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# Five-year monitoring of 19 illicit and legal substances of abuse at the inlet of a wastewater treatment plant in Barcelona (NE Spain) and estimation of drug consumption patterns and trends

Nicola Mastroianni [a], Ester López-García [a], Cristina Postigo [a,*], Damià Barceló [a,b], Miren López de Alda [a]

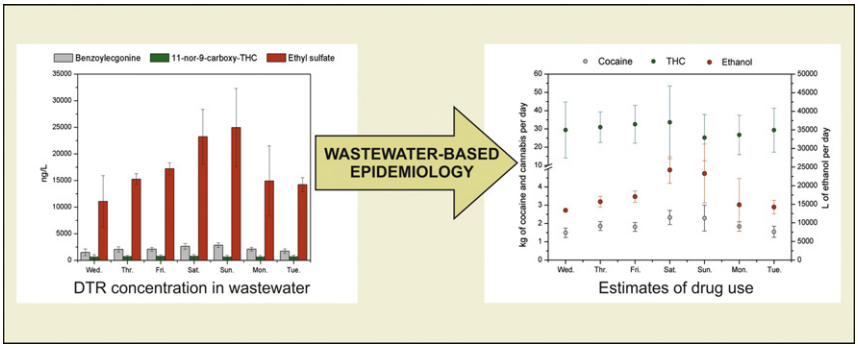
[a] Water and Soil Quality Research Group, Department of Environmental Chemistry, Institute of Environmental Assessment and Water Research (IDAEA-CSIC), Jordi Girona 18-26, 08034 Barcelona, Spain

[b] Catalan Institute for Water Research (ICRA), Parc Científic i Tecnològic de la Universitat de Girona, Edifici H2O, Emili Grahit 101, 17003 Girona, Spain

## HIGHLIGHTS

- Drug use in Barcelona during 5 years assessed using wastewater-based epidemiology.
- Alcohol, cannabis and cocaine were the most consumed drugs.
- Drug use increased from 2011 to 2015, contrary to national official data.
- Temporal trends of drug use were in agreement with regional official data.
- Consumption of alcohol, cocaine and MDMA increased during the weekend.

## GRAPHICAL ABSTRACT

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## ABSTRACT

Illicit and legal drugs of abuse, including alcohol, continue to be in the focus of many governmental national and international studies due to the important consequences of their consumption at both individual and social level. Estimation of drug use at the community level from the concentrations of the drugs themselves or their major metabolites measured in wastewater has become an increasingly accepted and extended tool, complementary to the methods traditionally used for this purpose. The present work describes the application of this approach, generally known as wastewater epidemiology, to investigate the latest drug consumption patterns and trends in the European city of Barcelona. To this end, a total of 19 selected drugs of abuse and metabolites were monitored at the inlet of one of the main wastewater treatment plants of Barcelona every day during one week in March between 2011 and 2015. Analysis of the selected drugs and metabolites in the wastewater samples was performed by means of two methodologies based on liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the concentrations obtained were translated into consumption data. In agreement with official records, alcohol,

*Abbreviations:* 6ACM, 6-acetylmorphine; ACN, acetonitrile; AEMPS, Spanish Agency for Medicines and Medical Devices; ALP, alprazolam; AM, amphetamine; ATS, amphetamine-type stimulant; BE, benzoylecgonine; CE, cocaethylene; COC, cocaine; DBAA, dibutylammonium acetate; DIA, diazepam; EDADES, Spanish household survey on alcohol and drugs; EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; EPH, ephedrine; ESI, electrospray ionization; Et-S, ethyl sulfate; HER, heroin; HPLC, high performance liquid chromatography; INE, Spanish National Statistics Institute; inh., inhabitant(s); LC, liquid chromatography; LOD, limit of detection; LSD, lysergic acid diethylamide; MA, methamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; METH, methadone; MOR, morphine; MS, mass spectrometry; MS/MS, tandem mass spectrometry; MSSSI, Spanish Ministry of Health, Social Services and Equality; N.D., not detected; OEDT, Spanish Observatory on Drugs and Drug Addiction; OH-LSD, 2-oxo-3-hydroxy-LSD; PET, polyethylene terephthalate; SPE, solid phase extraction; SRM, selected reaction monitoring; SS, surrogate standard; THC, $\Delta^9$–tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-THC; UNODC, United Nations Office on Drugs and Crime; WHO, World Health Organization; WBE, wastewater based-epidemiology; WWTP, wastewater treatment plant.

* Corresponding author.
*E-mail address:* cprqam@cid.csic.es (C. Postigo).

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Liquid chromatography-tandem mass spectrometry

followed by cannabis, cocaine, amphetamine-like compounds, and methadone were the most consumed drugs. Alcohol, cannabis, and cocaine consumption were on average 18 mL(14 g)/day/inhabitant (>15), 38 g/day/1000 inhabitants aging 15–64, and 2.4 g/day/1000 inhabitants aging 15–64, respectively. As for drug use trends, consumption increased over the 5 years monitored for all drugs, but for heroin and diazepam. Weekly profiles characterized by higher consumption over the weekend as compared to weekdays were observed only for alcohol, cocaine, and MDMA. Extrapolation of the data obtained for the area under study to the national Spanish territory yields consumption figures of 142 t of illicit drugs per year and >2500 million euro turnover per year in the black market.



## 1. Introduction

In recent years, illicit and legal substances of abuse and their human metabolites have emerged as environmental organic pollutants of concern. Due to their widespread production and use and incomplete removal in wastewater treatment plants (WWTPs), they have become ubiquitous pseudo-persistent compounds in the aquatic environment and consequently, their analysis in the water cycle has raised increasing interest (Evgenidou et al., 2015; Mastroianni et al., 2013; Pal et al., 2013; Postigo et al., 2010).

According to the last World Drug Report of the United Nations Office on Drugs and Crime (UNODC), 247 million people (5% of the world population) between 15 and 64 years consumed an illicit drug in 2014 (UNODC, 2016). This data was obtained by means of general population surveys on illicit drug use, sales data, drug seizures, medical records, etc. However, these approaches present some limitations like (i) lack of objectivity because the information gathered in the population surveys comes from the consumers themselves, (ii) insufficient spatial resolution to allow realistic drug use estimation at regional level due to the varying confounding socio-economic and cultural factors affecting consumer habits and trends, and (iii) delayed response time, since surveys and other statistical analyses involve long periods of realization and, in addition, are considerably expensive (van Nuijs et al., 2011a). Some of these limitations can be overcome through the use of the so-called wastewater-based epidemiology (WBE) approach to back-calculate drug use from the amount of a drug target residue (DTR) present in the wastewater of any given population. Zuccato et al. (2005) were the first to apply this approach in 2005 to estimate cocaine consumption in several cities in the North of Italy from the concentrations of this compound and its main human metabolite, benzoylecgonine, measured in untreated wastewater. Thereafter, this methodological approach, which allows obtaining realistic and reproducible drug consumption data in an objective and fast way, has been used and refined by a continuously increasing number of authors to estimate the consumption of a large variety of illicit drugs in many different geographic areas (Andrés-Costa et al., 2014; Baker et al., 2014; Castiglioni et al., 2006; Gatidou et al., 2016; Karolak et al., 2010; Khan et al., 2014; Kim et al., 2015; Klupczynska et al., 2016; Postigo et al., 2010, 2011; van Nuijs et al., 2011a,b).

The WBE approach relies on the fact that, after consumption, the drugs themselves and/or their metabolites are excreted via urine and feces, and subsequently collected and pooled by the sewage systems that carry them to WWTPs. Then, concentrations of these substances are measured in the water entering WWTPs and used to back-calculate drug consumption figures in the area served by the investigated WWTPs in kg/day, doses/day, kg/day/1000 inhabitants (inh.) or doses/day/1000 inh. Besides DTR concentrations in the WWTP influent, additional information such as the flow entering the WWTP during the sampling event, the metabolic excretion rate of the monitored DTR, and the population served by the WWTP are also required to back-calculate drug use by means of the WBE approach (van Nuijs et al., 2011a).

The present study aimed at estimating the consumption of various psychoactive illicit and legal drugs in Barcelona through a WBE approach and assessing weekly patterns of consumption and drug use trends in the investigated area over the past few years. To do this, a total of 19 compounds including various selected illicit drugs and metabolites and psychoactive pharmaceuticals were daily measured during one week for five consecutive years (2011–2015) at the inlet of a WWTP that receives most of the wastewater produced in Barcelona and its metropolitan area.

## 2. Materials and methods

### 2.1. Reagents and materials

High purity standard solutions (>97%) for the 19 selected analytes and corresponding isotopically labelled analogues, used as surrogate standards (SS), were purchased from Cerilliant (Round Rock, TX, U.S.) as solutions in methanol (MeOH) or acetonitrile (ACN) at a concentration of 1 mg/mL or 100 μg/mL. Drugs and metabolites selected for analysis belong to different chemical classes and the list includes the cocainic compounds cocaine (COC), benzoylecgonine (BE) (the major metabolite of COC) and cocaethylene (CE) (metabolite formed when cocaine and ethanol are simultaneously consumed); the amphetamine-type stimulants (ATS) amphetamine (AM), methamphetamine (MA), 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) and ephedrine (EPH); the hallucinogenic substance lysergic acid diethylamide (LSD) and its metabolite 2-oxo-3-hydroxy-LSD (OH-LSD); the opioids/opiates morphine (MOR), heroin (HER), 6-acetylmorphine (6ACM) (metabolite of HER), methadone (METH) and 2-ethylidene-1,5-dimethyl-3, 3-diphenylpyrrolidine (EDDP) (metabolite of METH); the cannabinoids $\Delta^9$-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-THC (THC-COOH) (metabolite of THC); the benzodiazepines alprazolam (ALP), and diazepam (DIA); and ethyl sulfate (Et-S) (minor but stable urinary human metabolite of ethanol (alcohol) (Mastroianni et al., 2014)).

Working standard solutions containing the target analytes and the corresponding SS were prepared at different concentrations by appropriate dilution of the individual stock solutions (100 μg/L) in methanol (MeOH), and stored in the dark at −20 °C until use. These solutions were used to construct calibration curves. In the case of illicit drugs and benzodiazepines analysis, calibration standards were freshly prepared by 1000-fold dilution of each working standard solution (0.1–2000 μg/L of each target analyte and a constant concentration of SS, i.e., 20 μg/L for CE-$d_3$, AM-$d_5$, MA-$d_{14}$, MDMA-$d_5$, LSD-$d_3$, HER-$d_9$, 6ACM-$d_6$, ALP-$d_5$, and DIA-$d_3$ and 50 μg/L for the remaining isotopically labelled compounds) in HPLC-grade water. For Et-S analysis, calibration standards were freshly prepared by 100-fold dilution of the working Et-S solutions (10–20,000 μg/L with a constant concentration of ethyl-$d_5$ sulfate (Et-S-$d_5$) of 2500 μg/L) in HPLC-grade water.

All solvents used were from J.T. Baker (Serviquimia, Barcelona) and were HPLC grade. Formic acid (>98%) was purchased from Merck (Darmstadt, Germany), and ammonium formate (>99%), dibutylamine (>99.5%) and ammonium acetate (≥98%) were supplied by Sigma-Aldrich (Steinheim, Germany). These chemicals were used as mobile phase modifiers.