al., 2008; Castiglioni et al., 2013). For heroin, we calculated consumption using 6-acetylmorphine (minor metabolite) instead of morphine (major metabolite). We also measured waterborne morphine, but we could not use morphine levels to estimate heroin consumption because we had to apply corrections to compensate for the contribution of therapeutic morphine and we did not have this information in Malé. Normally, 6-acetylmorphine is not considered a proper drug residue for estimating heroin consumption because of its rapid degradation in wastewater (Castiglioni et al., 2013), but no significant loss was observed in this study because the wastewater was sampled directly at the source. To compare consumptions of the different drugs that may be used at different doses we also estimated a "number of doses" consumed for each substance, considering the following mean doses: 100 mg for cocaine and MDMA, 30 mg for heroin, methamphetamine and amphetamine, and 125 mg for THC.

CAT. We only measured the mass loads of the parent substances. Consumption was not calculated because no information was available about human metabolism of these substances.

Alcohol. To estimate alcohol consumption, we measured EtS in wastewater and transformed the concentrations into alcohol consumption as described previously (Rodriguez-Alvarez et al., 2015). Briefly, concentrations were corrected for the excretion rate of EtS in man after the intake of alcohol, and the molar mass ratio between EtS and the parent substance (alcohol).

Nicotine and caffeine. Cotinine and trans-3'-hydroxycotinine were used to calculate nicotine consumption in the population, as previously described (Castiglioni et al., 2015). The number of cigarettes smoked was then calculated on the basis of the mean content of nicotine absorbed from one cigarette (1.25 mg). The mass loads of caffeine and its main urinary metabolites were calculated as specified at the beginning of this chapter and 1,7-dimethyluric acid was used as a target residue to estimate coffee consumption, according to a method previously described (Gracia-Lor et al., 2017).

PHARM. Daily mass loads of *PHARM* in wastewater were calculated from the parent substances and were directly used to assess consumption in the population by comparing the results with previous studies conducted in Italy.

3. Results and discussion

3.1 *IDs*: cocaine, heroin, amphetamine, methamphetamine, ecstasy, cannabis and *CAT*

Consumption was estimated as mg of pure substance/day in each of the nine sites of Malé served by the PSs. The different areas were numbered but not identified (numbers do not correspond to those reported in Figure 1) for privacy reasons, according to our ethics guidelines in WBE (Prichard et al., 2014). Table 1 reports the mean values for the "day" and "night" samples collected at the different PSs. The highest consumption in all sites was for cannabis and heroin and the lowest for cocaine. Raw data are reported Table S2. Considering only psychostimulants, the highest use was for MDMA (ecstasy) (Table 1 and Figure 2). Differences in use were observed among the sites: at sites 2, 3, 8 and 9 MDMA and methamphetamine were at the highest levels, while at sites 4 and 5 cocaine was at the highest levels (Table 1 and Figure 2). These differences corresponded to recreational activities or residential areas. The consumption of heroin and

242 cannabis was higher at sites 4 and 5 (Table 1). Some differences were also seen between day and
243 night (Table S1), but no general trend was identified.

244 The total daily consumption in Malé, calculated by summing up consumption at the nine
245 sites, was about 700 g of cannabis and 18 g of heroin (Table 2); consumption of cocaine and
246 amphetamines was lower (0.1-1.2 g/day). The total number of doses estimated for a rough
247 comparison of drug use with the available epidemiological information was about 5600 doses/day
248 of cannabis, 600 doses/day of heroin and 1-15 doses/day of cocaine and amphetamines (Table 2).
249 These results roughly agree with the number of drug users in Malé, which was 4342 in 2011-2012,
250 according to UNODC (UNODC, 2013) and with the drugs of choice, which were opioids and
251 cannabis, with rare use of cocaine and MDMA (United Nations. Economic and Social Commission
252 for Asia and the Pacific, 2003).

253 Comparing consumption in Malé with other countries, cocaine use (0.5 mg/day/1000
254 inhabitants, Table 2) was much lower than in Italy, Europe (600 and 700 mg/day/1000 inhabitants)
255 (Zuccato et al., 2016; Ort et al., 2014) and Australia (250 mg/day/1000 inhabitants) (Lai et al.,
256 2016), and more similar to New Zealand (30 mg/day/1000 inhabitants) (Lai et al., 2017).
257 Consumption of methamphetamine, amphetamine and ecstasy (3-8 mg/day/1000 inhabitants,
258 Table 2) was also lower than in Australia, New Zealand, USA, China and Europe (Lai et al., 2016,
259 2017; Subedi and Kannan, 2014; Li et al., 2014; Ort et al., 2014), but similar to Italy and South
260 Korea (Zuccato et al., 2016; Kim et al., 2015). Cannabis use in Malé was comparable to Italy
261 (Zuccato et al., 2016), while heroin use was almost ten times higher than in Italy (Zuccato et al.,
262 2016), and also higher than in other countries in Europe (van Nuijs et al., 2011).

263 We also measured ketamine and its metabolites nor- and dehydro nor-ketamine,
264 methadone and its metabolite ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP
265 perchlorate), hydrocodone and oxycodone. The results are not reported as these substances were

always undetectable or in low trace amounts. This indicates different patterns of use for ketamine compared to other countries in South Asia (Lai et al., 2013).

Table 3 and Table S3 show results for *CAT*. In this case, we measured residues in wastewater and expressed the results as mass loads. We could not measure consumption exactly, because excretion rates of cathinones in man are still unknown or uncertain. We used therefore *CAT* loads to have a rough estimate of the use. Only four substances were found (Table 3): methylone and butylone in one site each, ethylone and mephedrone in more sites. The highest total loads were 45 mg/day for ethylone and 390 mg/day for mephedrone, much greater than use found in Australia and in Italy, Spain, and UK (Chen et al., 2013; Gonzalez-Marino et al., 2016).

3.2 Alcohol

Table 4 reports the alcohol consumption for the nine sites of Malé served by the PSs and for the whole of Malé. Table S4 gives the raw data including the levels of EtS, the specific alcohol metabolite in humans. Total consumption in Malé was equivalent to 1.32 L/day/1000 inhabitants, with no marked differences between sites. There are no figures on alcohol consumption in Malé as alcohol use is not permitted. Comparison with other countries, however, showed that alcohol consumption was lower in Malé than in Europe, Canada and Australia, where wastewater analysis gave mean alcohol consumptions of 6.4-44.3 L/day/1000 inhabitants, which is 5-33-fold the consumption in Malé (Ryu et al., 2016). Studies in Belgium and Australia also showed higher consumption (15 L/day/1000 inhabitants in Belgium and 19 L/day/1000 inhabitants in Australia) (Boogaerts et al., 2016; Lai et al., 2018).

3.3 Nicotine, caffeine and metabolites

The total mass loads measured for nicotine, caffeine and their metabolites in Malé ranged between 115 and 332 g/day for nicotine and its metabolites, and from 300 to 1500 g/day for caffeine and its metabolites (Table 5 and Table S5). These mass loads were higher than for *IDs*, but lower than for alcohol, reflecting the different prevalence of use of these substances in the general population (Anderson, 2006).

The consumption of nicotine in Malé was measured from cotinine and trans-3'-hydroxycotinine and the total daily use was 394 g/day (Table 5), corresponding to 2.6 g of nicotine/day/1000 inhabitants and 2048 cigarettes/day/1000 inhabitants. A similar study in the city of Milan in 2012 gave similar results, reporting consumption of 1767 cigarettes/day/1000 inhabitants (Castiglioni et al., 2015). In Australia, a recent estimate gave slightly higher consumption, 2500 cigarettes/day/1000 inhabitants (Lai et al., 2018), while up to 5000 cigarettes/day/1000 inhabitants were found in some European cities (Baz-Lomba et al., 2016).

Caffeine consumption was estimated from the loads of 1,7 dimethyluric acid (Gracia-Lor et al., 2017) and showed total daily consumption of 9300 g/day, corresponding to about 60 g/day/1000 inhabitants, which is the caffeine in about 600 cups of coffee, considering a mean content of 100 mg per cup. Consumption in Malé was slightly lower than in some European cities, where it ranged from 86 g/day/1000 inhabitants (Milan, Italy) to 263 g/day/1000 inhabitants (Zurich, Switzerland) (Gracia-Lor et al., 2017).

3.4 Pharmaceuticals (*PHARM*)

Table S6 reports the loads of *PHARM*, metabolites and hormones (in total 37 substances) in wastewater in Malé. We found high levels of largely used substances, such as paracetamol

312 (acetaminophen) (162 g/day), NSAIDs such as diclofenac, ibuprofen and naproxene (46, 17, 18
313 g/day respectively), ranitidine, an anti-ulcer drug (126 g/day), and gemfibrozil, a lipid-lowering
314 agent (20 g/day). Other substances with loads between 2 and 9 g/day were some antibiotics
315 (ciprofloxacin, ofloxacin, dehydro-erythromycin, and clarithromycin), another NSAID
316 (ketoprofene), a cardiovascular drug (atenolol), an antiepileptic drug (carbamazepine), another
317 lipid-lowering drug (atorvastatin), diuretic agents (furosemide and hydrochlorothiazide) and an
318 anti-asthmatic agent (salbutamol) (Table S5). The total mass loads of the PHARM measured in the
319 different sites ranged from 27 to 70 g/day, with no marked differences (Figure 3). This was as
320 expected, considering the pattern of use of these *PHARM*, which are generally randomly
321 consumed by the population. Nevertheless, site 4, that receives discharges from the city hospital,
322 had the highest total mass load of *PHARM*.

323 The comparison with *PHARM* mass loads measured in Milan (data from Castiglioni et al., 2018)
324 shows some interesting differences (Table 6). In Malé, there was similar use of paracetamol and
325 diclofenac, greater use of gemfibrozil (a lipid-lowering drug), ranitidine (anti-ulcer drug) and
326 salbutamol (anti-asthmatic agent), and lower use of all the other pharmaceuticals among which
327 antibiotics, some NSAIDs (ibuprofen, ketoprofene, naproxen), a lipid-lowering drug (atorvastatin)
328 and cardiovascular agents (atenolol, enalapril). Some of these *PHARM* were also investigated in
329 wastewater in Oslo, Norway (Baz-Lomba et al., 2016), and gave higher levels than in Milan and
330 Malé. In Oslo, atenolol, carbamazepine, diclofenac and paracetamol loads were respectively 216,
331 2419, 961, and 11231 mg/day/1000 inahbitants. Unfortunately, in Malé it was not possible to
332 compare the amount of *PHARM* measured in wastewater with the local prescription data because
333 they were not available. Nevertheless, the application of WBE showed interesting differences in
334 the patterns of use of *PHARM* and demonstrated the usefulness of this approach to obtain
335 information on their local profiles, especially when official data are not available.

4. Conclusions

This is the first evaluation of the consumption of *IDs*, *CAT*, alcohol, nicotine, caffeine and *PHARM* in a South Asian city, Malé, the capital of the Republic of Maldives. Lifestyle habits were assessed by applying WBE in all the sites where wastewater was collected, nine pumping station all over the city. Consumption estimates could be ascribed to either local population or tourists, as WBE cannot distinguish these sources. However, there is evidence that results refer more to the local population, as tourists in Malé are generally in transit, waiting to be transferred to resorts on other islands and rarely spend a night in the city hotels. The overall results were in accordance with findings of surveys by the United Nations Office on Drugs and Crime (UNODC, 2013) for *IDs*, and provided almost unknown information about the use of other substances such as *CAT*, alcohol, tobacco and *PHARM*. The results could be of interest to the UNODC itself, the National Drug Agency (NDA), and the Ministry of Health of the Maldives for better knowledge of the consumption of stimulant substances, and/or to help plan and evaluate the effectiveness of drug use prevention programs in Malé, or of other health campaigns.

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Contributions

Sara Castiglioni, Ettore Zuccato, Maria Cristina Messa, Paolo Galli and Luca Fallati planned and designed the study. Luca Fallati, Sara Castiglioni, Ettore Zuccato and Mohamed Shifah performed sampling and drafted the manuscript. Sara Castiglioni, Francesco Riva, Emma Gracia-Lor, Iria González-Mariño, Nikolaos I. Rousis and Marina Vai developed analytical methods and performed analyses. Ettore Zuccato, Sara Castiglioni and Maria Grazia Strepparava interpreted results. All co-

authors critically revised the manuscript, are aware of the content, and accept responsibility for the manuscript.

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534

535 **Table 1.** *IDs* (mg/day with standard deviations -SD) in the different sites, as the mean of the "day"

536 and "night" samples and as the overall mean of the nine sites (PSs).

537

Illicit Drugs (*IDs*)	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Overall mean ± SD
Cocaine	4.2	2.9	2.5	16.9	17.3	8.4	10.8	10.4	2.3	**8.4 ± 5.9**
Heroin	1281	1510	2197	6478	1291	1040	855	2036	1710	**2044 ± 1719**
Amphetamine	30.1	50.1	43.0	60.1	40.1	43.0	30.1	50.1	40.1	**43 ± 9.7**
Methamphetamine	2.2	116	36.1	41.5	30.7	47.3	32.3	62.7	95.2	**51.5 ± 34.9**
MDMA (ecstasy)	105	242	182	43.1	15.2	37.9	4.3	284	268	**131.3 ± 113.8**
THC (cannabis)	39366	88995	105324	82710	114029	78334	53840	73355	61015	**77441 ± 23904**

Table 2. Summary of *IDs* consumption in Malé expressed as g/day of pure substance, doses/day and mg/day/1000 inhabitants (population 153,940).

Illicit Drugs (*IDs*)	Total consumption g/day (pure substance)	Total consumption doses/day	Total consumption mg/day/1000/inhabitants
Cocaine	0.1	0.8	0.5
Heroin	18.4	613	120
Amphetamine	0.4	13	2.5
Methamphetamine	0.5	15	3.0
MDMA (ecstasy)	1.2	12	7.7
THC (cannabis)	697	5576	4528

Table 3. *CAT* mass loads measured in the nine sites (PSs), expressed as mg/day and the total loads in Malé.

Sunthetic cathinones (*CAT*)	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Total loads
Methcatinone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Ethcathinone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Methedrone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
N,N-dimethylcathinone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
4-fluoromethcathinone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
3,4-dimethylmethcathinone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
4-methylethcathinone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Buphedrone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Pentedrone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Methylone	**12.5**	nd	nd	nd	nd	nd	nd	nd	nd	**12.5**
Ethylone	**9.7**	**15.4**	nd	nd	nd	**6.5**	**2.6**	**9.0**	nd	**44.6**
Butylone	nd	nd	nd	nd	nd	**8.5**	nd	nd	nd	**8.5**
Pentylone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
1-Naphyrone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Naphyrone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Methylenedioxypyrovalerone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Mephedrone	nd	nd	**11.7**	**3.7**	nd	**2.5**	**10.9**	**147.5**	**213.2**	**389.5**

Table 4. Alcohol consumption in the nine sites (PSs) and total consumption in Malé.

Alcohol	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Total Malé
g /day	11576	18266	16297	18461	13795	14065	8786	17476	20080	138802
L / day	14.7	23.1	20.7	23.4	17.5	17.8	11.1	22.1	25.5	176

Table 5. Loads of nicotine, caffeine and their metabolites in wastewater from the nine sites (PSs) and total loads in Malé, expressed as g/day. Estimated use of nicotine and caffeine (g/day).

Nicotine and caffeine	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9	Total Malé
Nicotine	16.5	53.2	40.9	44.5	31.0	39.1	29.1	40.7	36.5	331.5
Cotinine	4.8	15.8	14.4	14.6	16.1	11.5	12.7	12.6	12.9	115.3
Trans-3'-hydroxycotinine	7.4	24.7	21.7	23.4	23.2	19.7	18.2	19.4	18.9	176.6
Caffeine	47.0	132.1	113.7	179.6	107.2	141.5	84.0	221.5	161.2	1187.9
Paraxanthine	61.7	194.7	188.5	225.7	162.9	169.6	140.9	218.5	149.9	1512.4
1-methylxanthine	49.9	153.8	167.9	168.0	163.1	147.9	125.0	182.9	132.3	1290.6
7-methylxanthine	65.9	183.6	181.3	198.3	174.3	190.3	141.7	205.1	162.9	1503.5
1-methyluric acid	8.9	41.6	40.4	41.2	33.0	40.8	28.3	43.6	23.6	301.5
1,7-dimethyluric acid	39.1	73.1	62.4	95.0	101.9	60.6	54.8	64.4	76.9	628.3
Nicotine Use *	16.4	54.7	48.6	51.3	53.1	42.1	41.7	43.1	42.9	394.1
Caffeine Use§	579	1082	923	1406	1509	897	812	953	1139	9299

*Estimated following the procedure described in Castiglioni et al., 2015; § Estimated following the procedure described in Gracia-Lor et al., 2017.

Table 6. Comparison of *PHARM* mass loads (mg/day/1000 inh) in Malè and Milan.

PHARM Loads (mg/day/1000 inh)			
	Milan	Malè	Ratio Malè/Milan
Atenolol	596	58	**0.10**
Atorvastatin	42	26	**0.62**
Carbamazepine	111	38	**0.35**
Ciprofloxacin	353	36	**0.10**
Clarithromycin	423	47	**0.11**
Dehydro-erythromycin	134	33	**0.24**
Diclofenac	298	301	**1.01**
Enalapril	26	1	**0.04**
Furosemide	168	19	**0.11**
Gemfibrozil	67	130	**1.94**
Ibuprofen	775	110	**0.14**
Hydrochlorothiazide	260	13	**0.05**
Ketoprofen	445	37	**0.08**
Naproxen	440	115	**0.26**
Ofloxacin	277	20	**0.07**
Paracetamol	1105	1055	**0.95**
Ranitidine	58	819	**14.10**
Salbutamol	2.4	17	**7.04**

Figure 1. a. Map of the city of Malé with sewage and pumping stations (PSs); b. Sigma 900 portable sampler; c. Pumping station P2 with sampler in operation.

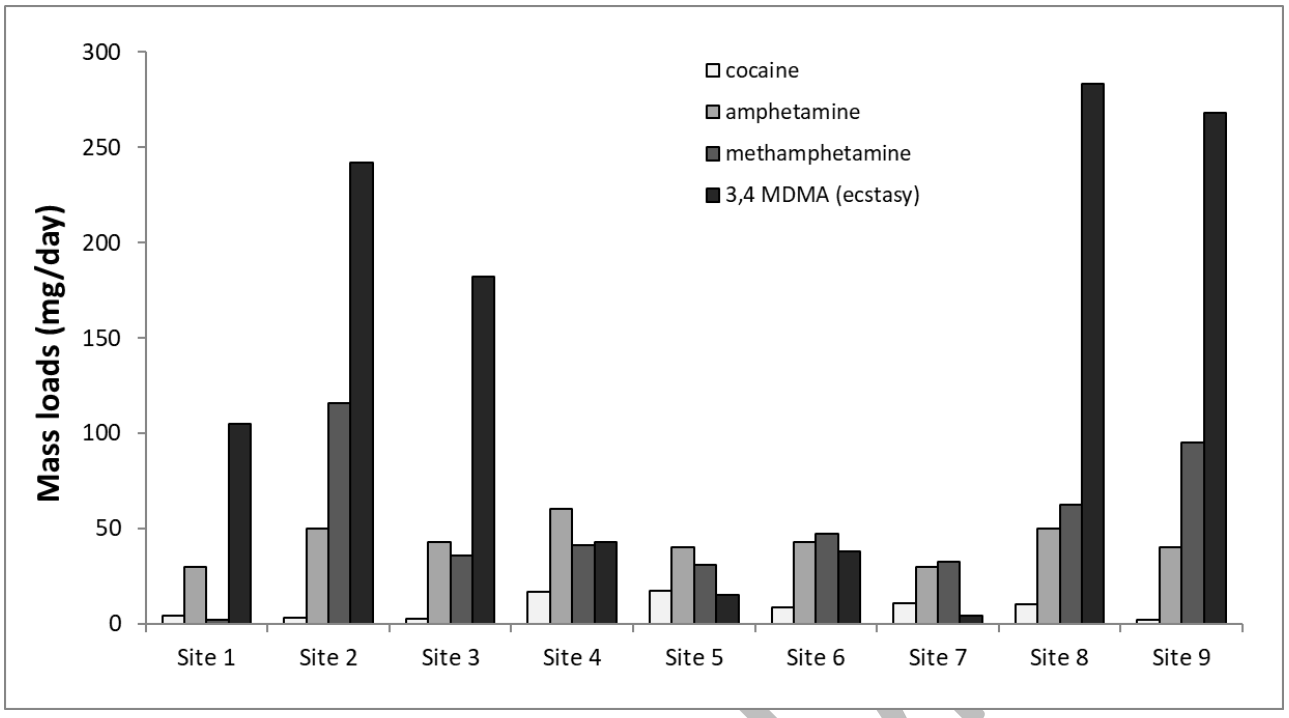

Figure 2. Daily mass loads of the psychostimulant drugs, cocaine, amphetamine, methamphetamine and ecstasy, in the nine sites (PSs).

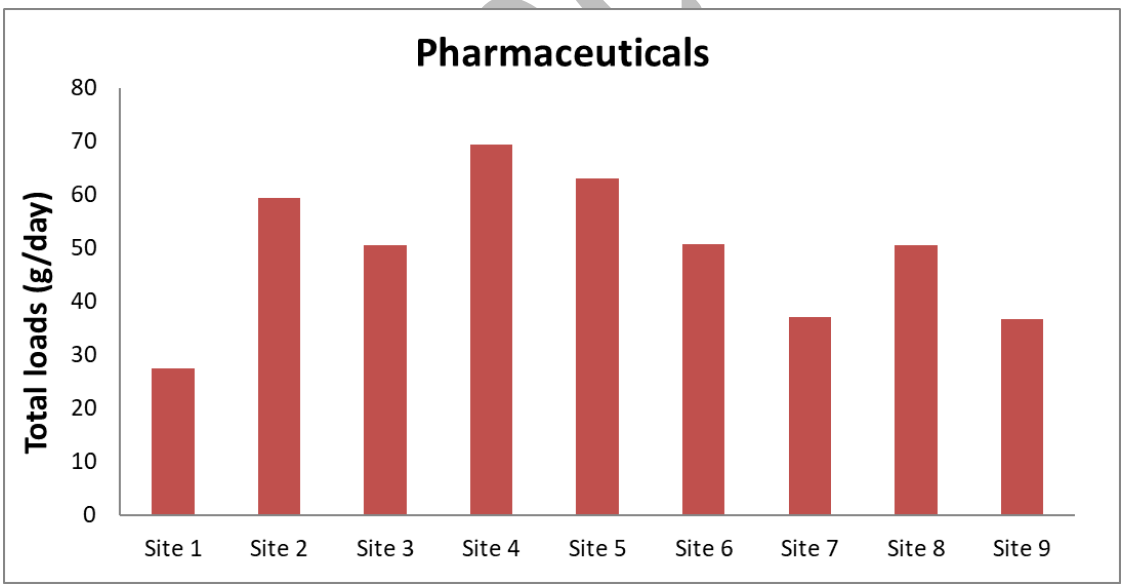

Figure 3. Total mass loads (g/day) of *PHARM* in the nine sites (PSs).