

Estimation of legal and illegal drugs consumption in Valencia City (Spain): 10 years of monitoring

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ABSTRACT

Wastewater-based epidemiology (WBE) approach provides objective, quantitative, near real-time profiles of illicit drug consumption by monitoring the concentration of unchanged parent drugs or their metabolites entering the municipal sewage system. Valencia is the third most populous city in Spain (an important country for the use and transit of several of these drugs). Estimations of consumption over long periods of time will help get better understanding of spatial and temporal trends in the use of licit and illicit drugs. Accordingly, applying the “best practice” protocol, 16 drugs of abuse and metabolites were monitored in this study, and 8 were daily measured during one-two weeks between 2011 and 2020 at the inlet of three wastewater treatment plants of Valencia City. Analysis of the selected compounds was performed by liquid chromatography-triple quadrupole mass spectrometry, and the concentrations obtained were used to back-calculate the consumption data. Cannabis, tobacco, and cocaine were the most consumed drugs whereas opioids were less used. Cannabis and cocaine consumption are on average 2.7–23.4 and 1.1–2.3 g/day/1000inh, respectively, and their use tended to increase since 2018. Weekly profiles were characterized by higher consumption of cocaine, ecstasy, and heroin during weekends compared to weekdays. Similarly, during “Las Fallas” (main local festivity), increased use of cocaine and amphetamine-type stimulants, mainly MDMA, was measured. WBE proved to be an objective and useful methodology to get more insight on temporal drugs of abuse consumption, and the changes derived from local festivities.

1. Introduction

Wastewater-based epidemiology (WBE) provides objective, quantitative, near real-time profiles of illicit and licit drug local consumption by monitoring the concentration of unchanged parent drugs or their metabolites entering the municipal sewage system (Bijlsma et al., 2021; González-Mariño et al., 2020; Lorenzo and Picó 2019; Mercan et al., 2019; Vitale et al., 2021). These concentrations in the influent of wastewater treatment plants (WWTPs) are used to back-calculate the mass loads of the parent drugs and/or metabolites and finally, to estimate the consumption (g/day or doses/day) according to the drug metabolism and excretion patterns. Additionally, with the population served by the WWTP and the standard dose in which drugs are consumed, the results can be normalized to g/day/1000 inhabitants or

doses/day/1000 inhabitants, and then used to make comparisons among locations (González-Mariño et al., 2020; Mercan et al., 2019).

Estimation of WBE has become complementary to general population surveys on drug of abuse consumption, sales data, medical records, drug seizures, etc. (Bijlsma et al., 2021; EMCDDA 2021; Ort et al., 2014). It is considered a suitable alternative to estimate objectively licit and illicit drugs consumption avoiding problems, such as the lack of objectivity of the information collected from population surveys (not all consumers would report it), the late response time of these surveys (long implementation periods), and their significantly higher cost as well as their uneven spatial resolution not granting realistic drugs use estimation at regional scales (the different socioeconomic and cultural factors defining consumers' habits and trends are not well represented) (Castiglioni et al., 2013; Mastroianni et al., 2017; van Nuijs et al. 2011a).

Abbreviations: AMP, Amphetamine; BECG, Benzoylcegonine; BUF, Bufotenine; COC, Cocaine; COCET, Cocaethylene; COD, Codeine; COTI, Cotinine; ECME, Ecgonine methyl ester; EDDP, 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; ETA, Etamine; KET, Ketamine; MAMP, Methamphetamine; MDMA, 3,4-Methylenedioxymethamphetamine or ecstasy; METH, Methadone; MOR, Morphine; THC-COOH, 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol.

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Currently, WBE is used by an increasing number of researchers to calculate the intake of a large variety of illicit drugs in cities from a number of European countries as in Belgium (van Nuijs et al. 2011b), France (Nefau et al., 2013), Spain (Andrés-Costa et al., 2014; Bijlsma et al., 2021; Estévez-Danta et al., 2022; Mastroianni et al., 2017), Germany and Switzerland (Been et al., 2016), Italy (Zuccato et al., 2016), Finland (Kankaanpää et al., 2016), Lithuania (Boogaerts et al., 2021), or Slovakia (Mackufak et al., 2014), as well as in other countries all over the world as in China (Du et al., 2015; Zhang et al., 2019; Zheng et al., 2021), South Korea (Kim et al., 2015), South Africa (Archer et al., 2018), Australia (Lai et al., 2016), Colombia (Bijlsma et al., 2016), Costa Rica (Causanilles et al., 2017b), Brazil (da Silva et al. 2018), or the United States (Bishop et al., 2020; Skees et al., 2018). Special mention to the studies compiling results of several cities to present estimates at higher scales as those made for Spain (13 cities (Bijlsma et al., 2021)), Europe (12 cities, (Thomas et al., 2012; van Nuijs et al. 2011a)) and even at global level (120 cities in 37 countries (González-Mariño et al., 2020)). Furthermore, WBE is also very helpful to identify changes during special events (i.e., festivals, sporting events, or holiday periods), to monitor variations in drugs use through time, and to recognize new habits or the emergence of new illicit drugs as the new psychoactive substances (Andrés-Costa et al., 2017; Bijlsma et al., 2021; González-Mariño et al., 2018).

Because of its increasing use, WBE is a methodology in continuous improvement (Causanilles et al., 2017a; Choi et al., 2018; Mercan et al., 2019; Vitale et al., 2021). The analytical procedures for the determination of the compounds, usually performed by solid-phase extraction (Fontanals et al., 2019) followed by high specific and sensitive determination techniques such as liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), have reached great robustness and excellent sensitivity and selectivity by using triple quadrupole (QqQ) or quadrupole linear ion-trap (QTRAP) analysers (Bijlsma et al., 2012; González-Mariño et al., 2018; Mastroianni et al., 2017). Moreover, less used high-resolution mass spectrometry (with time-of-flight or Orbitrap analysers) has proved outstanding performance for qualitative and quantitative analysis of illicit drugs and their metabolites (Andrés-Costa et al., 2017; Bijlsma et al., 2012; González-Mariño et al., 2012).

Great progress has also been achieved in the back-calculations that transform measured concentrations in wastewater into an amount of used illicit drugs, particularly in relation to the homogenization of correction factors (CFs) derived from the excretion (and in-sewer) degradation of each drug, and the dose used (Castiglioni et al., 2013; Du et al., 2015; Gracia-Lor et al., 2016; Postigo et al., 2011; Thai et al., 2016). Other factors creating uncertainty in the results of drug consumption have also been investigated and homogenized (i.e. sampling strategies, assessment of population size) to propose some “best practice” requirements for each of the steps in estimating community drug use in order to improve the reliability of such estimates (Castiglioni et al., 2013; Rico et al., 2017; SCORE 2020). Consequently, WBE has been endorsed since 2008 by the European Monitoring center for Drugs and Drug Addiction (EMCDDA), and since 2016 by the United Nations Office on Drugs and Crime (UNODC), both including the WBE results provided by the Sewage Analysis Core Group Europe network (SCORE) (SCORE 2020) in their annual drug reports (Bijlsma et al., 2021).

In Spain, national SCORE members have created the ESAR-net network (ESAR-net 2020) to support the WBE results and communicate them to authorities and policymakers. According to the reports of the EMCDDA, Spain is an important country of transit of several illicit drugs, such as cannabis and cocaine, due to its cultural, linguistic and colonial ties to Latin America and its proximity to Morocco (Bijlsma et al., 2021), and the quantity of seized ones, and the prevalence of their use rank Spain at the top of Europe (EMCDDA 2021). Valencia is the third most populous city in Spain with 1.2 million inhabitants (including its metropolitan area (Sadutto et al., 2021)), behind Madrid and Barcelona, and estimations of drug consumption over long periods of time will help get better understanding of spatial and temporal differences

and trends in use of illicit drugs. By means of the WBE approach, this study aims to: (i) estimate the consumption of 16 licit and illicit drugs in Valencia (Spain) during 10 consecutive years, although only 8 were actually determined annually; (ii) compare Valencia's WBE consumption estimates with those of other cities; (iii) establish temporal (weekly) patterns of drug use in the city between 2011 and 2020, and; (iv) assess the impact of the main local festivity (“Las Fallas”) in the estimated drugs' average consumption tendencies. To do this, 16 compounds including several licit and illicit drugs (cocaine, cannabis, tobacco, opiates and amphetamine-type stimulants) and their metabolites were daily monitored during one-two weeks between 2011 and 2020 at the inlet of three WWTPs treating the wastewater of Valencia City (Spain) and its surrounding towns.

2. Material and methods

2.1. Reagents and materials

High purity (>99%) standard solutions of cocaine compounds as benzoylecgonine (BECG), cocaine (COC), cocaethylene (COCET), ecgonine methyl ester (ECME), amphetamine-type stimulants as amphetamine (AMP), ketamine (KET), methamphetamine (MAMP), 3,4-methylenedioxymethamphetamine or ecstasy (MDMA), opioids as codeine (COD), morphine (MOR), methadone (METH) and 2-ethylidene-1,5-dimethyl-3, 3-diphenylpyrrolidine (EDDP) (metabolite of METH), and alkaloids as bufotenine (BUF), cotinine (COTI) (metabolite of nicotine) at 1000 mg/L and the cannabinoid 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THC—COOH) at 100 mg/L in methanol were obtained from Cerilliant (Austin, TX, USA) and LGC GMBH (Luckenwalde, Germany). Working standard solutions of the analytes were prepared at different concentrations by appropriate dilution of the individual stock solutions in methanol-water (1:9, v/v). The deuterated drug analogues AMP-d5, BECG-d3, COC-d3, KET-d4, MAMP-d5, MDMA-d5, MOR-d5, and THC—COOH-d3 used as internal standards (ISs) were also obtained from Cerilliant and LGC GMBH at a concentration of 100 mg/L in methanol. A working mix of ISs at 1 mg/L was prepared in methanol. Calibration standards were prepared by serial dilution of the mixed working solution ranging from 10 ng/mL to 500 ng/mL with addition of the ISs mix at a final concentration of 100 ng/mL. Stock and working solutions were stored at -20°C in the dark.

Water used for preparation of calibration standards and UHPLC-MS/MS mobile phase was purified by an Elix Milli-Q system (Millipore, Billerica, MA, USA). Methanol was purchased from VWR International (Barcelona, Spain) and formic acid was from Sigma-Aldrich (St. Louis, MO, EEUU). The cartridges used to extract analytes from samples were Strata-X 33 μm Polymeric Reversed Phase (200 mg/6 mL) from Phenomenex (Torrance, CA, USA).

2.2. Sampling

Samples were collected from the influent of three different WWTPs in Valencia (Pinedo 1, Pinedo 2 and Quart-Benager), receiving wastewater from Valencia and other small surrounding towns. The catchment area of Pinedo 1 (P1) and Pinedo 2 (P2) consists of about 351,000 and 943,000 inhabitants, respectively, while the catchment area of Quart-Benager (QB) consists of 215,000 inhabitants. The main characteristics of each WWTP are summarized in Table S1 (Supplementary Information). Sampling campaigns were carried out during 10 years thus: 2011 (March 10th to 16th), 2012 (April 17th to May 1st), 2013 (March 6th to 12th), 2014 (March 4th to 20th), 2015 (March 3th to 9th), 2016 (March 2th to 9th), 2017 (May 2nd to 8th), 2018 (April 10th to 16th), 2019 (March 5th to 11th), and 2020 (February 25th to March 2nd). It is important to highlight here that during 2014, samples were also gathered during “Las Fallas” (main local festivity), which is from March 15th to March 19th.

Samples (24 h composite) were collected using the operational equipment of the WWTPs in a time-proportional manner at 60 min time

intervals, which was fixed by the WWTPs and generally accepted because its uncertainty is lower than 5% (Castiglioni et al., 2013; McCall et al., 2016). Composite samples instead of grab samples were selected in this study to get the maximum representativeness according to the “best practice” protocol recommended for wastewater studies (Castiglioni et al., 2013; Rico et al., 2017; Vitale et al., 2021). All samples were stored in polyethylene terephthalate bottles. Once the samples arrived at the laboratory, they were immediately frozen at -20°C until analysis to prevent degradation of the compounds to be analysed.

2.3. Sample preparation

ISs were added to the samples (250 mL), which were then vacuum filtered using $0.60\ \mu\text{m}$ glass fiber filter (GA-55, 90 mm - purchased from ADVANTEC MFS, Dublin, USA) before solid-phase extraction procedure. For the latter, cartridges were previously conditioned with 6 mL methanol and 6 mL of Elix Milli-Q water. Illicit drugs were extracted using Polymeric Reversed Phase cartridges and a 12-port vacuum manifold Supelco Visiprep 57,030-U of Sigma-Aldrich (St. Louis, MO, EEUU). Samples without pH adjustment were passed through the cartridges under vacuum, at a flow rate of 10 mL/min. After that, the cartridges were washed with 6 mL of Elix Milli-Q water and dried under vacuum for 15 min. Analytes were eluted with 6 mL of methanol, evaporated to dryness, at 40°C using a combined sample concentrator model SBHCONC/1 and a heating plate model SBH130D/3 by Stuart® (Staford, UK), dissolved in 1 mL of water-methanol (90:10 v/v), and then, stored in 2-mL amber glass vials ready for analysis.

2.4. UHPLC-QqQ-MS/MS

Chromatographic separation was performed using an Agilent 1260 UHPLC (Agilent, Waldbronn, Germany). The separation was carried out with a Phenomenex Kinetex C18 ($1.7\ \mu\text{m}$, 100 Å, $50\times 2.10\ \text{mm}$) at temperature of 25°C and constant flow rate of 0.2 mL/min. The mobile phase was eluent A (formic acid 0.1% in water) and eluent B (formic acid 0.1% in methanol). The gradient elution was started at 10% B maintained for 5 min, then increased linearly to 95% B in 12 min and remained constant at 95% B up to 25 min, then it returns to the initial conditions with an equilibrium time of 15 min. The injection volume was 5 mL. The injection was long to use a flow compatible with MS detection. The UHPLC was coupled to an Agilent 6410 triple quadrupole mass spectrometer with an electrospray ionization source mode, 300°C gas temperature, 11 L/min gas flow and 25 psi nebulizer. The optimal quantification and confirmation transitions as well as the specific MS parameters were optimized for each compound (Table S2).

2.5. Quality control

Limits of quantification (LOQs), recovery, precision, and matrix effects are outlined in Table S3. The linearity was also evaluated by injecting in triplicate 5 concentration levels from 10 to 500 ng/L using IS calibration to avoid errors due to matrix effect. The combination of such matrix effect and extraction efficiency was estimated from the ISs, which were spiked at the same concentration into all samples. The lowest concentration used in the calibration curve is close to the LOQs (from 1.1 to 7.8 ng/L). For practical reasons to the common laboratory routine, it was much easier to select a value slightly over the LOQs. Calibration curves were linear with correlation coefficient $R^2 > 0.99$ for all compounds.

Extraction recoveries were evaluated in quintuplicated by spiking aliquots of deionized water with the analytes at the LOQ and at 500 ng/L of each analyte, and of influent wastewater at 100 and 500 ng/L. In the latter, as all analytes were in the sample, five aliquots of a sample with low concentrations were spiked at each concentration and other five aliquots of this sample were measured without analytes spike. Then, the spiked samples, after non-spiked sample signal subtraction, were

compared to the calibration curve. Recoveries were 65–126% in deionized water and 78–122% in influent wastewater. The repeatability and reproducibility between days of five samples spiked at 100 and 500 ng/L in both types of matrix, expressed as relative standard deviation (% RSD), were lower than 26% and 20%, respectively (Table S3).

2.6. Estimation of collective drug use

Drugs loads to WWTPs (Eq. (1)) and consumptions (Eq. (2)) were back-calculated from the measured daily concentration of the drug target according to the following equations (Andrés-Costa et al., 2014; Mastroianni et al., 2017):

$$L[\text{mg/day}] = C[\text{ng/L}] \cdot FR[\text{L/day}] \cdot 10^{-6} [\text{mg/ng}] \quad (1)$$

$$Q[\text{mg/day}/1000\text{inh}] = L[\text{mg/day}] \cdot CF \cdot 1000 / \text{Ninh} \quad (2)$$

Where L is the drug's load to the WWTP, C is its concentration, FR is the daily flow rate of each WWTP, Q is the drug's consumption, CF is the correction factor that takes into account the molar mass ratio between the parent drug and the drug residue as well as the percentage of metabolic excretion (for detailed values see (Castiglioni et al., 2013; Du et al., 2015; Gracia-Lor et al., 2016; Postigo et al., 2011; Thai et al., 2016) and Table S4), and Ninh is the number of inhabitants served by the WWTP estimated by means of the biological oxygen demand (BOD) of each sampled day (van Nuijs et al. 2011b).

Finally, it is important to mention that in order to minimize the uncertainty related to WBE estimates, we have adopted and strictly followed in this study the “best practice” requirements for each of the steps proposed (Castiglioni et al., 2013; SCORE 2020).

2.7. Statistical analysis

Normality of the data was tested using Shapiro-Wilk's test ($n < 50$) and homogeneity of variances by means of Levene's test. For the parametric analysis, differences in drug's concentrations and consumptions between years, days and WWTPs were established through one-way ANOVA. For non-parametric analysis, differences were determined by the tests of Mann-Whitney U (M-W) or Kruskal-Wallis (K-W). In all the cases, results were considered to be statistically significant at $p < 0.05$. All statistical analyses were carried out using IBM SPSS Statistics 27®.

3. Results

3.1. Occurrence of drugs in samples of Valencia wastewaters

The frequency, mean, minimum and maximum concentrations of the licit and illicit drugs and/or metabolites screened in this study are summarized in Tables S5 and S6. The former presents the results of the compounds analysed yearly from 2011 to 2020 (AMP, BECG, COC, KET, MAMP, MDMA, MOR, THC-COOH), whereas the latter shows the results of the other analytes (BUF, COCET, COD, COTI, ECME, EDDP, ETA, METH), which were analysed in different years (mainly 2014–2017). In general, all the screened compounds were present in all the samples analysed with frequencies higher than 80%. Only KET (<40%) and COCET (42%) showed lower occurrences.

Mean concentration values (in ng/L) measured each year were high for the metabolites of cocaine BECG (1127.9–3132.0) and of nicotine COTI (1105.8–3012.4). These are followed by COC (192.1–1238.2), COD (185.4–1202.0), the cannabinoid THC-COOH (63.6–593.2), and other cocaine metabolites as ECME (35.5–528.6) and COCET (11.7–112.4). Opioids showed low concentrations as MOR (25.5–201.1), EDDP (91.3–92.4) and METH (13.0–48.8), which were on the same range than amphetamine-type stimulants AMP (28.9–77.1), MDMA (13.1–84.5), KET (7.1–37.2), and MAMP (3.5–48.1), similarly to other drugs as BUF (11.5–56.6) and ETA (6.4–19.5) (Fig. S1).

According to these concentrations, there are some significant differences in their patterns between the three WWTPs considered for Valencia City and its surrounding towns. Averaging the whole study period, the concentration of THC—COOH and COTI were similar among WWTPs ($p>0.05$) although the former tended to be higher in P1 and the latter in QB. On the other hand, the concentrations of COC and all its metabolites (BECG, COCET and ECME) were significantly different ($p<0.05$) being higher in QB than in P1 and P2 ($QB>P1=P2$). In relation to amphetamine-type stimulants, significant differences ($p<0.05$) were found on the concentrations of AMP, MDMA ($P1>P2=QB$) and MAMP ($P1=P2>QB$) whereas those of KET tended to be higher in P1 and QB than in P2 ($p>0.05$). For the opioids, MOR concentrations tended to be higher in QB ($p>0.05$), EDDP levels followed the trend $P1=P2>QB$ ($p<0.05$), METH tended to be higher in P1 and P2 than in QB, and COD tended to be higher in P2 and QB than in P1 ($p>0.05$).

Based on the flows of each WWTP and the analytes concentrations found in them, loads (in g/day) of these substances arriving to Valencia's WWTPs were calculated (Tables S7 and S8). Mean values were BECG (121.5–288.4), COC (20.8–169.5), ECME (3.9–69.4) and COCET (1.1–10.7) followed by THC—COOH (6.9–65.9), and amphetamine type stimulants: MOR (2.8–21.3), AMP (3.6–9.7), MDMA (2.1–9.6), MAMP (0.4–7.5) and KET (0.9–3.7). Other compounds considered also showed high loads as COTI (117.5–333.3) and COD (23.3–132.2). The opioids EDDP (9.8–11.3) and METH (0.5–7.5), as well as BUF (1.5–8.3) and ETA (0.8–2.1) were in similar ranges, but it should be kept in mind that these analytes were measured during shorter periods. In general, the highest loads were observed in P2, followed by those of P1 and QB, which are directly related to their flows.

3.2. Estimation of drugs consumption in Valencia City

According to the results obtained (Tables 1 and 2), mean consumption of licit and illicit drugs (in mg/day/1000inh) in Valencia was high for cannabis (2748.9–23351.0) and tobacco (as nicotine 1893.3–5486.0), followed by cocaine (calculated through BECG (1126.4–2258.3), COC (553.6–4097.6), COCET (459.5–4649.1), or ECME (37.3–465.9)), then codeine (180.5–1046.3), buprenorphine (93.8–343.0), and amphetamine-type stimulants as MDMA (15.4–102.5), AMP (23.1–66.8), and MAMP (3.7–50.6). Heroin calculated by means of morphine (21.1–164.3) showed low consumption followed by ketamine (7.9–48.9), methadone as EDDP (21.0–37.9) or METH (13.8–41.7), and finally, etamine (4.1–15.8).

Despite the fact that consumption calculations are directly related to the WWTPs flows ($P2>P1>QB$), some trends can also be observed when they are compared. Averaging the whole study period, the consumption of cannabis was significantly different between WWTPs ($p<0.05$) with $P1=P2>QB$. Tobacco use tended to be higher in P2 than in QB and P1 ($p>0.05$). On the other hand, cocaine use tended to be higher in QB when calculated with BECG or COCET ($p>0.05$), in P1 and P2 when with COC ($p>0.05$), and in P1 and QB when using ECME ($p<0.05$). Amphetamine-type stimulants consumption showed significant differences among WWTPs ($p<0.05$), with amphetamine ($P1>P2>QB$), methamphetamine, ecstasy and ketamine ($P1>P2=QB$). In relation to opioids, heroin and codeine consumption tended to be higher in P1 and P2 than in QB ($p>0.05$), whereas methadone presented significant differences ($p<0.05$) when calculated with both EDDP and METH ($P1>P2=QB$).

Table 1

Consumption of licit and illicit drugs in Valencia City and surrounding towns (mean, range: minimum - maximum in mg/day/1000inh).

Year		AMP ¹	COCAINE		KET	MAMP	MDMA	HEROIN MOR ⁴	CANNABIS THC—COOH ⁵
			BECG ²	COC ³					
2011	Frequency	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$
	Mean	42.7 ^a	1868.2 ^{abc}	1031.0 ^{ab}	25.4 ^{bc}	50.6 ^c	16.95 ^a	83.1 ^b	2919.3 ^a
	Range	23.8–79.8	969.9–4405.7	454.3–2582.0	7.6–53.2	35.7–90.7	5.7–49.6	31.6–188.6	598.7–8980.3
2012	Frequency	$n = 45/45$	$n = 45/45$	$n = 45/45$	$n = 45/45$	$n = 45/45$	$n = 45/45$	$n = 45/45$	$n = 45/45$
	Mean	29.7 ^a	2014.8 ^{bc}	636.6 ^a	9.4 ^a	36.5 ^b	15.4 ^a	32.9 ^a	2748.9 ^a
	Range	0.8–58.9	963.1–4115.0	29.8–1757.0	0.3–32.6	1.1–68.6	0.4–41.9	1.0–91.8	730.9–7155.5
2013	Frequency	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	–	$n = 21/21$
	Mean	23.1 ^a	1666.0 ^{abc}	4097.6 ^d	15.7 ^{abc}	3.9 ^a	34.4 ^{ab}	–	13,743.3 ^{cd}
	Range	0.6–97.0	51.8–8476.5	92.7–13,804.7	0.6–62.0	0.2–10.2	0.4–211.9	–	582.3–52,115.8
2014	Frequency	$n = 49/51$	$n = 49/51$	$n = 49/51$	$n = 44/51$	$n = 40/51$	$n = 46/51$	$n = 49/51$	$n = 27/51$
	Mean	39.4 ^a	1489.2 ^{abc}	1918.4 ^{abc}	25.6 ^{bc}	7.6 ^a	57.6 ^{ab}	74.1 ^b	11,011.5 ^{bc}
	Range	5.3–118.0	294.4–3811.9	646.9–4738.4	4.7–55.4	2.0–22.6	3.8–347.7	24.1–179.3	1034.9–49,163.1
2015	Frequency	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 8/21$	$n = 10/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$
	Mean	38.7 ^a	1185.5 ^{ab}	1620.16 ^{abc}	7.9 ^a	4.9 ^a	41.6 ^{ab}	85.3 ^b	6234.0 ^{abc}
	Range	13.7–82.5	538.5–2451.3	597.7–3646.6	5.6–11.4	1.7–10.7	7.8–136.2	33.3–155.8	3749.8–11,166.3
2016	Frequency	$n = 24/24$	$n = 24/24$	$n = 24/24$	$n = 24/24$	$n = 21/24$	$n = 24/24$	$n = 24/24$	$n = 21/24$
	Mean	23.2 ^a	1126.4 ^a	1076.1 ^{ab}	13.7 ^{ab}	5.0 ^a	30.9 ^{ab}	21.1 ^a	7184.5 ^{abc}
	Range	5.9–71.5	136.2–2812.9	385.6–2860.1	4.7–31.2	1.1–13.4	10.4–89.7	5.2–38.2	3325.1–14,780.4
2017	Frequency	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 7/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$
	Mean	66.8 ^b	1829.0 ^{abc}	2547.5 ^c	16.2 ^{abc}	29.9 ^b	71.0 ^{bc}	104.2 ^b	13,624.1 ^{cd}
	Range	38.8–107.2	1021.7–4034.5	1414.5–5670.5	10.0–21.7	20.0–47.4	37.6–126.3	48.3–180.9	3691.3–28,555.5
2018	Frequency	$n = 21/21$	$n = 18/21$	$n = 21/21$	$n = 21/21$	$n = 20/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$
	Mean	36.3 ^a	2258.3 ^c	553.6 ^a	18.9 ^{abc}	3.7 ^a	46.7 ^{ab}	78.2 ^b	4857.6 ^{ab}
	Range	15.4–64.7	487.9–4908.2	420.1–787.4	8.3–31.3	1.1–9.8	9.6–111.1	37.4–122.7	2519.4–7241.0
2019	Frequency	$n = 20/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$
	Mean	32.7 ^a	1662.9 ^{abc}	2773.1 ^{cd}	48.9 ^d	29.7 ^b	102.4 ^c	164.3 ^c	21,654.4 ^{de}
	Range	6.1–127.8	535.6–4320.2	837.3–7083.5	12.1–146.0	16.2–42.3	16.7–352.2	57.0–446.6	6636.6–62,107.8
2020	Frequency	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	$n = 21/21$	–	$n = 21/21$
	Mean	32.1 ^a	1456.4 ^{abc}	2181.3 ^{bc}	31.2 ^c	7.8 ^a	17.3 ^a	–	23,351.0 ^e
	Range	21.8–51.6	795.9–2516.7	1375.4–3291.2	4.8–54.4	3.9–10.2	5.9–36.1	–	6439.0–60,441.1

¹ AMP: amphetamine, BECG: benzoylecgonine, COC: cocaine, KET: ketamine, MAMP: methamphetamine, MDMA: 3,4-methylenedioxyamphetamine, MOR: morphine, THC—COOH: 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol.

² Consumption of cocaine estimated from the BECG concentration in wastewater.

³ Consumption of cocaine estimated from the COC concentration in wastewater.

⁴ Consumption of heroin estimated from the MOR concentration in wastewater.

⁵ Consumption of cannabis estimated from the THC—COOH concentration in wastewater.

*Different letters indicate significant differences ($p<0.05$) between years for each compound.

Table 2

Consumption of licit and illicit drugs in Valencia City and surrounding towns (mean, range: minimum - maximum in mg/day/1000inh).

Year		BUFOTENINE	COCAINE		CODEINE	NICOTINE	METHADONE		ETAMINE
			COCET ²	ECME ³			EDDP ⁵	METH ⁶	
2011	Frequency			n = 21/21				n = 21/21	
	Mean			445.6 ^{bc}				31.5 ^b	
	Range			248.9–836.9				8.3–66.0	
2014	Frequency	n = 49/51	n = 49/51	n = 49/51	n = 49/51		n = 48/51	n = 49/51	n = 45/51
	Mean	343.0 ^b	1038.6 ^a	344.2 ^b	358.0 ^b		21.0 ^a	41.7 ^b	7.4 ^b
	Range	22.5–1516.6	219.3–2976.3	62.4–762.9	109.9–908.7		7.3–53.8	14.6–107.6	2.0–22.0
2015	Frequency	n = 21/21	n = 21/21	n = 14/21	n = 21/21		n = 20/21	n = 21/21	n = 21/21
	Mean	239.2 ^{ab}	788.2 ^a	465.9 ^c	852.8 ^c		37.9 ^b	32.7 ^b	4.1 ^a
	Range	98.3–489.2	301.9–1969.7	259.0–879.9	457.9–1339.4		12.8–69.1	18.3–52.7	2.2–7.9
2016	Frequency	n = 24/24	n = 10/24	n = 24/24	n = 24/24			n = 24/24	n = 23/24
	Mean	93.8 ^a	459.5 ^a	37.3 ^a	180.5 ^a			13.82 ^a	5.0 ^{ab}
	Range	26.9–196.3	107.9–957.9	9.4–87.1	50.7–443.3			3.8–38.0	1.4–17.1
2017	Frequency	n = 21/21	n = 21/21	n = 21/21	n = 21/21			n = 21/21	n = 21/21
	Mean	155.1 ^a	4649.1 ^b	103.9 ^a	1046.3 ^d			32.3 ^b	15.8 ^c
	Range	52.1–533.6	2105.8–13,523.3	64.0–212.3	456.2–2095.1			18.6–60.5	7.6–22.2
2018	Frequency					n = 21/21			
	Mean					5486.0 ^b			
	Range					3059.3–9526.2			
2020	Frequency					n = 21/21			
	Mean					1893.3 ^a			
	Range					1370.2–2606.0			

¹BUF: bufotenine, COCAE: cocaethylene, COD: codeine, COTI: cotinine, ECME: ecgonine methyl ester, EDDP: 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, ETA: etamine, METH: methadone.

² Consumption of cocaine estimated from the COCET concentration in wastewater.

³ Consumption of cocaine estimated from the ECME concentration in wastewater.

⁴ Consumption of tobacco estimated from the COTI concentration in wastewater.

⁵ Consumption of methadone estimated from the EDDP concentration in wastewater.

⁶ Consumption of methadone estimated from the METH concentration in wastewater.

*Different letters indicate significant differences ($p < 0.05$) between years for each compound.

3.3. Temporal trends of drugs consumption and influence of local festivities

Mean consumptions of selected illicit drugs were relatively homogeneous throughout the studied period, with significant higher values in different years (Tables 1 and 2). Worth mentioning are the higher values calculated in 2011 and 2012 for MAMP (90.7 and 60.6 mg/day/1000inh, respectively, $p < 0.05$). General tendencies cannot be established for the whole study period, although it can be stated that some increasing trends were observed in the last years, since 2018, with significantly higher consumption values calculated in 2019 for cannabis, particularly in P2 (62107.8 mg/day/1000inh), and for cocaine (7083.5 mg/day/1000inh), heroin (446.6 mg/day/1000inh) and ketamine (146.0 mg/day/1000inh) in QB.

Weekly consumption profiles of the different drugs are presented in Fig. 2 as the addition of the average daily use (mg/day/1000inh) calculated in each WWTP. Three drugs (cocaine, heroin, and ecstasy) showed a weekly trend, with significantly higher consumption values during the weekend compared to the weekdays ($p < 0.05$). While cocaine was more used from Thursday to Sunday, heroin and MDMA were from Friday to Sunday (in Fig. 2 these consumptions correspond to the values presented the day after, as the samples were collected from 8:30 am of the day before to 8:30 am of the day of sampling. This is, the value of Friday corresponds to the consumption of Thursday). As for cocaine consumption, weekend estimates averaged 5912.9 mg/day/1000inh, which is significantly higher ($p < 0.05$) than the value of weekdays 4192.8 mg/day/1000inh. Ecstasy's consumption during weekends was also significantly higher ($p < 0.05$) during the weekend (157.7 mg/day/1000inh) than in week days (104.6 mg/day/1000inh). On the other hand, similar weekly consumptions were assessed for tobacco, amphetamine, methamphetamine, ketamine, codeine and cannabis.

In relation to the consumption of drugs during special events, a local festivity called “Las Fallas” was monitored in 2014. This festivity starts the 15th March and finishes the 19th March of every year. Having this in mind, consumptions calculated between the 16th and the 20th of March

were compared with those of the days before observing a significant increase ($p < 0.05$) in the consumption of cocaine and amphetamine-type stimulants mainly MDMA, amphetamine, and methamphetamine (Fig. 3). The highest consumption growth was detected for the MDMA, which passed from 80.8 to 335.8 mg/day/1000inh. Cocaine consumption was also almost doubled during “Las Fallas” compared to previous days as proved the values calculated using BECG (5972.1 vs 3592.7 mg/day/1000inh), COC (7046.0 vs 4897.8 mg/day/1000inh), and COCET (4519.6 vs 2357.8 mg/day/1000inh). Amphetamine and methamphetamine consumption were also increased from 90.8 mg/day/1000inh (before festivity) to 168.2 mg/day/1000inh (during festivity), and from 13.2 to 29.2 mg/day/1000inh, respectively.

4. Discussion

4.1. Occurrence of drugs in samples of Valencia wastewaters

According to the European Monitoring center for Drugs and Drug Addiction (EMCDDA), around 83 million or 28.9% of adults (aged 15–64) in the EU are estimated to have used illicit drugs at least once in their lifetime. In 2020, about 17.4 million young adults (15–34) used drugs in the last year (16.9%) (EMCDDA 2021). Although these data should be regarded as a minimum estimate due to possible reporting biases, they highlight the relevance of the problem of illicit drug's use in EU not only for the health, but also for the safety and wellbeing of its citizens. Results of this study confirmed the elevated use of licit and illicit drugs in Valencia City and surrounding towns (Tables S5 and S6). Despite the fact that some spatial trends could be found among the levels found in the different WWTPs (P1 showed higher concentrations of THC—COOH, all the amphetamine-like stimulants, EDDP and METH, P2 of COD whereas QB presented higher concentrations of COTI, COC and its metabolites, and MOR) these will be discussed as averages for all the study area.

Cocaine (COC) and the metabolite benzoylecgonine (BECG) were the compounds more frequently detected and at higher concentrations

(reaching the $\mu\text{g/L}$) in the wastewater samples of Valencia city and surrounding towns (Tables S5 and S6). Similar pattern and concentrations were found in different cities of Spain (Bijlsma et al., 2021; Estévez-Danta et al., 2022), confirming previous data of Barcelona (Mastroianni et al., 2017), and different cities of France (Nefau et al., 2013). They were higher than those of Slovakia, Finland and Lithuania (Boogaerts et al., 2021; Kankaanpää et al., 2016; Mackuľak et al., 2014). High frequencies but low concentrations were reported in the USA (Bishop et al., 2020; Skees et al., 2018). Comparable BECG frequencies and concentrations were also found in Colombia (Bijlsma et al., 2016), and of COC in Costa Rica (Andrés-Costa et al., 2017). In other regions as Guangzhou (China), COC was not found in any sample and although BECG was quantified in 85% of samples its concentration was very low (Zhang et al., 2019). Cocaethylene (COCET), another metabolite of cocaine also showed high concentrations (tens-hundreds ng/L), as in Brazil (da Silva et al., 2018), but it was found in less of the half of samples analysed in 2014–2017. The 2021 European Drug Report identified cocaine as the second most prevalent and second most frequently seized illicit stimulant in Europe (EMCDDA 2021), and the 2021 Report of the Spanish Observatory on Drugs and Addictions (OEDA) confirmed cocaine as one of the drugs with the highest use prevalence (2.5%) among the Spanish population (15–64) in 2019–2020 (OEDA 2021).

In general, higher concentrations of BECG than of COC and ECME were measured in the three WWTP considered, which is expected since BECG excretion percentage after cocaine consumption is higher leading to concentrations superior to those of COC (Archer et al., 2018; da Silva et al., 2018; Nefau et al., 2013). BECG is considered more stable (no loss of analyte in sewage) up to 72 h at 4 °C, and up to 12 h at 20 °C (conditions respected in this study), and because COC can partially degrade (hydrolysis) to BECG in blood and urine (Castiglioni et al., 2013). Additionally, COC and ECME are less stable in sewage, and BECG could increase by as much as 20% over 24 h at 4 °C because of their biodegradation (Castiglioni et al., 2013; van Nuijs et al., 2011b). To check for excessive biotransformation of COC to BECG, the COC/BECG ratio has been calculated. Based on their molar mass relation and on the excretion rate limits as unchanged COC and as BECG, cut-off values of 0.75 and 0.27 have been used (Bijlsma et al., 2012). The ratios obtained in this study are between these two values, with some higher values, similarly to other studies (Andrés-Costa et al., 2017; Castiglioni et al., 2013; Mastroianni et al., 2017; Thai et al., 2016), suggesting other likely sources of COC to wastewater related to deliberate or accidental disposal of the drug into the sewer (Andrés-Costa et al., 2014), or to other routes of consumption.

Despite nicotine (metabolite measured COTI) was only analysed in the period 2014–2017, their high concentrations (in the range of $\mu\text{g/L}$) agree with the trends reported in a recent publication (Estévez-Danta et al., 2022), according to which the recreational drugs with the highest use prevalence among the Spanish population (15–64) are alcohol (63%) and tobacco (32%) (OEDA 2021). In this study, besides cocaine, cannabis was among the illicit drugs most frequently detected in wastewater samples. Based on data from 26 countries that undertook a survey between 2015 and 2020, last year cannabis use among EU inhabitants (15–34) is estimated at 15.4%, and general population surveys indicate around 1.8% of adults (15–64) in the EU are daily or almost daily cannabis users (EMCDDA 2021), with 37.5% of the Spanish population within this age that has ever used cannabis, 10.5% in 2020, and a consumption prevalence in the last month of 8% (OEDA 2021).

Cannabis active principle ingredient is Δ^9 -tetrahydrocannabinol (Δ^9 -THC), but its high metabolism leads to a very low excretion rate, making THC-COOH or 11-OH-THC the metabolites to be used for THC back-calculation. The former is preferred since it is a relatively stable biotransformation product in wastewater and because 11-OH-THC is rapidly oxidized to THC-COOH (Andrés-Costa et al., 2017; Gracia-Lor et al., 2016). These data help to explain the ubiquity of THC-COOH in the wastewater samples analysed, similarly to other studies (Bijlsma et al., 2021; Nefau et al., 2013; Zuccato et al., 2016). Additionally,

cannabis resin sold in Europe is now more potent than before (20–28% more THC), and there are high-THC content products and new forms of cannabis on the illicit market as well as a bunch of products containing cannabis extracts sold commercially (EMCDDA 2021), which can also be responsible of the high concentration values of the samples (Table S5), in the range of tens-hundreds of ng/L , as reported in several cities of Spain (Bijlsma et al., 2021; Estévez-Danta et al., 2022; Mastroianni et al., 2017), Slovakia (Mackuľak et al., 2014), Colombia (Bijlsma et al., 2016), Costa Rica (Andrés-Costa et al., 2017), USA (Skees et al., 2018) but lower than those found in some cities of France (Nefau et al., 2013).

Amphetamine-like stimulants (AMP, MAMP, KET and MDMA) can be considered as a third group of the illicit drugs more generally detected in Valencia City and surrounding towns' wastewater. According to the 2021 European Drug Report, amphetamine is the Europe's second most consumed stimulant drug after cocaine. Surveys from 25 countries (2015–2020) suggested that 1.4 million young adults (15–34) used amphetamine during the last year (1.4% of this age group), which would confirm the frequencies found in this study, similar to those of Barcelona (Mastroianni et al., 2017) but higher than those in France (Nefau et al., 2013), Italy (Zuccato et al., 2016) and even in China (Du et al., 2015). Seizures data also confirmed this trend, since in 2019, EU Member States reported 34000 seizures of amphetamine (amounting to 17.0 tonnes, t), and 10000 of methamphetamine (2.9 t of which 1.6 t were seized in Spain originating in Mexico). In relation to the high concentrations found in samples, besides the high number of users, these could be related to the increasing average purities reported in the EU (13–67% for amphetamine and 16–94% for methamphetamine in 2019) (EMCDDA 2021). Even though these concentrations are lower than those reported in other continents as North America (Skees et al., 2018).

Average AMP concentrations in Valencian WWTPs samples were higher than those of MAMP (Table S5). In addition to a possible higher number of users, and despite being considered generally stable (no loss of analyte in sewage in line with stability studies in urine at 37 °C for 3 days and longer (Castiglioni et al., 2013)), there is approximately 4–7% of MAMP that is excreted as AMP (González-Mariño et al., 2020). Besides AMP and MAMP can be directly disposed into sewer systems, there can also be a part derived from high prescribed use of AMP (in therapeutic drugs as amphetaminil, benzphetamine, clobenzorex, dimethylamphetamine, ethylamphetamine, fampofazone, fencamine, mefenorex, prenylamine, selegiline, etc.), an amount of drug that needs to be differentiated from that one consumed and excreted (e.g. by chiral chromatography and “fingerprint” analyses (Archer et al., 2018; Bijlsma et al., 2021)), but that is not corrected here (their prescription rates in Europe indicate that any contribution would generally be <1% of the total AMP amounts (Ort et al., 2014; Thomas et al., 2012)). AMP and MAMP concentrations in Valencia (tens of ng/L) were slightly lower than in Barcelona (Mastroianni et al., 2017), or cities in France, Slovakia and Finland (Kankaanpää et al., 2016; Mackuľak et al., 2014; Nefau et al., 2013), and USA (Bishop et al., 2020; Skees et al., 2018) (hundreds of ng/L). In the study of Bijlsma et al. (Bijlsma et al., 2021) considering 17 cities in Spain including Valencia, AMP and MAMP's concentrations of Barcelona and Bilbao were in the same range but those of Castellón, Guadalajara, Lleida or Toledo were lower or not detected. Results obtained in different cities of China, presented contrasted results. In a southern city, AMP concentrations were lower but MAMP were similar (Zheng et al., 2021), while in Guangzhou and other cities of China, those of AMP were similar while those of MAMP were higher (Du et al., 2015; Zhang et al., 2019).

According to Gracia-Lor et al. (Gracia-Lor et al., 2016), the unchanged MDMA and two of its metabolites HMMA (4-hydroxy-3-methoxymethamphetamine) and HHMA (3,4-dihydroxy-methamphetamine) can be considered for back-calculation in WBE studies. However, these authors also state that without actual data is difficult to predict if these conjugates will be fully reverted to the parent compound in sewage, and consequently the unchanged MDMA is advised to be measured. Europe remains an important source of MDMA products that

supply the global market. Surveys from 26 EU countries (2015–2020) suggest that 2 million young adults (15–34) used ecstasy in the last year (1.9% of this age group) (EMCDDA 2021), and 5% of the Spanish population (15–64) has ever used it (OEDA 2021). High frequencies of MDMA detection in the samples analysed (Table S5) are also supported by the increasing number of seizures of MDMA powder in the EU (0.3 t in 2016 to 2.2 t in 2018 and 2019, corresponding to 4.6 million MDMA tablets). Additionally, the high concentrations found here could be related to the 149% average increased quantity of MDMA in tablets measured since 2009, 118–210 mg MDMA/tablet in 2019, based on data of the EMCDDA's 2021 report (EMCDDA 2021). Concentrations of MDMA (tens of ng/L) in Valencia were similar to those of Slovakia (Mackufak et al., 2014), Colombia (less frequent) (Bijlsma et al., 2016), several other cities of Spain as Bilbao, Castellon, Palma de Mallorca or Santiago de Compostela (Bijlsma et al., 2021; Estévez-Danta et al., 2022) but slightly lower than in Barcelona (Mastroianni et al., 2017) or in France and Finland (Kankaanpää et al., 2016; Nefau et al., 2013) (hundreds of ng/L). MDMA's concentrations in Valencia were higher than the reported in cities of China (Zhang et al., 2019; Zheng et al., 2021).

Ketamine is drug available in Europe, but it is poorly monitored, and information on its use and impact on public health is limited (EMCDDA 2021). According to the EMCDDA, 250–600 kg of ketamine seizures were reported by at least 16 EU countries, an amount considerably lower compared to those of other amphetamine-like stimulants, which explain the low frequencies and concentrations detected here. KET concentrations in Valencia (tens of ng/L) were similar to the levels reported in other Spanish (Bijlsma et al., 2021), and Colombian cities (Bijlsma et al., 2016). It was ubiquitous in samples of different cities in China and at higher concentrations than those reported here (Du et al., 2015; Zhang et al., 2019; Zheng et al., 2021).

Concentration of opioids in Valencia were expected to be low. According to 2021 Report of the OEDA, 0.7% of the Spanish population (15–64) has used heroin at some time, and only 0.1% in the last year, an use that has stabilized since the mid-1990s (OEDA 2021). In the EU, the problems with this drug can be higher based on the 26000 heroin and other opioids seizures (7.9 t, average purity of heroin 11–51%) reported in 2019, with 1 million high-risk opioid users (EMCDDA 2021). Despite codeine was only analysed in the period 2014–2017, their high concentrations (in the range of µg/L) confirmed opioid analgesics as codeine and tramadol as the drugs with highest prevalence use among the population (15–64) (OEDA 2021). Their concentrations are higher than those reported in a community in the Midwestern United States (Skees et al., 2018). Codeine is reported to be stable in wastewater but it is rarely analysed, and even less information is found for bufotenine and etamine, which levels (tens of ng/L) makes suspect their relative low consumption in Valencia. COD presented high frequencies and concentrations in this study, which were higher than those reported in Costa Rica (hundreds of ng/L) (Andrés-Costa et al., 2017) or in Guangzhou (China) (ng/L) (Zhang et al., 2019).

In this study, heroin is back-calculated using MOR concentrations since it is considered as the most abundant metabolite of heroin. Nevertheless, it is also an indicator of the use of therapeutic morphine, codeine, ethylmorphine, pholcodine and nicomorphine, which concentrations should be differentiated from that one of MOR, but they are not corrected here since it is advised only for countries where the licit contributions of morphine can be higher than those of illicit heroin (Khan and Nicell 2011; Gracia-Lor et al., 2016). Concentrations measured in Valencia (hundreds of ng/L) were similar to the values detected in France (Nefau et al., 2013), but higher than in Costa Rica or USA (tens of ng/L) (Andrés-Costa et al., 2017; Skees et al., 2018), and China (Zheng et al., 2021). On the other hand, for methadone, its parent compound (METH) and its metabolite (EDDP) were used here. Despite METH and EDDP were not measured all years, their levels were similar (tens of ng/L) and alike to those reported in several cities of France (Nefau et al., 2013), and of USA (Bishop et al., 2020; Skees et al., 2018),

but higher than in China (ng/L) (Zheng et al., 2021). In order to check for possible transformation of METH to EDDP, the METH/EDDP ratio has been calculated obtaining values between 0.2 and 1.2, in the range of other studies (Castiglioni et al., 2013; Mastroianni et al., 2017; Thai et al., 2016; Zhang et al., 2019), which suggested deliberate or accidental disposal of the drug into the sewer.

4.2. Estimation of drugs consumption in Valencia City

As it was stated, despite the fact that WWTPs flows follow the trend $P2 > P1 > QB$, there are important differences between the population they serve. Only tobacco consumption tended to be higher in P2 than in QB and P1. For cannabis, cocaine (estimated through COC or ECME), all amphetamine-type stimulants and opioids, the trend was $P1 > P2 > QB$ (cocaine calculated by means of BECG or the COCET concentrations tended to higher in QB). It can be stated that the consumption of most of the drugs analysed in this study was higher for the population served by P1. This can be explained because this WWTP only treats water from Valencia City, which is the capital of the Community and the third largest city in Spain, with many leisure places and night life. On the other hand, P2 and QB treat, in addition to part of the wastewater of Valencia City, that of several surrounding towns and their industrial areas, and despite being known for their bars and discos their activity can be considered less intense.

In Valencia the most consumed drugs, according to our WBE analysis, were cannabis, tobacco and cocaine (Fig. 1). Although we only measured nicotine's metabolite from 2014 to 2017, the 2021 Report of the Spanish Observatory on Drugs and Addictions (OEDA) confirmed these three as the drugs with the highest use prevalence among the Spanish population (15–64) in the last year. Here they were followed by codeine (in 2014–2017), and amphetamine-type stimulants as MDMA, AMP, and MAMP. Heroin showed low consumption as well as ketamine, methadone, and etamine (Tables 1 and 2). In a previous study, Andrés-Costa et al. (Andrés-Costa et al., 2014) have proven that cannabis and cocaine were the most consumed drugs in Valencia, in agreement with results of WBE studies in other Spanish cities as Barcelona (Mastroianni et al., 2017) and western European countries as Italy (Zuccato et al., 2016), and France (methadone was also high) (Nefau et al., 2013). Similarly, in these studies amphetamine, methamphetamine and ecstasy were reported as a second group of illicit drugs with lower consumptions, whereas opioids (heroin and/or methadone) were the less consumed ones.

4.2.1. Cannabis and tobacco

Cannabis consumption in Valencia (Table 2) was comparable to other Spanish cities (e.g. Madrid and Bilbao, (Bijlsma et al., 2021) (Table S9), but lower than in Barcelona (Mastroianni et al., 2017), which continuously increased since 2012 becoming almost three times higher in four years and the highest in Spain (Bijlsma et al., 2021). In 2019, EU Member States reported 326000 seizures of cannabis resin amounting to 465 t and 313000 seizures of herbal cannabis amounting to 148 t (EMCDDA 2021), which confirm the very high amount of cannabis moving across the EU. Its use in Valencia is higher than in other European cities as those from Italy (Zuccato et al., 2016), France (Nefau et al., 2013), Germany and Switzerland (Been et al., 2016), and Slovakia (Mackufak et al., 2014), but lower than in Netherlands, and particularly than Amsterdam, one of the highest cannabis consumption in Europe (Ort et al., 2014; SCORE 2020; Thomas et al., 2012). In contrast to the other studied drugs, no clear geographical patterns have been observed for cannabis use in the different European cities, with similar values in smaller towns than in larger cities. In a wider analysis, cannabis consumption in Valencia was higher than in different cities of Colombia (Bijlsma et al., 2016), and Costa Rica (Andrés-Costa et al., 2017), but similar to the one reported in a community in the Midwestern United States (Skees et al., 2018).

Despite the highest use prevalence of tobacco among the European

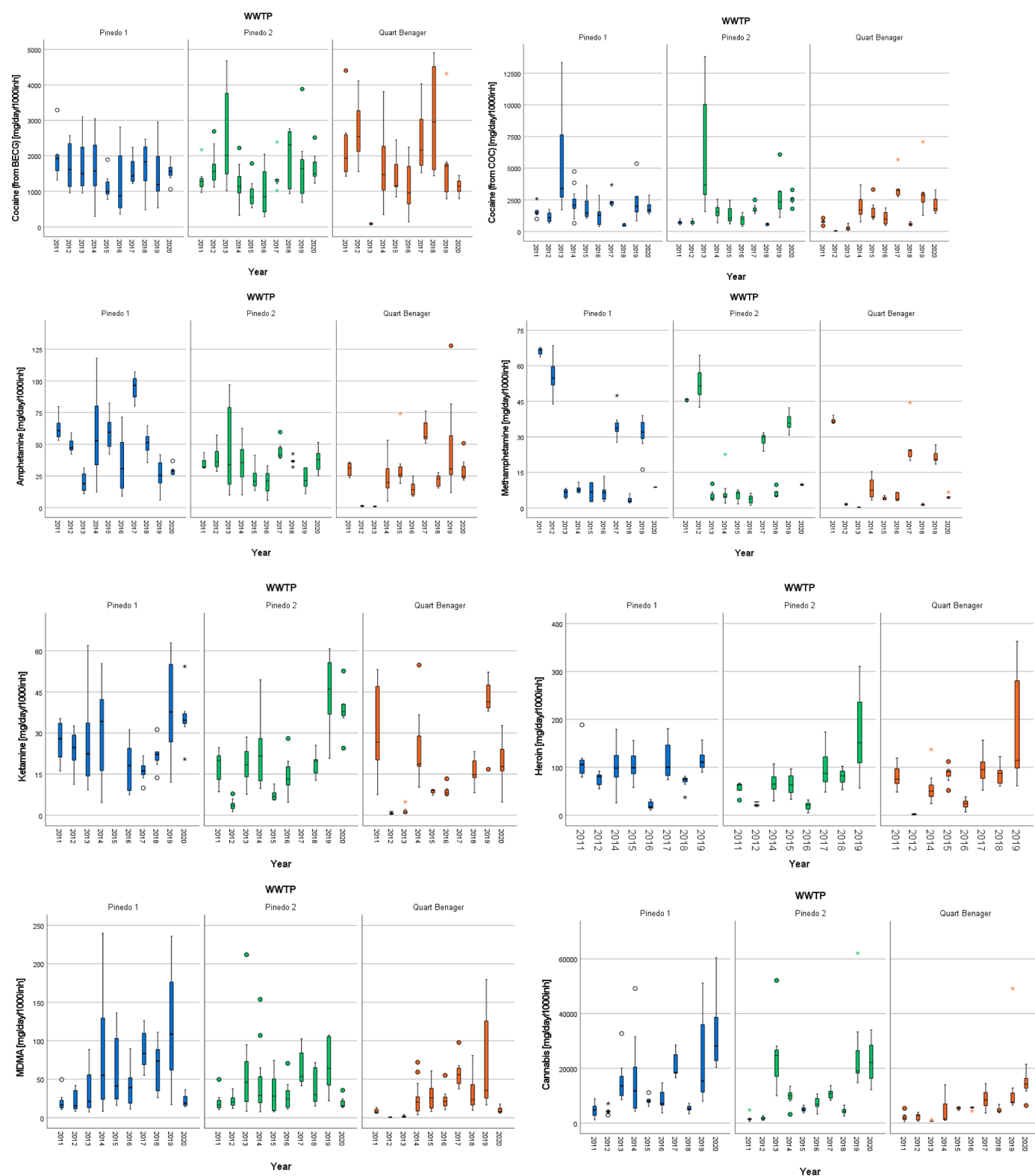


Fig. 1. Consumption (mg/day/1000inh) of illicit drugs in Valencia City between 2011 and 2020.

population, it should be highlighted that very few WBE studies focussed on its consumption have been published. Results of a study performed in four cities of Spain (Bilbao, Vitoria-Gasteiz, Castellon and Santiago de Compostela) and two of Portugal (Porto and Vila do Conde) reported similar tobacco consumption to Valencia (Estévez-Danta et al., 2022). On the other hand, the consumption of nicotine performed in Lithuania was estimated by using the metabolites COT/COT-OH and comparison

with data calculated in this study is not straightforward (Boogaerts et al., 2021).

4.2.2. Cocaine

In this study, significant differences in the estimated cocaine consumption were found depending on the use of the parent compound or its metabolites. Thus, by using COC the results were significantly higher

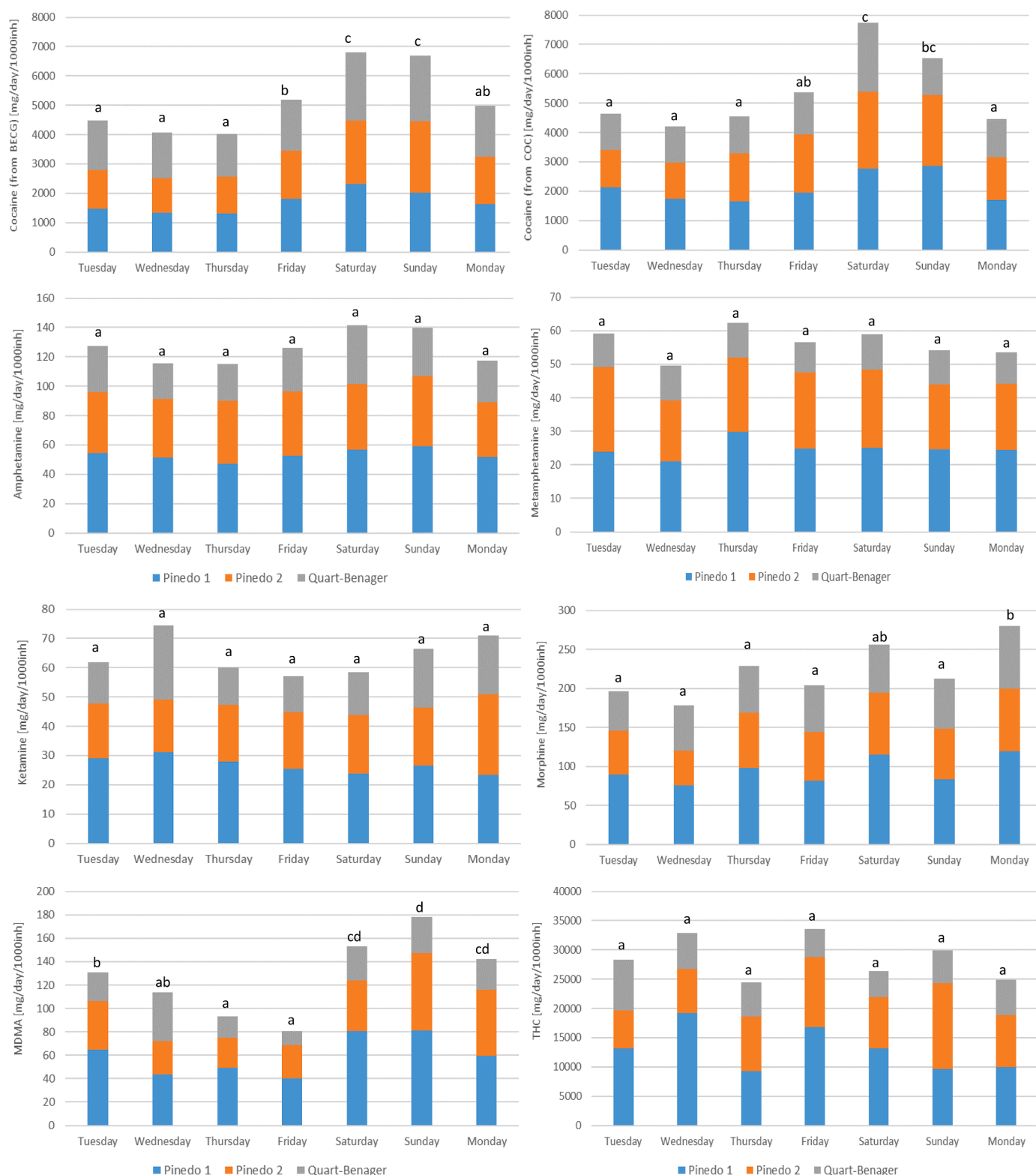


Fig. 2. Weekly consumption (mg/day/1000inh) of illicit drugs in Valencia City between 2011 and 2020. Different letters indicate significant differences ($p < 0.05$) between years for each compound.

than those of BECG, COCET, and ECME ($p < 0.05$). This result is not in agreement with those of Colombia and Costa Rica where the cocaine consumption showed differences (BECG > COC) (Andrés-Costa et al., 2017; Bijlsma et al., 2016), or in Brussels (van Nuijs et al. 2011b) where it was the same (BECG = ECME), supporting the idea of deliberate or accidental disposal of the drug into Valencia's sewer stated above. In

general, studies reporting all cocaine metabolites concentrations finally select BECG for calculation because of its higher stability compared to other cocaine residues (Andrés-Costa et al., 2017; da Silva et al. 2018; Mackulak et al., 2014; Nefau et al., 2013) (Table S9). Cocaine consumption, calculated from BECG concentration, in Valencia was similar than in Barcelona (Mastroianni et al., 2017) as concluded also by the

ESAR-net network (ESAR-net 2020). In the study of Bijlsma et al. cocaine consumption was calculated in 17 Spanish cities, in 2021, finding values in the range of g/day/1000inh in Valencia, Castellon, Reus, and Palma de Mallorca, positioning Spanish cities at the top of the cocaine consumer markets (Bijlsma et al., 2021; ESAR-net 2020; OEDA 2021).

The international wastewater monitoring campaigns performed yearly by SCORE report, together with a number of publications (González-Mariño et al., 2020; Mackufak et al., 2014; Ort et al., 2014; SCORE 2020), have demonstrated a clear geographical difference in the consumption of cocaine, with higher use in Southern and Western Europe. The record 213 t of cocaine seized in 2019 indicates an expanding supply in the EU. Cocaine purity has been increasing over the last decade, and the numbers of people entering treatment for the first time have risen over the last 5 years. Among the 26 countries reporting surveys (2015–2020), last year prevalence of cocaine use among young adults (15–34) was 0.2–4.6%, with 8 countries reporting rates over 2.5% (EMCDDA 2021).

Average cocaine use in Valencia was higher than that observed in main cities from northern and eastern European countries as Finland, Germany, Switzerland, Lithuania, and Slovakia (Been et al., 2016; Boogaerts et al., 2021; Kankaanpää et al., 2016; Mackufak et al., 2014), close to those of Brussels (van Nuijs et al. 2011b), and several cities of France (Nefau et al., 2013). It was also of the same order of magnitude than countries of America as Costa Rica (Andrés-Costa et al., 2017), USA (Bishop et al., 2020; Skees et al., 2018), and Colombia (Bijlsma et al., 2016), known as one to the main cocaine-producing countries in the world, but lower than in Brazil (da Silva et al. 2018). In most of these studies, it has been demonstrated that the consumption of cocaine is higher in larger cities compared to smaller towns. The calculated consumption of cocaine during 3 months in Guangzhou (China) was two orders of magnitude lower (Zhang et al., 2019) than those of Europe or America demonstrating that cocaine is not a popular illicit drug in this country. In Africa, the only country reporting cocaine consumption data is South Africa and these can also be considered low (Archer et al., 2018), in the same range to those reported in Australia (Lai et al., 2016).

4.2.3. Amphetamine-type stimulants

This group of drugs is the second most consumed in Valencia City and surrounding towns. The fluctuations observed in amphetamine and methamphetamine consumptions (Fig. 1) can reflect changes in the market, with consumers using one substance or the other depending on availability. At a national level, amphetamine consumption in Valencia (Table 1) was lower than in Barcelona (Mastroianni et al., 2017) and Bilbao (Bijlsma et al., 2021). As reported by the 2021 European Drug Report and several studies, amphetamine, methamphetamine are the drugs most consumed in north-central and east Europe, respectively (Bijlsma et al., 2021; EMCDDA 2021; Mackufak et al., 2014). For amphetamine the highest consumptions have been reported in Denmark, Norway, Iceland and, especially, Belgium and Netherlands, which exceed by far the means found in the rest of the continent (González-Mariño et al., 2020; Ort et al., 2014; SCORE 2020; Thomas et al., 2012; van Nuijs et al. 2011b) (Table S9). Comparatively, consumptions measured in southern European cities were much lower, as those reported for Valencia and several cities in France (Nefau et al., 2013).

Although the average use of methamphetamine in Europe is low when compared to other stimulants, some important hotspots have been identified mostly in eastern and northern countries as there is a market expansion from the East to North and Central Europe (González-Mariño et al., 2020; Ort et al., 2014). Methamphetamine consumption in Valencia was lower than in other investigated cities as Barcelona (Mastroianni et al., 2017), Slovakia (one of highest methamphetamine consumption rates in Europe) (Mackufak et al., 2014), Finland, Lithuania, Germany and Switzerland (Been et al., 2016; Boogaerts et al., 2021; Kankaanpää et al., 2016), but higher than in cities of Italy

(Zuccato et al., 2016), and Belgium (van Nuijs et al. 2011b). Amphetamine and methamphetamine were not detected in Colombia (Bijlsma et al., 2016), and in several cities of Spain (e.g. Castellon, Guadalajara, Lleida, Toledo) where it seems that their consumption is very low and not largely extended (Bijlsma et al., 2021; Estévez-Danta et al., 2022). In other continents, methamphetamine consumption in South Africa (Archer et al., 2018), Guangzhou and other Chinese cities (Du et al., 2015; Zhang et al., 2019) as well as in Australia (Lai et al., 2016) was much higher than in Valencia, which was similar to the consumption in five cities of South Korea (Kim et al., 2015). Amphetamine and methamphetamine consumptions showed the highest levels found in literature in the United States (Skees et al., 2018). In contrast to cocaine use, the difference in amphetamine and methamphetamine consumptions between smaller towns and bigger cities within a country is less clear (González-Mariño et al., 2020; Lai et al., 2016).

Latest epidemiological indicators and WBE data point to a revival of MDMA in Europe in recent years (EMCDDA 2021; ESAR-net 2020). However, a factor that could contribute to these higher values is the known increased content of MDMA in ecstasy tablets since 2010–11 (EMCDDA 2021; González-Mariño et al., 2020). In general, Spain is considered a low-MDMA-usage country, but wastewater data reported to EMCDDA indicates an increasing trend in its use over the years for the four cities participating in SCORE and ESAR-net, i.e., Barcelona, Castellon, Santiago de Compostela, and Valencia (Bijlsma et al., 2021; EMCDDA 2021; ESAR-net 2020; Estévez-Danta et al., 2022). Ecstasy's consumption in Valencia (Table 1) was of the same order than in Bilbao, Madrid, and Palma de Mallorca, higher than in Castellon and Toledo (Bijlsma et al., 2021), but lower than in Barcelona (Mastroianni et al., 2017). The highest use of MDMA has been observed in Western European locations compared to Northern and Eastern Europe ones (González-Mariño et al., 2020; Ort et al., 2014). The ecstasy's use estimated here is similar than in other European cities as those of Belgium (van Nuijs et al. 2011b), France (Nefau et al., 2013), but higher than in Italy, Finland, Slovakia, Germany and Switzerland (Been et al., 2016; Kankaanpää et al., 2016; Mackufak et al., 2014; Zuccato et al., 2016). Outside Europe, the use of MDMA is generally low as in South American countries (Bijlsma et al., 2016) or in Guangzhou (China) where seizures of ecstasy tablets containing little or no MDMA confirmed to low consumptions levels reported in South-East and East Asia (Zhang et al., 2019). Similar low consumption values have been reported for the first time in South Africa (Archer et al., 2018), and several states and territories in Australia (Lai et al., 2016). As cocaine, MDMA use is generally higher in larger cities compared to smaller towns (González-Mariño et al., 2020; Thomas et al., 2012).

Ketamine is considered a “dissociative anesthetic” used in powdered or liquid form. Despite its original design as human and, more commonly, veterinary anesthetic, ketamine has gained popularity as “club drug” over the past few years. According to recent studies, ketamine is among the emerging drugs used in bars and discos, together with other synthetic drugs as LSD, MDMA, phencyclidine and alkyl nitrites (i. e. poppers) (Bijlsma et al., 2016). Despite the fact that ketamine was only found in 40% of samples analysed, the consumptions calculated in this study can indicate that its use is not sporadic, and it has increased as drug of abuse in front of its use as pharmaceutical. Concentrations and/or consumptions of this drug and its metabolite norketamine have been mainly reported in East and South-East Asia (Du et al., 2015), suggesting its use particularly in this region as in Guangzhou (China) where ketamine was the drug most consumed among the six substances monitored during 8 weeks in 2017 (Zhang et al., 2019). Ketamine consumption in Valencia is higher than in other cities as those of Colombia (Bijlsma et al., 2016).

4.2.4. Opioids

Heroin consumption in this study was back-calculated by means of the concentrations of MOR, and although therapeutic morphine should be differentiated from that one of the illicit drug, this is not corrected

here since it is advised only for countries where the licit contributions of morphine can be higher than those of illicit heroin (Khan and Nicell, 2011; Gracia-Lor et al., 2016). According to the EU Report, Member States reported 26000 heroin seizures amounting to 7.9 t in 2019, with indexed trends showing that the average purity of heroin rose by 23% between 2009 and 2019, while its price dropped 17% (EMCDDA 2021). These figures would help to explain consumption values calculated in Valencia, which were similar to those of different cities in Italy reported using MOR (Zuccato et al., 2016), but also those using 6MAM (6-mon-oacetylmorphine) as in Barcelona (Mastroianni et al., 2017). These were higher than in Germany and Switzerland (Been et al., 2016), or in Finland where it is absent (Kankaanpää et al., 2016), but lower than in Brussels (van Nuijs et al. 2011b) (Table S9). Outside Europe, heroin levels were very high in USA (Bishop et al., 2020; Skees et al., 2018), in Colombia they were too low to be detected (Bijlsma et al., 2016), while in Costa Rica they were lower than in Valencia (Causanilles et al., 2017b). Similarly, in South Africa, despite heroin is considered the most commonly-abused opioid in the country, it was not detected at any of the WWTWs analysed in 2017 (Archer et al., 2018).

Methadone consumption has shown high values in Western Europe. In Valencia, it was estimated through EDDP or METH concentrations resulting in lower values than in other places, mainly calculated by using EDDP, as Barcelona (Mastroianni et al., 2017), Brussels (van Nuijs et al. 2011b), and several cities in France (Nefau et al., 2013). Methadone consumption in different cities of USA was calculated using METH obtaining much higher levels than in this study (Bishop et al., 2020; Skees et al., 2018). Values reported for these cities are about 60 times higher than in Guangzhou (China) (Zhang et al., 2019). On the other hand, codeine use in Valencia can be considered high if it is compared with the values reported in cities of Costa Rica (Causanilles et al., 2017b), USA (Bishop et al., 2020; Skees et al., 2018), China (Guangzhou) (Zhang et al., 2019), or South Korea (Kim et al., 2015).

Finally, it is important to state that even following the “best practice” requirements for each of the steps proposed by different authors and the SCORE network (Castiglioni et al., 2013; SCORE 2020), some uncertainty related to the sampling protocol, measurement of the flow rate, stability of the compounds in wastewater, chemical analysis performed, estimation of the population size and correction factors (CFs) applied in the back-calculations, is unavoidable and consequently, the validity and reliability of the results obtained and subsequent estimations made in this study have to be taken with caution.

As stated by these authors, the loss or formation of sewage drug biomarkers is generally lower than 10% (negligible uncertainty) if the mean residence time of sewage in the sewer systems is 0.5 – 15 h, as in this study. Other factors as adsorption onto the solid particulate matter (SPM) and the conjugation of drug residues are not important since percentages of adsorption are estimated to be COC <3.1%, BECG <0.5%, AMP <8.6%, MDMA <2.4% and METH <2.3% (Castiglioni et al., 2013). However, adsorption onto SPM could be a relevant issue for cannabis due to its low polarity, and therefore, our values for cannabis consumption could be underestimated. To calculate the population size to normalize the data to the number of inhabitants served by each WWTP, we have used real-time calculations based on the COD (128 g/day) as suggested by different authors (Bijlsma et al., 2016; Causanilles et al., 2017b; van Nuijs et al. 2011b). In relation to CFs, this research has adopted the most recently refined and accepted CFs (based on local data on the preferential route of administration) to reduce WBE uncertainty and to improve comparability of the results within different studies (Castiglioni et al., 2013; Gracia-Lor et al., 2016; Thai et al., 2016). However, most of the literature summarised in this study used different CFs and consequently, caution should be paid with the comparisons made herein. We have not presented our data in doses/day/1000inh, since it is a factor that adds additional uncertainty to the back-calculated drug use values.

4.3. Temporal trends of drugs consumption and influence of local festivities

In relation to temporal trends, it can be stated that cannabis and cocaine consumption have increased in Valencia City and surrounding towns comparing the values obtained in this study, in 2018–2020, with those reported previously for 2011–2013 (Andrés-Costa et al., 2014). Although there are small differences in the CFs used in both researches, consumptions were similar for methamphetamine, decreased for amphetamine, and increased for ecstasy, which can also be associated to the higher MDMA purity observed in last years (Gracia-Lor et al., 2017; SCORE 2020). Ketamine consumption estimated for 2017–20 is significantly lower than the one reported for 2011–13 (Andrés-Costa et al., 2014), but this is related to different CFs used. Heroin in the previous study could not be calculated by means of 6-MAM compared to this one in which it was calculated through MOR, showing low consumptions as methadone that was not reported in 2011–13 for Valencia (Andrés-Costa et al., 2014).

Cannabis consumption remarkably increased also in Barcelona between 2011 and 2015 (Mastroianni et al., 2017). Increasing trends have also been reported in Italy in 2010–14 (Zuccato et al., 2016). The increased cocaine consumption values in Valencia City and surrounding towns agrees with the general tendency observed across Europe within the last years (González-Mariño et al., 2020; Zuccato et al., 2016). Although this can be explained by a higher prevalence of cocaine use, or a similar number of consumers using a higher amount of drug, it can also be related to an increased drug purity (~32–54% from 2009 to 2016) (EMCDDA 2021). According to the EMCDDA, of the 49 cities that have data on cocaine residues in municipal wastewater for 2019 and 2020, 19 reported an increase, 14 a stable situation and 16 a decrease. The most recent data indicate that cocaine is becoming more common in cities in the east of Europe, although detection levels remain low (EMCDDA 2021; SCORE 2020).

Fluctuations detected for amphetamine and methamphetamine levels during the study period (Fig. 1) have also been observed in Barcelona, where an increasing trend was observed within 2011–15, then it seems to be stabilized or even slightly decreased in most recent years (Mastroianni et al., 2017). In the EU, of the 48 cities with data on amphetamine residues in municipal wastewater for 2019 and 2020, 20 reported an increase, 9 a stable situation and 19 a decrease (EMCDDA 2021). On the other hand, methamphetamine use in Barcelona increased considerably since 2011 as in some cities of Finland and Switzerland where considerable increases were measured for 2014–17 (Bijlsma et al., 2021; González-Mariño et al., 2020; Kankaanpää et al., 2016). Of the 50 cities that have data on methamphetamine residues in municipal wastewater for 2019 and 2020, 15 reported an increase, 14 a stable situation and 21 a decrease (Bijlsma et al., 2021; EMCDDA 2021). Among the countries consistently providing data on purity and price, the average purity of amphetamine has increased markedly over the past decade, while the price has remained relatively stable, whereas the overall average purity and price of methamphetamine in 2019 were comparable to the values reported in 2009 (EMCDDA 2021).

Outside Europe, methamphetamine and ketamine use (2012–14) in several Chinese cities were reported to significantly increase and decrease, respectively, (Du et al., 2015). Recently, consumption of both drugs was detected to be reduced in Guangzhou (China) from May to October 2017, and explained because of a series of law enforcement anti-narcotics operations that destroyed several large-scale transnational channels of methamphetamine trafficking (Zhang et al., 2019). Declining consumptions of methamphetamine (14% per year) and ketamine were reported in a city in southern China (2012–18) (Zheng et al., 2021).

MDMA underwent an intermittent upsurge in Europe during 2011–17 (González-Mariño et al., 2020), while it was stable over the period 2012–18 in China (Zheng et al., 2021). Of the 49 cities that have data on MDMA residues in municipal wastewater in 2019–20, 18

reported an increase, 7 a stable situation and 24 a decrease (EMCDDA 2021). Among these cities, MDMA use has increased in Finland, Germany and Switzerland (Been et al., 2016; Kankaanpää et al., 2016), but particularly in Amsterdam, likely reflecting its position as a tourism and nightlife destination. The average annual use of heroin in Barcelona (2011–15), in several cities of Italy (2010–14) and in China (2012–18) showed a decreasing trend (Mastroianni et al., 2017; Zheng et al., 2021; Zuccato et al., 2016). Although with some fluctuations, methadone was stable over the period 2012–18 in China (Zhang et al., 2019; Zheng et al., 2021) and codeine in Guangzhou during 3 months in 2017 (Zhang et al., 2019).

4.3.1. Weekly patterns of drugs use in Valencia City

Weekly patterns of drugs use were deduced by the changes observed in their concentrations at the inlet of WWTPs confirming the recreational character of some of these substances. In Valencia City and its surrounding towns three drugs, namely, cocaine, ecstasy, and heroin showed a weekly trend, with significantly higher consumption values during the weekend compared to the weekdays. The first two were

expected because of their popularity in the dance and music scene, but the higher use of heroin was unexpected although positive detections in samples collected in Barcelona from Friday to Monday suggest a comparable pattern (Mastroianni et al., 2017). Similar results were already reported in Valencia in 2011–13 but instead of heroin, amphetamine was reported (Andrés-Costa et al., 2014). Other European cities (Ort et al., 2014; Thomas et al., 2012), including those of Belgium (van Nuijs et al. 2011b), France (Nefau et al., 2013), Italy (Zuccato et al., 2016) and Slovakia (Mackulák et al., 2014), together with some in South America as Brazil (da Silva et al. 2018), Africa as South Africa (Archer et al., 2018), and Oceania as Australia (Lai et al., 2016) highlighted also the higher use of drugs such as amphetamine, cocaine and ecstasy during weekends indicating that the consumption of these drugs is associated with recreational and socializing purposes. Worth mentioning is the case of Barcelona where MDMA consumption was duplicated during weekends, reaching maxima on Sunday (251 ± 31 g/day) (Mastroianni et al., 2017). In Valencia City, the significant higher use of MDMA (Friday to Sunday) is shifted with one day compared with cocaine (Thursday to Sunday), which can be due to different usage trends of both illicit drugs,



Fig. 3. Consumption¹ (mg/day/1000inh) of illicit drugs in Valencia City during 2014 festivity “Las Fallas”.

but also to differences in the excretion patterns (maximal concentrations in urine, half-lives,...) (van Nuijs et al. 2011b).

Tobacco, cannabis, amphetamine, methamphetamine, ketamine, methadone, and codeine concentrations were relatively constant throughout the week as it has been observed previously in Valencia (Andrés-Costa et al., 2014), and other European cities (Nefau et al., 2013; Ort et al., 2014; Thomas et al., 2012; Zuccato et al., 2016), but also in Colombia (Bogota and Medellin) for cannabis (Bijlsma et al., 2016) and in Guangzhou for methamphetamine, ketamine, methadone and codeine (Zhang et al., 2019). The lack of weekend effect for amphetamine can be due to the fact that is also legally used in the treatment of several disorders (narcolepsy and ADHD) and it is also a metabolite of several pharmaceuticals (fenethylline, fenproporex, and selegiline) (van Nuijs et al. 2011b), as for methadone that is prescribed for a daily intake (van Nuijs et al. 2011b).

4.3.2. Impact of the main local festivity in the drugs' use of Valencia City

Finally, significant increases in the consumption of cocaine, amphetamine, methamphetamine, and mainly MDMA were observed during "Las Fallas" in 2014 (Fig. 3). Cocaine, amphetamine and methamphetamine consumption were almost doubled but the highest growth was detected for the MDMA, which was around four times higher. A previous study has already reported the increased use of alcohol during these festivities (Andrés-Costa et al., 2016). Similar results have been reported in different festivals, special events or holiday periods in different cities of the world. In Slovakia (Mackuľak et al., 2014), higher consumption of methamphetamine (163 mg/day/1000inh), and cocaine (up to 1800 mg/day/1000inh) were measured in the Lodenica country and folk music festival. Ecstasy consumption was festival dependent with an extremely high use during the music festival in Trenčín, whereas no significant increase in the cannabis consumption was found during the two music festivals. In Brussels, the highest level of cocaine use was observed on New Year's Eve (1544 mg/day/1000inh), Christmas period (1063 mg/day/1000inh) and during Easter holiday (1032–1048 mg/day/1000inh) (van Nuijs et al. 2011b). MDMA's peak use was observed at New Year's Eve and around Easter (286 and 144 mg/day/1000inh, respectively). In Amsterdam, high ecstasy's consumption values estimated were related to a big Halloween dance party (van der Aa et al. 2013).

Outside Europe, a significantly higher consumption of methamphetamine (+42%) and cocaine (+47%) was observed during the Spring Festival week of Guangzhou (China) compared with the control period. Similarly, higher mean consumption (+37%) of MDMA was observed during National Day holidays. In Brazil, a significant high cocaine use was observed in the Carnival Day of 2018 (6229 mg/day/1000inh) being one of the highest reported in the literature (da Silva et al. 2018).

5. Conclusion

WBE methodology was successfully applied to assess the occurrence and tendencies of various licit and illicit drugs in Valencia City and surrounding towns during one-two weeks between 2011 and 2020. Consumption estimates indicate that cannabis, tobacco, and cocaine are the most consumed drugs in the study area. Temporal trends were difficult to evaluate but it seems that drug use increased since 2018, which is in agreement with the official statistics in the region. Consumption of cocaine, amphetamine, and MDMA was found to be higher during the weekends confirming the recreational purposes of these drugs. Similarly, during "Las Fallas" (main local festivity) increased use of cocaine and amphetamine-type stimulants mainly MDMA was measured. Results of this research highlights the relevance of WBE, which can complement classic epidemiological indicators (e.g. prevalence data and seizures statistics) to jointly draw a more comprehensive picture of the drug use patterns in Valencia City.

WBE estimates allowed us to evaluate data on drug use in a specific region in an objective, fast, inexpensive, and anonymous way. In

relation to the uncertainties associated to this approach, the current CFs need to be updated and harmonized to be used as part of the "best practice" protocol. Annual more intensive sampling (>1week) is also advised to assess temporal variations more clearly. WBE is an extremely flexible tool for application at different spatial and temporal scales, which can help us to get more insight on the tendencies on licit and illicit drugs consumption and the changes derived from local festivities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

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