Wastewater-based epidemiology for illicit drugs

A critical review on global data

Huizer, M.; ter Laak, T.L.; de Voogt, P.; van Wezel, A.P.

DOI
10.1016/j.watres.2021.117789

Publication date
2021

Document Version
Final published version

Published in
Water Research

Water Research 207 (2021) 117789

Contents lists available at ScienceDirect

Water Research

journal homepage: www.elsevier.com/locate/watres

Review

Wastewater-based epidemiology for illicit drugs: A critical review on global data

Marit Huizer [a,*], Thomas L. ter Laak [a,b], Pim de Voogt [a,b], Annemarie P. van Wezel [a]

[a] Institute for Biodiversity and Ecosystem Dynamics (IBED), University of Amsterdam, Amsterdam, the Netherlands
[b] KWR, Nieuwegein, the Netherlands

ARTICLE INFO

Keywords:
Wastewater-based epidemiology
Illicit drugs
MDMA
Cocaine
Amphetamine
Methamphetamine

ABSTRACT

Illicit drug use is complex, hidden and often highly stigmatized behaviour, which brings a vast challenge for drug surveillance systems. Drug consumption can be estimated by measuring human excretion products in untreated wastewater, known as wastewater-based epidemiology (WBE). Over the last decade, the application of wastewater-based epidemiology to monitor illicit drug loads increased and WBE is currently applied on a global scale. Studies from over the globe are evaluated with regard to their sampling method, analytical accuracy and consumption calculation, aiming to further reduce relevant uncertainties in order to make reliable comparisons on a global level. Only a limited number is identified as high-quality studies, so further standardization of the WBE approach for illicit drugs is desired especially with regard to the sampling methodology. Only a fraction of the reviewed papers explicitly reports uncertainty ranges for their consumption data. Studies which had the highest reliability are recently published, indicating an improvement in reporting WBE data. Until now, WBE has not been used in large parts of Africa, nor in the Middle East and Russia. An overview of consumption data across the continents on commonly studied drugs (cocaine, MDMA, amphetamine and methamphetamine) is provided. Overall, high consumption rates are confirmed in the US, especially for cocaine and methamphetamine, while relatively low illicit drug consumption is reported in Asia.

1. Introduction

Illicit drug use is complex, hidden and often highly stigmatized behaviour, which brings a vast challenge for drug surveillance systems. The traditional way of monitoring illicit drug use is through population surveys, consumer interviews and police seizures. These methods yield qualitative data and provide useful information such as age, sex, behaviour and the mode of use (ingestion, injection or inhalation). However, due to several limitations such as self-report bias and limited population coverage, survey-based results have difficulties in reflecting detailed spatial and temporal differences of illicit drug use. To get access to quantitative data, the human metabolic excretion products resulting from drug consumption can be measured in untreated wastewater. The measured parent compound or metabolite can be used to calculate the daily mass loads entering a wastewater treatment plant (WWTP) for these compounds. With the knowledge of human drug metabolism and excretion rates, together with in-sewer transformation rates, the relation to consumption (g/day) can be calculated from these mass loads. When dividing this by the served population at the point of measurement in the sewage system, the amount of illicit drugs consumed in g/day/inhabitant can be estimated allowing for comparisons between locations (van Nuijs et al., 2020). While this approach provides no knowledge about the behaviour of single users, it is useful for identifying the spectrum of substance use for a population serving a particular WWTP. This approach provides near real-time information for a specific city or region and gives insight about temporal trends. It is also a promising tool to estimate the illicit drug market size. Together with survey-based monitoring, wastewater-based epidemiology (WBE) can evaluate drugs abuse more comprehensively and potentially support governments in developing policies to scale down drug abuse (Lai et al., 2016).

Using WBE to detect illicit drugs was first introduced by Daughton et al. in 2001 (Daughton, 2001) and first applied by Zuccato et al. (Zuccato et al., 2005) in 2005 to monitor cocaine use and track trends in local illicit drug use in Italy. In 2012 the first international assessment in 19 European cities was published by Thomas et al. (Thomas et al., 2012). A paper discussing the uncertainties within the WBE approach has been published in 2013 by Castiglioni et al. (Castiglioni et al., 2013) and a global overview of results was presented by Feng et al. (Feng et al.,

* Corresponding author.
E-mail address: marithuizer@hotmail.com (M. Huizer).

https://doi.org/10.1016/j.watres.2021.117789
Received 24 February 2021; Received in revised form 30 September 2021; Accepted 16 October 2021
Available online 21 October 2021

2018) covering publications between 2005 and 2017. WBE has shown to be an innovative and promising tool, and sophisticated methodologies have been published for measuring a great variety of illicit drugs (Choi et al., 2018; F. Hernández et al., 2019; F. Hernández et al., 2018)

Despite the fact that WBE provides an evidence-based estimation on illicit drug use for a specific population, it brings a number of uncertainties related to the sampling methodology, the analytical procedure and the consumption calculation (Castiglioni et al., 2013; Zheng et al., 2019). One of the main challenges in WBE is reducing the uncertainty for each of these variables in order to make respectable comparisons on an international level.

Synchronising wastewater sampling and analysis will allow more accurate data (O'Brien et al., 2019). The European network of sewage analysis, Sewage analysis CORe group Europe (SCORE) coordinates and ensures quality control in international WBE studies. This way, research can be done with the same validated methods, which makes results robust and comparable. Data on illicit drugs collected under SCORE supervision is therefore used annually by the European Monitoring center for Drug and Drug Addiction (EMCDDA) (González-Mariño et al., 2020). Wastewater is an important source of public health information and can be applied in many fields of expertise, like for diet and nutrition, pesticide use, public health and doping, and currently it is used to monitor the SARS-CoV-2 virus (Bivins et al., 2020).

The present paper first investigates the potential and reliability of WBE methodologies by critically looking at the literature published in the last decade. The key areas that are evaluated to determine the reliability are; the sampling methodology, the analytical accuracy and the consumption estimation, and overall reliability scores are considered. Then, an overview of consumption data on the most commonly studied drugs (cocaine, MDMA, amphetamine and methamphetamine) is provided, evaluating spatial trends. European-wide studies are frequently published and discussed (Castrignanò et al., 2018; Krizman-matasic et al., 2019; Ort et al., 2014; Thomas et al., 2012), but here we provide the first overview on a global scale, based on a large number of data from published literature on intercontinental level. Finally, suggestions to further improve future WBE studies are provided.

2. Methods

2.1. Literature search

One hundred and ten studies reporting on wastewater-based epidemiology of illicit drugs were extracted from the Scopus database and reviewed systematically (Haddaway et al., 2017, 2015; Xiao and Watson, 2019). Used search strings were 'wastewater-based epidemiology' or 'sewage epidemiology' and 'illicit drug' or 'drugs of abuse' in studies published between 2010 and 2020. Export data were filtered based on relevance; reports that did not provide new data, concerned only new psychoactive substances (NPS), did not calculate the drug consumption, or were not representative for the community, were removed (S.I.1). Searches were performed until March 2020. Fifty-two papers are included and reviewed on the estimated drug consumption and the overall reliability of the methodology.

2.2. Assessment of method reliability

The reliability of the selected papers was assessed based on factors introducing uncertainties as described by (Ort et al., 2010a; van Nuijs et al., 2018; Feng et al., 2018; Castiglioni et al., 2013) and (Fernández de Córdova and Medina, 2014). The studies are reviewed with regard to their sampling uncertainty, analytical accuracy and the consumption estimation. Each of the three main criteria was assessed based on specific sub-criteria (Table 1).

For each sub-criterion, a value of 2, 1 or 0 is assigned, which indicates the reliability of each aspect with a maximum of 6 for the sampling uncertainty, a maximum of 10 for the analytical accuracy and a maximum of 6 for the consumption estimation. The overall reliability score per study has a maximum of 22. When no information is reported in the reviewed literature for a specific criterion, '0' will always be assigned. Table 2 lists the cut-off per sub-criterion, which is further explained and justified per sub-criterion in the sections below.

Table 1
Main criteria including sub-criteria to assess the quality of WBE papers. Sub-criteria that have a larger weight in the scoring system are underlined.

Sampling uncertainty (Max 6)	Analytical accuracy (Max 10)	Consumption estimation (Max 6)
Mode of sampling	Detection technique	Stability of the drug
Sample Volume	Analytical Conditions	Metabolites
Long term variations	LOD/LOQ	Equation
Short term variations	Replicates	Population estimation
	Positive control samples	Reporting measured concentrations
	Negative control samples	
	Internal standards	

2.3. Comparison of international drug consumption

The selected fifty-two papers were reviewed on drug consumption. Median consumptions of cocaine, amphetamine, methamphetamine, and MDMA were used to compare consumption on an intercontinental scale.

3. Results and discussion

3.1. Reliability of methods

In this study, the reliability of literature on WBE and illicit drugs published in the last decade is critically reviewed with regard to the sampling uncertainty, analytical accuracy and consumption estimations. Over all 52 papers that are evaluated, the mean score of the studies is 14.3 out of a maximum of 22, ranging from 10 to 18 (Table 3). According to the criteria used in this study, especially with regard to the sampling and its description there are major possibilities for further improvement. Fig. 1 shows the percentages of studies with a positive score per sub-criterion, further details on assigned points per sub-criterion per study can be found in S.I.2.

3.1.1. Sampling uncertainty

3.1.1.1. Long- and short-term variations. Sampling can be a dominant source of uncertainty for the determination of illicit drugs in wastewater as both short-term variations such as diurnal patterns in consumption and human behaviour, festivals or rainfall, and long-term variations such as week-weekend and seasonal changes do occur (Ort et al., 2010, 2010a). Extreme weather changes and human behaviour will change the daily flow of wastewater to a WWTP and therefore will cause variability and dilution (Banta-Green et al., 2016; Ort et al., 2010, 2010a). The concentration of the analyte is also highly dependant on the season, due to wet and dry weather conditions (Loraine and Pettigrove, 2006). However, these sporadically extreme weather (short-term) events do not give the same uncertainty as (long-term) seasonal changes, which are more constant.

The concentration of illicit drugs can increase significantly during special events and during the weekends (Bijlsma et al., 2014; Foppe et al., 2018). This brings variability in human behaviour when it comes to drug consumption and will bias the overall consumption of a certain community. A similar bias applies to work-commuters and tourists who only take part a community for a certain amount of time. Therefore, these are important factors regarding the uncertainty (Foppe et al., 2018).

Table 2
Cut-off for assigning '1' or '0' for each sub-criterion, when no information is reported '0' will be assigned as indicated with *.

Sub-criterion	Assigned 2	Assigned 1	Assigned 0
Mode of sampling	Flow-proportional sampling mode is applied	Volume- or time-proportional sampling is applied	Grab samples are used
Sample volume		Sample volume is ≥1 L	Sample volume <1 L
Short term variations		Conditions during the sampling are reported regarding short term variations (diurnal patterns in consumption, human behaviour, festivals and rainfall)	*
Long term variations		Conditions during the sampling are reported regarding long term variations (week-weekend & seasonal variations)	*
Detection technique	High resolution mass spectrometry identification (MS/MS, QTOF, Triple Quadrupole, Orbitrap)		Not using mass spectrometry (i.e. UV-detection)
Analytical Conditions		Analytical conditions are described in detail or referring to other paper where described in detail.	
LOD/LOQ	Average concentrations are <10 times the LOD or LOQ		Average concentrations are >10 times the LOD or LOQ
Replicates		Number of replicates is reported ≥ 3	< 2
Positive control samples		Representative replicated positive controls are reported, concentration and purity of standards used is reported	The purity/concentration of the positive standard is not specified, or positive controls are lacking
Negative control samples		Clearly indicated that actual sample results are corrected for blanks	*
Internal standards	Use of isotopic labelled internal standard		Internal standard is not isotopic labelled
Stability of the drug		Correction factors on stability are used during consumption calculation	*
Metabolites		Metabolites are measured and applied in consumption calculation	*
Equation		Consumption calculation is described explicitly	Parameters in equation are not explained
Population estimation	Estimation of population is reported per individual WWTP and estimation-method for population is explained	Estimation of population is reported per individual WWTP	Population is reported for a country, or for multiple WWTPs serving a region
Reporting measured concentrations		Measured concentrations before calculation are reported in paper or supplementary data	*

In general, long-term variations are commonly reported (68%) whereas short term variations are reported in only 39% of the papers. This was expected because long-term variations are easier to track since these are more constant factors. To give a reliable estimate of illicit drug use by the local community, preferably measurements should be performed during a 'normal week'.

3.1.1.2. Mode of sampling. The systematic sampling error depends on the sampling mode. The use of 24-hour composite sampling is most common in WBE. Composite sampling has a clear advantage over grab sampling with respect to local heterogeneity (Minkkinen and Esbensen, 2009). As influent flow and composition may vary significantly over the timespan of sampling, composite sampling can be challenging (Feng et al., 2018; Ort et al., 2010b). Composite sampling can be performed by three approaches, i.e., flow-proportional, volume-proportional, or time-proportional. Flow-proportional composite sampling takes a subsample volume proportional to the flow in the sewer at a constant time interval, subsamples are weighted individually to form a composite sample. Volume-proportional sampling takes samples more frequently during higher flows and less frequently during lower flows, the sampling volume remains constant. However, this cannot provide a true average concentration since only the frequency changes and individual samples are not weighted properly according to the flow in the sewer. In time proportional sampling both frequency and sampling volume are constant and therefore does not provide a true average concentration as well. The flow-proportional mode of sampling is regarded as most reliable choice for data on illicit drug consumption and is favoured over time- and volume proportional sampling because subsamples are weighted individually. (Ort et al., 2010, 2010a).

The majority of reviewed papers use 24 h composite influent samples, while several studies used grab samples (Banta-Green et al., 2016; Feng et al., 2018; Fernández de Córdova and Medina, 2014; Ort et al., 2010, 2010a; van Nuijs et al., 2018). Whether the composite samples are volume-proportional, flow-proportional or time-proportional is not always reported. When a detailed description of the sampling methodology is specified, flow-proportional is most prevalent. In total, only 21% of the papers specify the use of flow-proportional composite sampling. Thus, lack of (description of) use of flow-proportional composite sampling importantly contributes to sampling uncertainty.

3.1.1.3. Sample volume. Low sample volumes reduce the power of a study and will increase error (Einax, 2004; Koelmans et al., 2019). Detection limits benefit from large sample volumes as extracts can reach high concentration factors. Because of the relatively low concentration of certain excreted illicit drugs in wastewater. Most common illicit drugs (cocaine, amphetamines) will be present in wastewater with relatively high concentrations but for NPS the concentration can be much lower, and therefore a larger sample volume is required. A total sample volume of 1 L for influent is considered sufficient (Ort et al., 2010). Subsamples can be taken for sample preparation and chemical analysis.

More than half (58%) of the studies do not report on sample size or do not meet the requirement of collecting 1 L influent. Publishing full information regarding detailed sampling methodologies is crucial to interpret the obtained results. Together with the long- and short-term variations, the sample size was often not reported and therefore a factor in reducing the sampling uncertainty of these methods.

3.1.2. Analytical accuracy

3.1.2.1. Identification technique. Analytical uncertainty is commonly well specified in WBE studies (Ort et al., 2010a). The fact that most illicit drugs are of medium to high polarity makes LC-MS/MS the most attractive method for their identification and quantification. All papers report a sophisticated analytical method; analytical technique is described in 100% of the studies, and in 98% of the studies the technique of choice is liquid chromatography coupled to mass spectrometry (LC-MS) or tandem mass spectrometry (LC-MS/MS). One exception is analysing methamphetamine using gas chromatography coupled to mass spectrometry as the main analytical tool (GC–MS/MS) (Wang et al., 2019). LC-MS/MS is commonly used to investigate pharmaceuticals and

Table 3
Overview of individual and total scores of papers reporting illicit drug concentrations using a wastewater-based epidemiology approach.

Study	Country	Sampling uncertainty (max 6)	Analytical accuracy (max 10)	Consumption estimation (max 6)	Overall reliability of method (max 22)
Postigo et al., 2010	Spain	1	8	5	14
Terzic et al., 2010	Croatia	2	8	5	15
Karolak et al., 2010	France	5	8	2	15
van Nuijs et al., 2011	Belgium	3	7	5	15
Harman et al., 2011	Norway	3	8	2	13
Irvine et al., 2011	Australia	4	7	4	15
Baker et al., 2012	Czech Republic	1	8	4	13
Nefau et al., 2013	France	4	7	4	15
Khan et al., 2014	China	1	8	4	13
Devault et al., 2014	Martinique	4	7	5	16
Baker et al., 2014	UK	3	7	4	14
Mackuľak et al., 2014	Slovakia	3	8	2	13
Kankaanpää et al., 2014	Finland	2	6	3	11
Östman et al., 2014	Sweden	2	10	4	16
Reid et al., 2014	Norway	1	10	5	16
Andres-Costa et al., 2014	Spain	2	8	3	13
Nowicki et al., 2014	Poland	1	6	4	11
Subedi and Kannan, 2014	USA	1	9	5	15
Yong et al., 2015	South-Korea	3	9	3	15
Rodríguez-álvarez et al., 2015	Spain & Italy	3	8	5	16
Palardy et al., 2015	Canada	2	6	2	10
Baz-lomba et al., 2016	European countries	3	6	3	12
Kankaanpää et al., 2016	Finland	3	8	3	14
Krizman et al., 2016	Croatia	3	8	4	15
Mackul'ak et al., 2016	Slovakia & Czechia	4	8	4	16
Klupczynska et al., 2016	Poland	2	8	3	13
Bodík et al., 2016	Slovakia	4	6	2	12
Lai et al., 2016	Australia	2	8	4	14
Bijlsma et al., 2016	Colombia	2	8	5	15
Causanilles et al., 2017	Costa Rica	2	7	4	13
Mastroianni et al., 2017	Spain	4	9	4	17
F. Sodré et al., 2017	Brazil	3	9	4	16
Archer et al., 2018	South-Africa	3	7	5	15
Nguyen et al., 2018	Vietnam	1	9	5	15
F. F. Sodré et al., 2018	Brazil	3	8	3	14
Castrignanò et al., 2018	European countries	4	9	3	16
Löve et al., 2018	Scandinavia	4	8	3	15
Cosenza et al., 2018	Italy	1	9	4	14
Skees et al., 2018	USA	2	10	5	17
Foppe et al., 2018	USA	4	9	5	18
Y. X. Zhang et al., 2019	China	2	7	4	13
Mercan et al., 2019	Turkey	2	9	4	15
Daglioglu et al., 2019	Turkey	4	7	4	15
Y. X. Zhang et al., 2019	China	3	8	4	15
Kumar et al., 2019	New Zealand	3	7	5	15
Mariño et al., 2019	Brazil & Spain	2	9	2	13
Fallati et al., 2020	Maldives	3	8	3	14
Deng et al., 2020	China	2	10	3	15
Du et al., 2020	Malaysia	2	9	5	16
Shao et al., 2020	China	2	9	5	16
Croft et al., 2020	USA	2	7	4	13
Kim and Oh, 2020	South-Korea	4	8	3	15
Average					
Minimum		**2.6**			
Maximum					
1					
5	**7.9**				
4					
10	**3.8**				
2					
6	**14.3**				
10					
18					

their metabolites because of the robustness and excellent reproducibility (van Nuijs et al., 2011; Zheng et al., 2019), and therefore also a favoured technique to measure concentrations of illicit drugs. Triple quadrupole mass analysers are used most and considered the reference technique to quantify illicit drugs and their metabolites (Hernández et al., 2018). This technique is both sensitive and suitable for quantitative analysis, and selective for identification, and an excellent tool for targeted analysis. New methodologies are expected to increase in the coming years, e.g., based on mixed-mode liquid chromatography–tandem mass spectrometry (Koelmans et al., 2019), or high-resolution mass spectrometers such as orbitrap and time-of-flight (QTOF) analysers in combination with ultra-high-performance chromatography (UHPLC), which are more suitable for untargeted/suspect screening. Combined, these techniques will enhance the sensitivity of the overall method (Baz-lomba, Reid, and Thomas, 2016).

3.1.2.2. Analytical conditions. Specification of the analytical conditions is crucial to make a reliable estimation of the accuracy. The polar/ionic analytes require specific chromatographic separation. Separation modes are usually reversed phase (RP) chromatography and hydrophilic interaction liquid chromatography (HILIC). In RP, a hydrophobic stationary phase is used for retention and a mobile phase consisting of a mixture of organic modifier and a water phase for elution. In HILIC, the analytical column is polar combined with a highly organic mobile phase in which water is introduced as the eluting solvent. The most commonly reported detection technique is mass spectrometry (MS) with electrospray ionisation (ESI). All studies report the analytical methodology used, either in the report, supplementary data or referring to previous work. Analytical conditions are reported in more detail compared to the sampling methodologies. All studies provided a detailed description of the analytical conditions. This can be related to quality control protocols which are well-developed (Krizman-matasic et al., 2019) and the fact that the analytical conditions are easier to control for researches.

3.1.2.3. Method validation (Internal standards, replicates, positive- and negative controls). Prior to application, the analytical methodology needs to be completely validated for all analytes in terms of trueness/accuracy (evaluated by recovery experiments) and precision (as repeatability), selectivity/specificity, and limits of detection (LOD) and quantification (LOQ) (Hernández et al., 2018). A drawback in this field is the lack of guidelines specifically directed toward the analysis of illicit drugs and their metabolites in wastewater (Hernández et al., 2018).

In ESI, ion suppression is a major issue due to the co-eluting matrix constituents of raw wastewater (van Nuijs et al., 2011; Zheng et al., 2019) resulting in a decrease in sensitivity and unacceptable errors in quantification. Matrix effects can be corrected using isotopic labelled internal standards (ILIS), which are commercially available for most common illicit drugs and their metabolites (van Nuijs et al., 2011; Zheng et al., 2019). During method validation, there is an absolute need to thoroughly evaluate if the labelled IS accurately corrects for matrix effects (Hernández et al., 2018). Indeed, 98% of all studies report the use of isotopic labelled internal standards.

When two or more samples from the same sampling location and time carried through identical analytical steps are investigated, the variance of the total method can be assessed. To examine the reproducibility of the analytical method including a standard deviation, a minimum number of three samples is required. Only 35% of the reviewed studies reported on analysing in triplicates.

Positive and negative control samples are commonly used in analytical chemistry and described in almost all quality control protocols. To verify quantitative recoveries during sample collection and preparation and the analytical measurement procedure, representative positive control samples should be analysed. To correct an analytical method for contaminations during sample collection, preparation and the analytical identification procedure, blanks should be analysed.

54% of the reviewed studies reported on positive controls, whilst the use of blanks was reported for 44% papers. The low percentages in these categories might be explained by poor reporting.

3.1.2.3. LOD/LOQ. The limit of detection (LOD) and limit of quantification (LOQ) indicate the capability to reliably and sensitively detect and/or quantify an analyse. Reckoning of LODs and LOQs is usually performed based on a signal-to-noise (s/n) ratio of 1:3 and 1:10, respectively (Hernández et al., 2018). Estimating LODs and LOQs in wastewater is difficult regarding the notable variations in chemical composition (Hernández et al., 2018). For a reliable analysis, the analyte should be at least 10 times the LOD or LOQ for a sufficient sensitivity. In recent years, the low LOD and LOQs reported are mostly due to modern highly sensitive techniques that are, as mentioned in previous paragraphs, used in all reviewed studies. 81% of the studies reviewed report LOD and LOQ values that are sufficient to analyse illicit drugs and their metabolites.

3.1.3. Consumption estimation

The relation between known amounts consumed by the population and the consumption as estimated from concentrations of drug residues and metabolites measured in wastewater is well described for a number of pharmaceuticals (Heberer and Feldmann, 2005; Lindberg et al., 2007; Zuccato et al., 2008). The reliability of the consumption estimate can be evaluated when the original measured concentrations of the drug and/or metabolite in the influent are reported. Comparing data amongst studies using different calculation methods based on other approaches or equations is then feasible. For 58% of the reviewed papers, the measured influent concentrations are reported. Other important aspects to reliably estimate consumption are the stability of the molecules in wastewater, the measurement of parent compounds and/or metabolites, the population estimated being served by a WWTP and the exact equation used for the calculation of consumption.

3.1.3.1. Consumption calculation & metabolites. The reliability of calculation of drug use depends on the selection of an appropriate drug target residue (DTR), which can be either the illicit drug itself or one of its metabolites. Due to the stability of the drugs in wastewater and human metabolism/excretion, it can be necessary to base consumption estimates upon metabolites. For example, the parent compound of cocaine is excreted in urine only for 1–9% of the original intake, while benzoylecgonine and ecgoninemethylester are excreted in urine for 35–54% and 32–49% of the parent compound intake (van Nuijs et al., 2011). The first formulas for the back calculation of 1) cocaine and 2) amphetamine-like stimulants were proposed by Zuccato et al. in 2008 based on the main excretion products. This could be summarized per DTR specifically as followed:

$$Consumption\left(\frac{mg}{day}\ per\ 1000inh\right) = Load\ of\ DTR\left(\frac{mg}{day}\ per\ 1000inh\right) * \frac{1}{Stability\ of\ DTR} * \frac{1}{Excretion\ of\ DTR} * \frac{MWdrug}{MWdtr}$$

Where, the excretion rate of the DTR is following the use of an illicit drug of interest; stability of DTR is the ratio of DTR concentration after

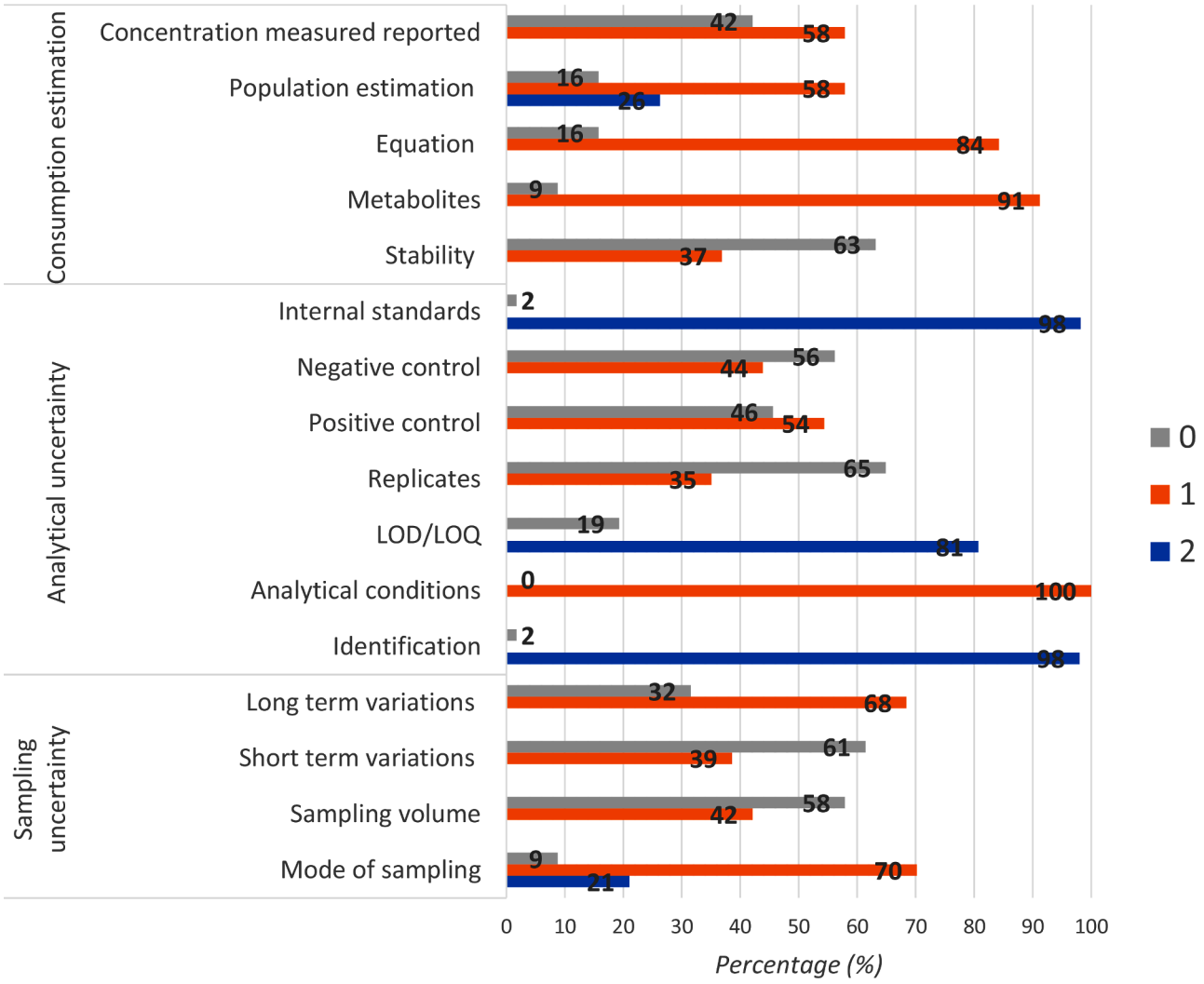

Fig. 1. Percentage of studies scoring '0' (grey), '1' (orange) or '2'(blue) per criterion.

in-sewer losses due to transformation and adsorption to biofilm/sewer sediment, and suspended solids to initial concentration. Biofilm and sewer sediment grow on sewer walls and can potentially change biomarkers due to chemical and microbial processes. This adds to the uncertainty of the back-estimation (Li et al., 2020).

MW Drug is the molecular weight of the drug of interest and MW DTR is the molecular weight of the DTR. However, accurate excretion rates of DTRs are not always available, due to the lack of pharmacokinetic data (Feng et al., 2018; Gracia-Lor et al., 2016), or are not determined for the applied administration route (snoring, ingestion or intravenous injection) or dose.

The equation used for the consumption estimation is in 16% of the reviewed studies not explained at all. From concentrations of the metabolite (ng/L), the flow rate (L/day) of the wastewater stream and a correction factor, parent compound loads (g/day) can be calculated. The correction factor is established based on the excretion rates and degradation in waste water for the parent drug and its metabolite (van Nuijs et al., 2011; Zuccato et al., 2008, 2005).

Amphetamine, methamphetamine and MDMA are excreted unchanged in urine up to 30, 43 and 65%, respectively (McCall et al., 2016; van Nuijs et al., 2011; Postigo et al., 2010; Zuccato et al., 2008) for cocaine, only 1–9% is excreted in urine unchanged (Gracia-Lor et al., 2016). Been et al. (Been et al., 2016) reported the estimated errors using Monte Carlo simulations resulting in excretion rates of 30.58% for benzoylecgonine (main metabolite of cocaine), 15.78% for MDMA, 29.12% for amphetamine and 28.56% for methamphetamine.

3.1.3.2. Stability. An important factor to estimate consumption is the stability of the excretion products in the sewer system (Daughton, 2001; Zuccato et al., 2008) (Zheng et al., 2019). Ignoring losses due to sorption/degradation of illicit drugs or the excreted metabolite in the sewer, and presumably microbial degradation of cocaine which results in the formation of BE may lead to a significant underestimation (A.K. Mccall et al., 2016; Thai et al., 2014; Zheng et al., 2019). Methamphetamine and MDMA have a relatively high stability (A. Mccall et al., 2016). Cocaine is unstable in wastewater, the degradation of cocaine could lead to benzoylecgonine, so by using benzoylecgonine as a DTR cocaine consumption could be overestimated. However, only 37% of the reviewed studies discuss sewer stability of the DTR and incorporated this in the consumption calculation.

3.1.3.3. Population estimation. An estimation of the population being served by a WWTP is a critical factor in the back calculation of drug consumption (Feng et al., 2018). Drug loads have to be normalized to the population in order to enable comparison of the data between different WWTPs. An accurate population estimate is challenging because the actual number of persons being served by a particulate WWTP might vary in time due to commuting, seasonal variability, holidays, and/ or special events (Feng et al., 2018; Lai et al., 2013). The determination of biological oxygen demand, chemical oxygen demand, total phosphorus

and nitrogen in wastewater or the measurement of a stable indicator of human metabolism have been proposed for the estimation of population served by the WWTP (van Nuijs et al., 2011; Castiglioni et al., 2013). Many of these parameters reflect human activities rather than the population size (Feng et al., 2018). Other sources such as industrial and commercial discharges may cause significant variability (Feng et al., 2018). Some studies based consumption as measured at a WWTP on the total population of the country, which is only applicable for countries with a small population like The Maldives (Fallati et al., 2020). In total, fifteen papers reported a rational estimation of the population, based on the amount of people serving a specific WWTP (Baker et al., 2012; Been et al., 2015; Bijlsma et al., 2016; Causanilles et al., 2017; Croft et al., 2020; Devault et al., 2014a; Klupczynska et al., 2016; Krizman et al., 2016; Kumar et al., 2019; Mercan et al., 2019; Reid and Thomas, 2014; Rodríguez-álvarez et al., 2015; Shao et al., 2020; X. X. Zhang et al., 2019; Y. Y. Zhang et al., 2019).

3.1.4. Critical perspective on the scoring system

The systematic scoring system approach described in this paper gives a general overview of the three main sources of uncertainty in WBE and how the literature from the last decade was dealing with these uncertainties. However, even though the criteria should be as independent as possible, some criteria might cross-affect each other. The scoring system does not correct for this issue. An example is that the sampling procedure (accurate measurement of the flow rate) affects the back-calculation, and the mode of sampling affects the sample volume uncertainty.

Another issue that is not recognized by the scoring system is the co-consumption of drugs in an area. This can affect universal correction factors based on urinary extraction.

For extreme weather events are less likely to occur in certain areas, this might explain why some papers lack information on the weather during sampling. Another potential cause of uncertainty is leakage or overflowing of the sewers since this could lead to underreporting. The scoring system did not take this into account. Another limitation of the score system is that no distinguishing is made between analyte-ILIS and non-analyte-ILIS, which is of great relevance for matrix effects correction and accurate quantification.

Some papers intentionally only show temporal trends and thus are not as dependant on the uncertainties as other reports. The scoring system does not correct for this, and these papers will most likely score lower due to underreporting, even though these uncertainties are not as applicable.

3.1.5. Overall reliability of methods

For each of the reviewed studies, quality criteria and the overall reliability is assessed (Table 3). None of the reviewed papers met the maximum achievable score of 22, one study had the highest score of 18 (Foppe et al., 2018) and two studies had the second-best score of 17 (Mastroianni et al., 2017; Skees et al., 2018). These studies were published in 2017 or later, indicating an improvement in the reporting on WBE approaches.

The average scores are 2.6/6 for the sampling method, 7.9/10 for the analytical accuracy and 3.8/6 for the consumption estimation, and 14.3/22 overall. Thus sampling uncertainty scored the poorest, in agreement with conclusions stated by Ort et al. (Ort et al., 2010a). There is inherent sampling variability due to weather variation, sporadic events, and fluctuating flowrates. Still, most studies fail to report sufficient details with respect to the sampling method. Sampling should be based on current knowledge, and not just be based on the available equipment (Ort et al., 2010). The analytical accuracy gave the best score. The analytical method can be controlled by researchers, whereas sample collection usually involves voluntary cooperation of treatment plant staff. For this reason, it was expected that this type of uncertainty would be reported in more detail and result in the best score.

3.2. International Drug consumption

In the last decade, the application of wastewater-based epidemiology to monitor illicit drug loads quickly increased, and the approach is currently applied on a global scale. Data on consumption of illicit drugs and their metabolites is reported for each continent except Antarctica. The variability of illicit drug consumption across the globe gives insight in substance abuse and can potentially assist health and law enforcement agencies to register and cut down drug related incidents and substance abuse (Lai et al., 2016). An overview of drug consumption per country from literature published over the last decade is shown in Table 4 for the four substances that are investigated most often. These studies evaluated illicit drug use patterns in urban and rural areas and investigated weekly patterns as well as use on specific events.

The highest number of WBE studies was conducted in Europe, from where we evaluated twenty-eight selected studies reporting in eighteen different countries (Table 4). Studies on a growing number of participating cities are now organized on yearly basis by SCORE and reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Therefore, also general time trends on illicit drug use in Europe are well reported based on a certain period of sampling each year. Nowadays around 70 cities are included in this project (EMCDDA, 2020). For these Europe-wide studies by the EMCDDA the protocol to monitor drug loads is fixed, and common quality control is used in all locations which makes true comparison possible. Overall reliability scores for European-wide studies are amongst the highest (Table 3). The consumption of cocaine is most abundant in western European cities, but a new increase in eastern European cities is also reported by the EMCDDA (EMCDDA, 2020). For amphetamine, highest levels are detected in north and eastern Europe and lower in southern Europe. Methamphetamine consumption is relatively low in Europe overall, with the exception of Slovakia. Since 2019, an increase has been reported by the EMCDDA in eastern Germany, Spain and Cyprus (EMCDDA, 2020). Consumption of MDMA is the highest in The Netherlands, Belgium and Germany, but consumption peaks are also observed in England and Scandinavia (González-Mariño et al., 2020) (Table 4).

The majority of the studies in Europe show an increase of drug use during weekends compared to weekdays, with an exception for methamphetamine (EMCDDA, 2020). These trends were also observed and reported by González-Mariño et al. (González-Mariño et al., 2020).

Within the USA, illicit drug use is a major concern (Foppe et al., 2018). The first study using the wastewater-based epidemiology approach in the USA was in 2009 (Banta-Green et al., 2009). More recent studies in the USA (Croft et al., 2020; Foppe et al., 2018; Skees et al., 2018; Subedi and Kannan, 2014) and Canada (Palardy et al., 2015) followed since then. Here, we evaluated five selected studies, reporting on five different states (Table 4). A high cocaine consumption was measured in New York, as well as for use of amphetamine and methamphetamine in urban and rural areas in the midwestern United States (Croft et al., 2020). A high methamphetamine concentration can affect the amphetamine concentration due to biotransformation, the data was corrected for this issue.

MDMA loads were low for urban areas and not detected in rural areas of the midwestern States, but higher in the state of New York. In Tennessee, reported consumption data of methamphetamine and amphetamine are higher than data from New York state and Kentucky, whereas the cocaine consumption was lower (Skees et al., 2018). Illicit drug use in the midwestern United States is measured during week with special events, showing significantly increased consumption during a festive week (Foppe et al., 2018).

Compared to Western countries, WBE is not as often applied in South America. We evaluated six selected studies, reporting on two different illicit drugs in four different countries (Table 4). WBE in South America has been applied in Brazil (Mariño et al., 2019; F. F. Sodré et al., 2018; F. Sodré et al., 2017), Colombia (Bijlsma et al., 2016), Costa Rica (Causanilles et al., 2017) and the island of Martinique (Devault et al., 2014b)

Table 4
Overview of drug consumption on a global scale (in mg/day/1000inhabitants).

Study	City	Country	Cocaine	Methamphetamine	MDMA	Amphetamine
Postigo et al., 2010		Spain	17.93		0.6	9.19
Terzic et al., 2010	Zagreb	Croatia	166		3.6	9.7
Karolak et al., 2010	Paris	France	645.0 to 979.3		7.2 to 15.4	
van Nuijs et al., 2011	Brussels	Belgium	519		13	76
Harman et al., 2011		Norway	20–70	400		190
Irvine et al., 2011	Regional	Australia	<LOQ-14	40	27	
	Metropolian	Australia	11.5	85.1	39.3	
Baker et al., 2012		Czech Republic	186	412	162	44
Nefau et al., 2013		France	111 −130		5 - 167	
Khan et al., 2014	Beijing	China	0.2–0.3	21.4	0.3	1.8–4
	Shanghai	China	0.2–0.3	35.5	0.2–0.4	5
	Guangzhou	China	0.2–0.3	121.7	0.5–1.9	21.9
	Shenzhen	China	0.2–0.3	21.7	0.6–1.5	3.7
Devault et al., 2014b	Fort de France	Martinique	976 ± 392			
Baker et al., 2014		UK	1263	17	148	86
Jaroslav et al., 2014	Petrzalka	Slovakia	69	169		
Kankaanpää et al., 2014		Finland	12	26	73	190
Östman et al., 2014		Sweden	0.1–2	1.0–32		10 - 140
Reid and Thomas, 2014	Oslo	Norway	14.7	117.3	5.9	
	Bergen	Norway	5.4	70.04		
	Hamar	Norway	1	39.39		
Andres-Costa et al., 2014	Valencia	Spain	11.1 – 13.7			70.8 – 13.5
Nowicki et al., 2014	Poznan	Poland	0.53	0.47	0.26	
Subedi and Kannan, 2014	New York	USA	807–1380	4.41–12.8	19.1- 85.6	175–312
Yong et al., 2015	Busan	South-Korea	1.2–11.4			
	Ulsan	South-Korea		2.1–15.1		
	Kimhae	South-Korea		14.8		
	Changwon	South-Korea		5.56		
	Milyang	South-Korea		29.2		
Rodríguez-álvarez et al., 2015	Milan	Italy	800			
	Santiago	Spain	632			
Palardy et al., 2015		Canada	36 - 53			
Baz-lomba et al., 2016	Oslo	Norway	151.5		37.7	294.7
	Castellon	Spain	463.9		5.4	0.8
	Brussels	Belgium	390.9		25.4	3.5
	Bristol	England	528.7		86.3	41.6
	Utrecht	The Netherlands	299.5	121.5	52.9	
	Milan	Italy	380.9		15.5	10.4
	Zurich	Switzerland	672.6		64.8	32
	Copenhagen	Denmark	337.2		53.1	11.7
Krizman et al., 2016		Croatia	2		8.3	13
Mackul'ak et al., 2016		Slovakia	77–126		3.0–11	2.0–57
		Czech Republic	1.0–3.0		0.6–2.9	8.0–21
Klupczynska et al., 2016		Poland	8.44	0.9	4.57	85.48
Bodík et al., 2016	Bratislava	Slovakia	74–112	146–165		
Yin et al., 2016	South East Queensland	Australia	416	1126	237	
Bijlsma et al., 2016	Bogota	Colombia	742		1.5	
	Medellin	Colombia	3022	4.4		47
Causanilles et al., 2017	El Roble	Costa Rica	2390 ± 520			
	Liberia	Costa Rica	1880 ± 395 to 2550 ± 536 mg			
Mastroianni et al., 2017	Barcelona	Spain	2400	157	188	90
F. Sodré et al., 2017	Brazilian Federal District	Brazil	777 ± 54			
Maida et al., 2017	Palermo	Italy	1900			
Archer et al., 2018	Johannesburg	South-Africa	155.8 to 263.8			
	181.9 to 532.5	2.2 and 4.9				
	Cape Town	South-Africa	342.0 to 533.0	675.0 to 1184.8	9.0 to 61.6	
Nguyen et al., 2018	Ho Chi Minh	Vietnam		170 −220		
F. F. Sodré et al., 2018	Brazilian Federal District	Brazil	777 ± 54			
Castrignanò et al., 2018	Oslo	Norway	172.4	37.7	122.3	
	Castellon	Spain			3.2	
	Brussels	Belgium		3.6	21.9	58.3
	Bristol	England		1.4	53.1	82.6
	Utrecht	The Netherlands			62	36.4
	Milan	Italy		10.3	6.8	10.3
	Zurich	Switzerland		20.2	43.5	29.3
	Copenhagen Denmark		6.6	32	76.5	
Löve et al., 2018	Helsinki	Finland	16.7	83.4	34.2	101
	Oslo	Norway	132	55.7	91	110

(continued on next page)

Table 4 (*continued*)

Study	City	Country	Cocaine	Methamphetamine	MDMA	Amphetamine
	Stockholm	Sweden	153	25.3	39.6	208
	Reykjavik	Iceland	136	32.6	51.5	217
	Torshavn	Faroe Islands		4.6		
Cosenza et al., 2018	Southern region	Italy	150 - 170			
Skees et al., 2018	Midwestern states	USA	938 ± 706	1740 ± 1190		967 ± 455
Foppe et al., 2018	Kentucky B	USA	434	1240	59	526
	Kentucky A	USA	1970	3090	1.72	919
Wang et al., 2019	Dalian	China	53.9			
Mercan et al., 2019	Istanbul - Beyoğlu	Turkey	754	449	632	46.1
	Istanbul - Çatalca	Turkey	15.6	195	29.3	8.38
Daglioglu et al., 2019		Turkey	14	2	87	8.7
X. X. Zhang et al., 2019	Guangzhou	China	0.9–9.5	14.7–470.7	1.7–18.4	
Kumar et al., 2019		New Zealand	94 ± 34	484 ± 73	16 ± 1	
Mariño et al., 2019	Brasília north	Brazil	997			
	Brasília south	Brazil	565			
	Santiago de Compostela	Spain	455			
Fallati et al., 2020	Male	Maldives	0.5	3	7.7	2.5
Deng et al., 2020	Changzhou	China	0.02±0.15	5.89±8.74	0.02–0.16	0.84±0.62
Du et al., 2020	Kuala Lumpur	Malaysia	9 - 4 to 14 ± 6	468 ± 64 to 687 ± 112	558 ± 373 to 850 ± 177	
Shao et al., 2020	Chongqing	China		328 ± 36		
	Chengdu	China		170 ± 1		
	Guiyang	China		249 ± 19		
	Changdu	China		99.7 ± 15.8		
	Kunming	China		133 ± 17		
	Dalian	China		55.7 ± 4.8		
	Harbin	China		96.5 ± 1.1		
	Changzhou	China		72.3 ± 25.2		
	Hefei	China		119 ± 3.5		
	Qingdao	China		162 ± 3		
	Jinan	China		68.6 ± 2.1		
	Weihai	China		159 ± 10		
	Beijing	China		88.6 ± 3.4		
	Huhehot	China		99.5 ± 0.7		
	Baoding	China		6402 ± 589		
	Zhengzhou	China		368 ± 11		
	Xiangtan	China		162 ± 8		
	Guangzhou	China		85.2 ± 9.8		
	Xi'an	China		37.6 ± 5		
	Lanzhou	China		229 ± 28		
	Dingxi	China		23.0 ± 2.6		
	Yinchuan	China		124 ± 13		
Croft et al., 2020	Kentucky Urban	USA	3830	1030		400
	Kentucky Rural	USA	864	1660		738
Kim and Oh, 2020	Busan	South-Korea		14.9 – 28.6		

to estimate the overall cocaine consumption for specific areas. Overall, cocaine consumption in South- and Central America is reported to be relatively high compared to Europe/globe, possibly related to the proximity to the production and the relatively high purity of street cocaine (Bijlsma et al., 2016).

During the last decade, the WBE approach became a more popular indicator for drug consumption in Asia. We evaluated thirteen selected studies, reporting on five different countries (Table 4). Studies from China (Khan et al., 2014; Jing Li et al., 2014; Shao et al., 2020), South-Korea (Kim and Oh, 2020; Yong et al., 2015), Vietnam (Nguyen et al., 2018), the Maldives (Fallati et al., 2020) and Malaysia (Du et al., 2020) have been published in the last decade. Four megacities in China (Beijing, Guangzhou, Shenzhen and Shanghai) show significantly lower drug consumption data compared to other continents (Khan et al., 2014). Where cocaine is a popular recreational drug in North- and South America and Europe, it is consumed much less in China. However, consumption of methamphetamine in China is relatively high. Methamphetamine use is concentrated in the centre of urban areas, indicating a relation with the availability to entertainment activities. Even higher methamphetamine rates are reported in Ho Chi Min, Vietnam and Kuala Lumpur, Malaysia (Table 4). Lower drug consumption is reported in South-Korea. During New Year's Day and Christmas day the methamphetamine no noticeable changes in consumption were observed. Consumption of MDMA and amphetamine is relatively low in China and South-Korea, but MDMA consumption for the Maldives and Malaysia is reported to be comparable to the high levels observed in northern Europe (i.e., The Netherlands, Belgium). The Maldives and Malaysia are popular holiday destinations which might explain why synthetic drugs are more popular in these places compared to the rest of Asia (Du et al., 2020), supported by the fact that drug consumption increases during the holiday season.

With regards to Australia, we evaluated four selected studies in three different states (Table 4). The first study that used WBE as a tool to estimate illicit drug use in Australia was in 2011(Irvine et al., 2011). Similar trends are observed as in Asia, the cocaine consumption is lower than consumption of methamphetamine, while consumption of MDMA is closer to European consumption data. MDMA and methamphetamine are more popular in rural areas whereas cocaine is more frequently used in urban areas. Noticeable is an increase in drug consumption during weekends for popular drugs such as cocaine, amphetamine, methamphetamine and MDMA. Daily illicit drug consumption on an annual music festival in Australia also shows an increase in MDMA compared to the data from a normal week (Lai et al., 2013). A large investigation is described on illicit use of cocaine, methamphetamine and MDMA (Lai et al., 2016), identifying an overall increase in illicit drug consumption in both metropolitan and rural communities over a six year period. In Australia, as in Western Europe, synthetic drugs are more popular. Levels similar to those in Australia of methamphetamine and cocaine

consumption are found in New Zealand (Kumar et al., 2019), although MDMA consumption is relatively low.

The application of WBE to monitor illicit drug use is still largely lacking in Africa. So far, only two WWTPs located in Johannesburg and Cape Town, South-Africa, have been monitored to estimate drug use patterns (Archer et al., 2018). Methamphetamine is the primary substance detected, at consumption data comparable to USA and Australia. Clandestine manufacturing of illicit methamphetamine results in dumping events of chemical waste, which could be traced via spikes including the precursors used in the production process observed at the WWTP in Johannesburg (Archer et al., 2018). Cocaine consumption is found to be similar to European consumption data, while consumption data for MDMA are low compared to Australia, the USA and Europe.

Fig. 2 illustrates the global consumption distribution for MDMA (purple), methamphetamine (blue), cocaine (red) and amphetamine (orange). So far, WBE has not been used to determine illicit drug consumption in most of the African continent, the Middle East and Russia

Overall, high consumption rates are found in the USA, especially for cocaine and methamphetamine (Fig. 3). For Asia, except for methamphetamine, lowest consumption is reported.

Cocaine production expressed as a percentage of the gross domestic product (GDP) is the highest for Colombia (2 to 3%) (INCB, 2002). while for the USA profits from drugs traffic are estimated to be 0.5% of GDP (INCB, 2002). Within Europe, the cocaine market is the second largest illicit drugs market with an estimated retail value of 9.1 billion euros in 2017 (EMCDDA and Europol, 2019). The total value for the retail market for illicit drugs in Europe was estimated at 30 billion euros in 2017 (EMCDDA and Europol, 2019). The consumption of synthetic drugs, such as amphetamine and MDMA, in Europe increased in the last decade, especially for the northern and eastern regions of Europe. Similar trends are observed in Europe's synthetic drug market, which has rapidly grown in the past ten years (EMCDDA and Europol, 2019). Large-scale production of MDMA and amphetamine remains concentrated in the Netherlands and Belgium, while production of methamphetamine is mainly concentrated in central Europe (EMCDDA and Europol, 2019). In Asia, drug consumption is relatively low compared to other continents. According to a report by the United Nations Office on Drugs and Crime (UNODC) in Asian regions, illicit drug production in Asia is increasing for amphetamine-like substances (Liu et al., 2013; UNODC, 2008). This is proportional to the increase in methamphetamine consumption in China and South-Korea.

The reported results should be viewed with an assured degree of uncertainty. Consumption values are frequently reported without calculated uncertainty values (Ort et al., 2010a). Only a handful of the reviewed papers (Causanilles et al., 2017; Deng et al., 2020; Devault et al., 2018; Du et al., 2020; Kumar et al., 2019; Shao et al., 2020; Skees et al., 2018; F. F. Sodré et al., 2018) explicitly reported on uncertainty values for their consumption data ($\pm xy$). The complete uncertainty assessment would include the sampling uncertainty, analytical uncertainty and the uncertainty for the consumption estimation as mentioned in the previous chapter. The trueness of the final consumption data should undergo a suitable statistical propagation. Various studies have used Monte Carlo analysis (Been et al., 2015; Croft et al., 2020; Jones et al., 2014; Shao et al., 2020; Y. Y. Zhang et al., 2019; Zheng et al., 2019) to calculate the uncertainties. Fig. 3 shows the distribution of all reviewed papers per drug for each continent including the reliability of the method used to obtain the data points. For many drug/continent combinations, the majority of the data fall within one order of magnitude.

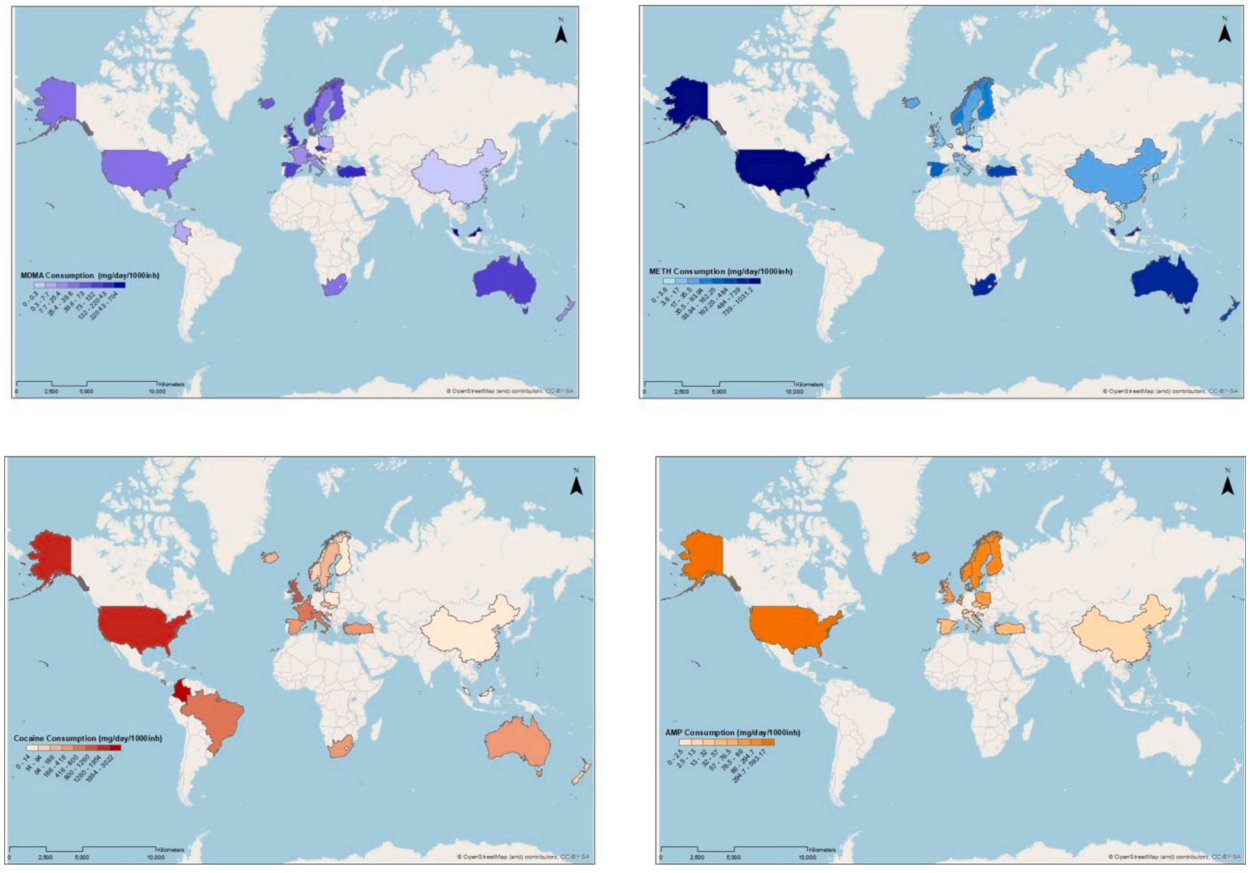

Fig. 2. : Average illicit drug consumption per country for MDMA (purple), methamphetamine (blue), cocaine (red) and amphetamine (orange) based on data published over the last decade.

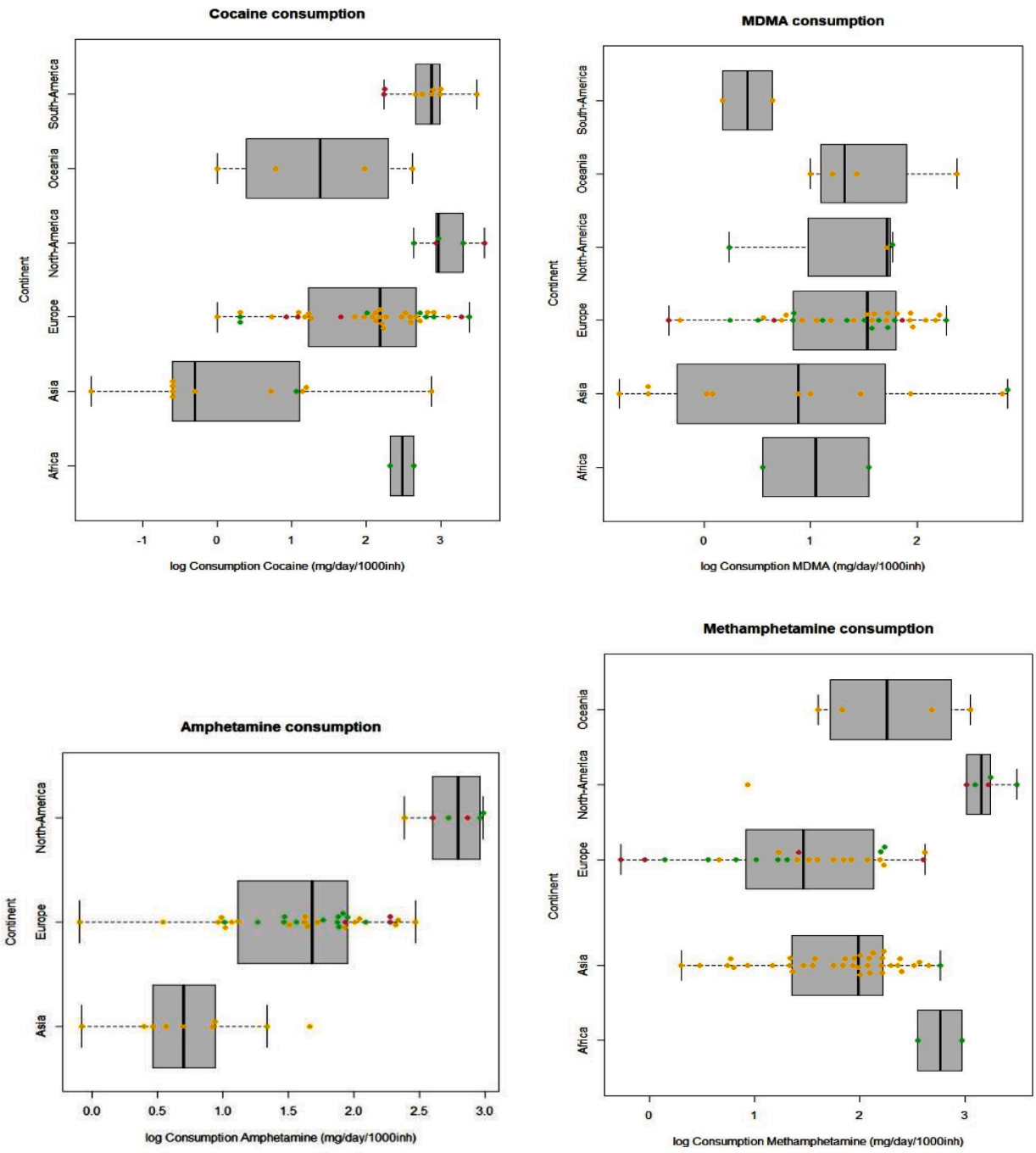

Fig. 3. Boxplots showing distributions in drug consumption (mg/day/1000inh) for cocaine, MDMA, amphetamine and methamphetamine. Individual data points per reviewed study are indicated via dots in red (low reliability score 10,11,12), yellow (medium reliability score 13,14,15) or green (high reliability score 16, 17 and 18).

4. Conclusion

Based on the relatively limited number of studies that could be identified as high quality, further advancement of the WBE approach for illicit drugs is desired especially with regards to the sampling methodology. However, studies carried out in Europe within the SCORE research group, have been using a systematic analytical approach, including annual interlaboratory exercises as an important factor in making data more comparable. Notable is that over the years, the analytical methodology is rapidly improving, and the implementation of high-resolution mass spectrometry techniques will allow more efficient methodologies for wide-scope screening, identification of untargeted/suspect compounds, or for the detection of metabolites and transformation products. Due to more advanced analytical approaches in the last decades, detection limits are decreasing and became less challenging when measuring low concentrations. Publishing full information regarding detailed sampling and analytical methodologies, even if only in the supplementary data, is crucial for the interpretation of obtained results. It will be necessary to harmonize the criteria for reliable identification/confirmation and accurate quantification of compounds detected in samples, reliable sampling, and less uncertainty in population estimation. This way, data collected from different laboratories in different parts of the world would become more comparable to each other and valid conclusions can be drawn on illicit drug consumption in

different communities on a global level.

This study provides an overview of the available literature, reporting data on drug consumption using the wastewater-based epidemiology approach. Overall, high consumption rates are found in the USA, especially for cocaine and methamphetamine consumption, while lowest illicit drug consumption is reported in Asia. These results agree with data reported by the EMCDDA (Europe) and the UNODC (other continents). The WBE approach can identify trends in consumption quickly which makes it extremely useful in generating data on illicit drug use.

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.

Acknowledgements

Ross O'Connell from University College Cork is acknowledged for his help with the maps, Sjoerd van der Bok from Avans University of Applied Sciences for his help with processing the statistical data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.watres.2021.117789.

References

Andres-Costa, M.J., Rubio-Lopez, N., Suarez-Varela, M.M., Pico, Y., 2014. Occurrence and removal of drugs of abuse in Wastewater Treatment Plants of Valencia (Spain) María Jesús Andr e. Environ. Pollut. 194, 152–162. https://doi.org/10.1016/j.envpol.2014.07.019.

Archer, E., Castrignanò, E., Kasprzyk-Hordern, B., Wolfaardt, G.M., 2018. Wastewater-based epidemiology and enantiomeric profiling for drugs of abuse in South African wastewaters. Sci. Total Environ. 625, 792–800. https://doi.org/10.1016/j.scitotenv.2017.12.269.

Baker, D.R., Barron, L., & Kasprzyk-hordern, B. (2014). Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part A : chemical analysis and drug use estimates. *Sci. Total Environ.*, 487, 629–641. 10.1016/j.scitotenv.2013.11.107.

Baker, D.R., Kvicalova, M., Kasprzyk-hordern, B., 2012. Drugs of abuse in wastewater and suspended particulate matter — further developments in sewage epidemiology. Environ. Int. 48, 28–38. https://doi.org/10.1016/j.envint.2012.06.014.

Banta-Green, C.J., Brewer, A.J., Ort, C., Helsel, D.R., Williams, J.R., Field, J.A., 2016. Using wastewater-based epidemiology to estimate drug consumption—statistical analyses and data presentation. Sci. Total Environ. 568, 856–863. https://doi.org/10.1016/j.scitotenv.2016.06.052.

Banta-Green, C.J., Field, J.A., Chiaia, A.C., Sudakin, D.L., Power, L., De Montigny, L., 2009. The spatial epidemiology of cocaine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) use: a demonstration using a population measure of community drug load derived from municipal wastewater. Addiction 104 (11), 1874–1880. https://doi.org/10.1111/j.1360-0443.2009.02678.x.

Baz-lomba, J.A., Reid, M.J., Thomas, K.V., 2016a. Target and suspect screening of psychoactive substances in sewage- based samples by UHPLC-QTOF. Anal. Chim. Acta 914 (0349), 81–90. https://doi.org/10.1016/j.aca.2016.01.056.

Baz-lomba, J.A., Salvatore, S., Gracia-lor, E., Bade, R., Castiglioni, S., Castrignanò, E., Thomas, K., 2016b. Comparison of pharmaceutical, illicit drug, alcohol, nicotine and caffeine levels in wastewater with sale, seizure and consumption data for 8 European cities. BMC Public Health 16 (1035), 1–11. https://doi.org/10.1186/s12889-016-3686-5.

Been, F., Benaglia, L., Lucia, S., Gervasoni, J., Esseiva, P., Delémont, O., 2015. Data triangulation in the context of opiods monitoring via wastewater analyses. Drug Alcohol Depend. 151, 203–210. https://doi.org/10.1016/j.drugalcdep.2015.03.022.

Been, F., Bijlsma, L., Benaglia, L., Berset, J.D., Botero-Coy, A.M., Castiglioni, S., Ort, C., 2016. Assessing geographical differences in illicit drug consumption-A comparison of results from epidemiological and wastewater data in germany and switzerland. Drug Alcohol Depend. 161, 189–199. https://doi.org/10.1016/j.drugalcdep.2016.02.002.

Bijlsma, L., Botero-coy, A.M., Rincón, R.J., Peñuela, G.A., Hernández, F., 2016. Estimation of illicit drug use in the main cities of Colombia by means of urban wastewater analysis. Sci. Total Environ. 565, 984–993. https://doi.org/10.1016/j.scitotenv.2016.05.078.

Bijlsma, L., Serrano, R., Ferrer, C., Tormos, I., Hernández, F., 2014. Occurrence and behavior of illicit drugs and metabolites in sewage water from the Spanish Mediterranean coast (Valencia region). Sci. Total Environ. 487, 703–709. https://doi.org/10.1016/j.scitotenv.2013.11.131.

Bivins, A., North, D., Ahmad, A., Ahmed, W., Alm, E., Been, F., Bibby, K., 2020. Wastewater-Based Epidemiology: global Collaborative to Maximize Contributions in the Fight Against COVID-19. Environ. Sci. Technol. 54 (13), 7754–7757. https://doi.org/10.1021/acs.est.0c02388.

Bodík, I., Fáberová, M., Ivanová, L., 2016. Occurrence of illicit drugs and selected pharmaceuticals in Slovak municipal wastewater. Environ. Sci. Pollution Res. 23, 21098–21105. https://doi.org/10.1007/s11356-016-7415-5.

Castiglioni, S., Bijlsma, L., Covaci, A., Emke, E., Hernández, F., Reid, M., Zuccato, E., 2013. Evaluation of uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers. Environ. Sci. Technol. 47 (3), 1452–1460. https://doi.org/10.1021/es302722f.

Castrignanò, E., Yang, Z., Bade, R., Baz-lomba, J.A., Castiglioni, S., Causanilles, A., Thomas, K.V., 2018. Enantiomeric pro fi ling of chiral illicit drugs in a pan-European study. Water Res. 130, 151–160. https://doi.org/10.1016/j.watres.2017.11.051.

Causanilles, A., Ruepert, C., Ibáñez, M., Emke, E., Hernández, F., de Voogt, P., 2017a. Occurrence and fate of illicit drugs and pharmaceuticals in wastewater from two wastewater treatment plants in Costa Rica. Sci. Total Environ. 599–600, 98–107. https://doi.org/10.1016/j.scitotenv.2017.04.202.

Causanilles, A., Ruepert, C., Ibáñez, M., Emke, E., Hernández, F., Voogt, P.De, 2017b. Science of the Total Environment Occurrence and fate of illicit drugs and pharmaceuticals in wastewater from two wastewater treatment plants in Costa Rica. Sci. Total Environ. 599–600, 98–107. https://doi.org/10.1016/j.scitotenv.2017.04.202.

Choi, P.M., Tscharke, B.J., Donner, E., O'Brien, J.W., Grant, S.C., Kaserzon, S.L., Mueller, J.F., 2018. Wastewater-based epidemiology biomarkers: past, present and future. Trends Anal. Chem. 105, 453–469. https://doi.org/10.1016/j.trac.2018.06.004.

Cosenza, A., Massimo, C., Piscionieri, D., Fanara, S., Di, F., Viviani, G., 2018. Occurrence of illicit drugs in two wastewater treatment plants in the South of Italy. Chemosphere 198, 377–385. https://doi.org/10.1016/j.chemosphere.2018.01.158.

Croft, T.L., Huffines, R.A., Pathak, M., Subedi, B., 2020. Prevalence of illicit and prescribed neuropsychiatric drugs in three communities in Kentucky using wastewater-based epidemiology and Monte Carlo simulation for the estimation of associated uncertainties. J. Hazard. Mater. 384 https://doi.org/10.1016/j.jhazmat.2019.121306. September 2019.

Daglioglu, N., Yavuz, E., Kilercioglu, S., 2019. Assessment of illicit drugs in wastewater and estimation of drugs of abuse in Adana Province, Turkey. Forensic Sci. Int. 294, 132–139. https://doi.org/10.1016/j.forsciint.2018.11.012.

Daughton, C.G. (2001). Illicit drugs in municipal sewage: proposed new nonintrusive tool to heighten public awareness of societal use of illicit-abused drugs and their potential for ecological consequences, 348–363.

Deng, Y., Guo, C., Zhang, H., Yin, X., Chen, L., Wu, D., Xu, J., 2020. Occurrence and removal of illicit drugs in different wastewater treatment plants with different treatment techniques. Environ. Sci. Europe 32 (28), 1–9. https://doi.org/10.1186/s12302-020-00304-x.

Devault, D.A., Maguet, H., Merle, S., Péné-annette, A., Lévi, Y., 2018. Wastewater-based epidemiology in low Human Development Index states : bias in consumption monitoring of illicit drugs. Environ. Sci. Pollution Res. 25 (28), 27819–27838.

Devault, D.A., Thomas, N., Hélène, P., Sara, K., & Yves, L. (2014a). First evaluation of illicit and licit drug consumption based on wastewater analysis in Fort de France urban area (Martinique, Caribbean), a transit area for drug smuggling. *Sci. Total Environ.*490, 970–978. 10.1016/j.scitotenv.2014.05.090.

Devault, D.A., Thomas, N., Hélène, P., Sara, K., Yves, L., 2014b. First evaluation of illicit and licit drug consumption based on wastewater analysis in Fort de France urban area (Martinique, Caribbean), a transit area for drug smuggling. Sci. Total Environ. 490, 970–978. https://doi.org/10.1016/j.scitotenv.2014.05.090.

Du, P., Liu, X., Zhong, G., Zhou, Z., Thomes, M.W., Lee, C.W., Li, X., 2020. Monitoring Consumption of Common Illicit Drugs in Kuala Lumpur, Malaysia, by Wastewater-Cased Epidemiology. Int. J. Environ. Res. Public Health 17 (889), 1–11.

Einax, J.W., 2004. Chemometrics in analytical chemistry. Anal. Bioanal. Chem. 380, 368–369. https://doi.org/10.1007/s00216-004-2792-x, 3 SPEC.ISS.

EMCDDA. (2020). *Wastewater Analysis and drugs : a European multi-City Study*. Lisbon.

EMCDDA, & Europol. (2019). *EU Drug Markets Report 2019*. 10.2810/53181.

Fallati, L., Castiglioni, S., Galli, P., Riva, F., Gracia-Lor, E., González-Mariño, I., Zuccato, E., 2020. Use of legal and illegal substances in Malé (Republic of Maldives) assessed by wastewater analysis. Sci. Total Environ. 698, 134207 https://doi.org/10.1016/j.scitotenv.2019.134207.

Feng, L., Zhang, W., Li, X., 2018. Monitoring of regional drug abuse through wastewater-based epidemiology—a critical review. Sci. China Earth Sci. 61 (3), 239–255. https://doi.org/10.1007/s11430-017-9129-x.

Fernández de Córdova, M.L., Medina, A.R., 2014. *Analytical Methods for Determination of Polyphenols in Beer. Processing and Impact on Antioxidants in Beverages*. Elsevier. https://doi.org/10.1016/B978-0-12-404738-9.00029-5.

Foppe, K.S., Hammond-weinberger, D.R., Subedi, B., 2018. Estimation of the consumption of illicit drugs during special events in two communities in Western Kentucky, USA using sewage epidemiology. Sci. Total Environ. 633, 249–256. https://doi.org/10.1016/j.scitotenv.2018.03.175.

González-Mariño, I., Baz-Lomba, J.A., Alygizakis, N.A., Andrés-Costa, M.J., Bade, R., Barron, L.P., Ort, C., 2020. Spatio-temporal assessment of illicit drug use at large scale: evidence from 7 years of international wastewater monitoring. Addiction 115 (1), 109–120. https://doi.org/10.1111/add.14767.

Gracia-Lor, E., Zuccato, E., Castiglioni, S., 2016. Refining correction factors for back-calculation of illicit drug use. Sci. Total Environ. 573, 1648–1659. https://doi.org/10.1016/j.scitotenv.2016.09.179.

Haddaway, N.R., Collins, A.M., Coughlin, D., Kirk, S., 2017. A rapid method to increase transparency and efficiency in web-based searches. Environ. Evid. 6 (1), 1–14. https://doi.org/10.1186/s13750-016-0079-2.

Haddaway, N.R., Woodcock, P., Macura, B., Collins, A., 2015. Making literature reviews more reliable through application of lessons from systematic reviews. Conserv. Biol. 29 (6), 1596–1605. https://doi.org/10.1111/cobi.12541.

Harman, C., Reid, M., Thomas, K.V., 2011. In Situ Calibration of a Passive Sampling Device for Selected Illicit Drugs and Their Metabolites in Wastewater, And Subsequent Year-Long Assessment of Community Drug Usage. Environ. Sci. Technol. 45 (13), 5676–5682.

Heberer, T., Feldmann, D., 2005. Contribution of effluents from hospitals and private households to the total loads of diclofenac and carbamazepine in municipal sewage effluents - Modeling versus measurements. J. Hazard. Mater. 122 (3), 211–218. https://doi.org/10.1016/j.jhazmat.2005.03.007.

Hernández, F., Bakker, J., Bijlsma, L., de Boer, J., Botero-Coy, A.M., Bruinen de Bruin, Y., Hogendoorn, E.A., 2019. The role of analytical chemistry in exposure science: focus on the aquatic environment. Chemosphere 222, 564–583. https://doi.org/10.1016/j.chemosphere.2019.01.118.

Hernández, Félix, Castiglioni, S., Covaci, A., de Voogt, P., Emke, E., Kasprzyk-hordern, B., Bijlsma, L., 2018. Mass spectrometric strategies for the investigation of biomarkers of illicit drug use in wastewater. Mass Spectrom. Rev. 37, 258–280. https://doi.org/10.1002/mas.

INCB. (2002). *Illicit Drugs and Economic Development*.

Irvine, R.J., Kostakis, C., Felgate, P.D., Jaehne, E.J., Chen, C., White, J.M., 2011. Population drug use in Australia : a wastewater analysis. Forensic Sci. Int. 210 (1–3), 69–73. https://doi.org/10.1016/j.forsciint.2011.01.037.

Jaroslav, Š., Grabic, R., Ryba, J., Biro, L., Fedorova, G., Viera, Š., Bodík, I., 2014. National study of illicit drug use in Slovakia based on wastewater analysis. Sci. Total Environ. 495, 158–165. https://doi.org/10.1016/j.scitotenv.2014.06.089.

Jones, H.E., Hickman, M., Kasprzyk-hordern, B., Welton, N.J., Baker, D.R., Ades, A.E., 2014. Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part B : placing back-calculations in a formal statistical framework. Sci. Total Environ. 487, 642–650. https://doi.org/10.1016/j.scitotenv.2014.02.101.

Kankaanpää, A., Ariniemi, K., Heinonen, M., Kuoppasalmi, K., Gunnar, T., 2014. Use of illicit stimulant drugs in Finland : a wastewater study in ten major cities. Sci. Total Environ. 487, 696–702. https://doi.org/10.1016/j.scitotenv.2013.11.095.

Kankaanpää, A., Ariniemi, K., Heinonen, M., Kuoppasalmi, K., Gunnar, T., 2016. Current trends in Finnish drug abuse: wastewater based epidemiology combined with other national indicators. Sci. Total Environ. 568, 864–874. https://doi.org/10.1016/j.scitotenv.2016.06.060.

Karolak, S., Nefau, T., Bailly, E., Solgadi, A., Levi, Y., 2010. Estimation of illicit drugs consumption by wastewater analysis in Paris area. Forensic Sci. Int. 200, 153–160. https://doi.org/10.1016/j.forsciint.2010.04.007.

Khan, U., Nuijs, A.L.N.Van, Li, J., Maho, W., Du, P., Li, K., Covaci, A., 2014. Application of a sewage-based approach to assess the use of ten illicit drugs in four Chinese megacities. Sci. Total Environ. 1–12. https://doi.org/10.1016/j.scitotenv.2014.01.043.

Kim, K.Y., Oh, J.-E., 2020. Evaluation of pharmaceutical abuse and illicit drug use in South Korea by wastewater-based epidemiology. J. Hazard. Mater., 122622 https://doi.org/10.1016/j.jhazmat.2020.122622.

Klupczynska, A., Derezinski, P., Krysztofiak, J., Kokot, Z.J., 2016. Estimation of drug abuse in 9 Polish cities by wastewater analysis. Forensic Sci. Int. 260, 14–21. https://doi.org/10.1016/j.forsciint.2015.12.042.

Koelmans, A.A., Mohamed Nor, N.H., Hermsen, E., Kooi, M., Mintenig, S.M., De France, J., 2019. Microplastics in freshwaters and drinking water: critical review and assessment of data quality. Water Res. 155, 410–422. https://doi.org/10.1016/j.watres.2019.02.054.

Krizman-matasic, I., Senta, I., Kostanjevecki, P., Ahel, M., Terzic, S., 2019. Long-term monitoring of drug consumption patterns in a large-sized European city using wastewater-based epidemiology : comparison of two sampling schemes for the assessment of multiannual trends. Sci. Total Environ. 647, 474–485. https://doi.org/10.1016/j.scitotenv.2018.07.441.

Krizman, I., Senta, I., Ahel, M., Terzic, S., 2016. Wastewater-based assessment of regional and temporal consumption patterns of illicit drugs and therapeutic opioids in Croatia. Sci. Total Environ. 566–567, 454–462. https://doi.org/10.1016/j.scitotenv.2016.05.075.

Kumar, R., Tscharke, B., Brien, J.O., Mueller, J.F., Wilkins, C., Padhye, L.P., 2019. Assessment of drugs of abuse in a wastewater treatment plant with parallel secondary wastewater treatment train. Sci. Total Environ. 658, 947–957. https://doi.org/10.1016/j.scitotenv.2018.12.167.

Lai, F.Y., O'Brien, J., Bruno, R., Hall, W., Prichard, J., Kirkbride, P., Mueller, J., 2016. Spatial variations in the consumption of illicit stimulant drugs across Australia: a nationwide application of wastewater-based epidemiology. Sci. Total Environ. 568 (June), 810–818. https://doi.org/10.1016/j.scitotenv.2016.05.207.

Lai, F.Y., Thai, P.K., Brien, J.O., Gartner, C., Bruno, R., Kele, B., … Mueller, J.F. (2013). Using quantitative wastewater analysis to measure daily usage of conventional and emerging illicit drugs at an annual music festival, *61*(November), 594–602. 10.1111/dar.12061.

Li, Jiaying, Gao, J., Thai, P.K., Mueller, J.F., Yuan, Z., Jiang, G., 2020. Transformation of Illicit Drugs and Pharmaceuticals in Sewer Sediments. Environ. Sci. Technol. 54 (20), 13056–13065. https://doi.org/10.1021/ACS.EST.0C04266.

Li, Jing, Hou, L., Du, P., Yang, J., Li, K., Xu, Z., Li, X., 2014. Estimation of amphetamine and methamphetamine uses in Beijing through sewage-based analysis. Sci. Total Environ. 490, 724–732. https://doi.org/10.1016/j.scitotenv.2014.05.042.

Lindberg, R.H., Björklund, K., Rendahl, P., Johansson, M.I., Tysklind, M., Andersson, B.A. V., 2007. Environmental risk assessment of antibiotics in the Swedish environment with emphasis on sewage treatment plants. Water Res. 41 (3), 613–619. https://doi.org/10.1016/j.watres.2006.11.014.

Liu, J., Hebenton, B., Jou, S., 2013. Handbook of Asian criminology. Handb. Asian Criminol. 1–443. https://doi.org/10.1007/978-1-4614-5218-8.

Loraine, G.A., Pettigrove, M.E., 2006. Seasonal variations in concentrations of pharmaceuticals and personal care products in drinking water and reclaimed wastewater in Southern California. Environ. Sci. Technol. 40 (3), 687–695. https://doi.org/10.1021/es051380x.

Löve, A.S.C., Baz-lomba, J.A., Reid, M.J., Kankaanpää, A., Gunnar, T., Dam, M., Thomas, K.V., 2018. Analysis of stimulant drugs in the wastewater of fi ve Nordic capitals. Sci. Total Environ. 627, 1039–1047. https://doi.org/10.1016/j.scitotenv.2018.01.274.

Mackul'ak, T., Bodı, I., Hasan, J., Grabic, R., Golovko, O., Ga, M., Brandeburova, P., 2016. Dominant psychoactive drugs in the Central European region : a wastewater study ˇova. Forensic Sci. Int. 267, 42–51. https://doi.org/10.1016/j.forsciint.2016.08.016.

Maida, C.M., Gaudio, F.Di, Tramuto, F., Mazzucco, W., Piscionieri, D., Cosenza, A., Viviani, G, 2017. Illicit drugs consumption evaluation by wastewater-based epidemiology in the urban area of Palermo city (Italy). Ann Ist Super Sanità 53 (3), 192–198. https://doi.org/10.4415/ANN.

Mariño, I.G., Quintana, J.B., Danta, A.E., Manuela, K., Silva, D., Sodré, F.F., Cela, R., 2019. Profiling cocaine residues and pyrolytic products in wastewater by mixed - mode liquid chromatography – tandem mass spectrometry. Drug Test. Anal. 11 (7), 1018–1027. https://doi.org/10.1002/dta.2590.

Mastroianni, N., López-garcía, E., Postigo, C., Barceló, D., López, M., Alda, D., 2017. 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. Sci. Total Environ. 609, 916–926. https://doi.org/10.1016/j.scitotenv.2017.07.126.

Mccall, A., Bade, R., Kinyua, J., Yin, F., Thai, P.K., Covaci, A., Ort, C., 2016. Critical review on the stability of illicit drugs in sewers and wastewater samples. Water Res. 88, 933–947. https://doi.org/10.1016/j.watres.2015.10.040.

McCall, A.K., Bade, R., Kinyua, J., Lai, F.Y., Thai, P.K., Covaci, A., Ort, C., 2016. Critical review on the stability of illicit drugs in sewers and wastewater samples. Water Res. 88, 933–947. https://doi.org/10.1016/j.watres.2015.10.040.

Mercan, S., Kuloglu, M., Tekin, T., Turkmen, Z., Ozgur, A., Safran, A.N., Asicioglu, F., 2019. Wastewater-based monitoring of illicit drug consumption in Istanbul : preliminary results from two districts. Sci. Total Environ. 656, 231–238. https://doi.org/10.1016/j.scitotenv.2018.11.345.

Minkkinen, P.O., Esbensen, K.H., 2009. Grab vs. composite sampling of particulate materials with significant spatial heterogeneity-A simulation study of "correct sampling errors. Anal. Chim. Acta 653 (1), 59–70. https://doi.org/10.1016/j.aca.2009.08.039.

Nefau, T., Karolak, S., Castillo, L., Boireau, V., Levi, Y., 2013. Presence of illicit drugs and metabolites in in fl uents and ef fl uents of 25 sewage water treatment plants and map of drug consumption in France. Sci. Total Environ. 462, 712–722. https://doi.org/10.1016/j.scitotenv.2013.05.038.

Nguyen, H.T., Thai, P.K., Kaserzon, S.L., Brien, J.W.O., Eaglesham, G., Mueller, J.F., 2018. Assessment of drugs and personal care products biomarkers in the in fl uent and ef fl uent of two wastewater treatment plants in Ho Chi Minh. Sci. Total Environ. 631–632, 469–475. https://doi.org/10.1016/j.scitotenv.2018.02.309.

Nowicki, P., Klos, J., Kokot, Z.J., 2014. Trends of Amphetamine Type Stimulants DTR Mass Load in Poznan Based on Wastewater Analysis. Iran. J. Public Health 43 (5), 610–620.

Nuijs, A.L.N.Van, Castiglioni, S., Tarcomnicu, I., Postigo, C., Lopez, M., Alda, D., Covaci, A., 2011. Illicit drug consumption estimations derived from wastewater analysis : a critical review. Sci. Total Environ. 409, 3564–3577. https://doi.org/10.1016/j.scitotenv.2010.05.030.

Nuijs, A.L.N.Van, Castiglioni, S., Tarcomnicu, I., Postigo, C., Lopez, M., Alda, D., … Covaci, A. (2020). Illicit drug consumption estimations derived from wastewater analysis : a critical revie. *Sci. Total Environ.*409(19), 3564–3577. 10.1016/j.scitotenv.2010.05.030.

O'Brien, J.W., Grant, S., Banks, A.P.W., Bruno, R., Carter, S., Choi, P.M., Mueller, J.F., 2019. A National Wastewater Monitoring Program for a better understanding of public health: a case study using the Australian Census. Environ. Int. 122, 400–411. https://doi.org/10.1016/j.envint.2018.12.003. December 2018.

Ort, C., Lawrence, M.G., Reungoat, J., Mueller, J.F., 2010. Sampling for PPCPs in wastewater systems: comparison of different sampling modes and optimization strategies. Environ. Sci. Technol. 44 (16), 6289–6296. https://doi.org/10.1021/es100778d.

Ort, C., Lawrence, M.G., Rieckermann, J., Joss, A., 2010a. Sampling for Pharmaceuticals and Personal Care Products (PPCPs) and Illicit Drugs in Wastewater Systems : are Your Conclusions Valid ? A Critical Review. Environ. Sci. Technol. 44 (16), 6024–6035.

Ort, C., Lawrence, M.G., Rieckermann, J., Joss, A., 2010b. Sampling for pharmaceuticals and personal care products (PPCPs) and illicit drugs in wastewater systems: are your conclusions valid? A critical review. Environ. Sci. Technol. 44 (16), 6024–6035. https://doi.org/10.1021/es100779n.

Ort, C., Nuijs, A.L.N.Van, Berset, J., Bijlsma, L., Castiglioni, S., Covaci, A., Thomas, K.V., 2014. Spatial differences and temporal changes in illicit drug use in Europe quantified by wastewater analysis. Addiction 109, 1338–1352. https://doi.org/10.1111/add.12570.

Östman, M., Fick, J., Näsström, E., Lindberg, R.H., 2014. A snapshot of illicit drug use in Sweden acquired through sewage water analysis. Sci. Total Environ. 472, 862–871. https://doi.org/10.1016/j.scitotenv.2013.11.081.

Palardy, A., Gagné, J.P., Tremblay, L., 2015. Presence of illicit drugs and pharmaceutical residues in the wastewaters of an eastern Canadian city. J. Xenobiotics 5 (2), 37–39. https://doi.org/10.4081/xeno.2015.5773.

Postigo, C., José, M., Alda, L.De, Barceló, D, 2010. Drugs of abuse and their metabolites in the Ebro River basin : occurrence in sewage and surface water, sewage treatment plants removal ef fi ciency, and collective drug usage estimation. Environ. Int. 36 (1), 75–84. https://doi.org/10.1016/j.envint.2009.10.004.

Reid, M.J., Thomas, K.V., 2014. Analysis of new classes of recreational drugs in sewage : synthetic cannabinoids and amphetamine-like substances. Drug Test. Anal. 6, 72–79. https://doi.org/10.1002/dta.1461.

Rodríguez-álvarez, T., Racamonde, I., González-mariño, I., Borsotti, A., Rodil, R., Rodríguez, I., Castiglioni, S., 2015. Alcohol and cocaine co-consumption in two European cities assessed by wastewater analysis. Sci. Total Environ. 536, 91–98. https://doi.org/10.1016/j.scitotenv.2015.07.016.

Shao, X., Liu, Y., Tan, D., Wang, Z., Zheng, X., Wang, D., 2020. Methamphetamine use in typical Chinese cities evaluated by wastewater-based epidemiology. Environ. Sci. Pollution Res. 27, 8157–8165.

Skees, A.J., Foppe, K.S., Loganathan, B., Subedi, B., 2018. Contamination pro fi les, mass loadings, and sewage epidemiology of neuropsychiatric and illicit drugs in wastewater and river waters from a community in the Midwestern United States. Sci. Total Environ. 631–632, 1457–1464. https://doi.org/10.1016/j.scitotenv.2018.03.060.

Sodré, F.F., Feitosa, R.S., Jardim, W.F., Maldaner, A.O., 2018. Wastewater-Based Epidemiology of Cocaine in the Brazilian Federal District: spatial Distribution, Weekly Variation and Sample Preservation Strategies. J. Braz. Chem. Soc 29 (11), 2287–2298.

Sodré, F., Souza, G., Feitosa, R., Pereira, C., Maldaner, A., Sodré, F.F., Maldaner, A.O., 2017. Illicit Drugs, Metabolites and Adulterants in Wastewater: monitoring Community Drug Abuse in the Brazilian Federal District during the 2014 Soccer World Cup. J. Braz. Chem. Soc. 28 (11), 2146–2154. https://doi.org/10.21577/0103-5053.20170063.

Subedi, B., Kannan, K., 2014. Mass Loading and Removal of Select Illicit Drugs in Two Wastewater Treatment Plants in New York State and Estimation of Illicit Drug Usage in Communities through Wastewater Analysis. Environ. Sci. Technol. 48 (12), 6661–6670.

Terzic, S., Senta, I., Ahel, M., 2010. Illicit drugs in wastewater of the city of Zagreb (Croatia) e Estimation of drug abuse in a transition country. Environ. Pollut. 158 (8), 2686–2693. https://doi.org/10.1016/j.envpol.2010.04.020.

Thai, P.K., Jiang, G., Gernjak, W., Yuan, Z., Lai, F.Y., Mueller, J.F., 2014. Effects of sewer conditions on the degradation of selected illicit drug residues in wastewater. Water Res. 48 (1), 538–547. https://doi.org/10.1016/j.watres.2013.10.019.

Thomas, K.V., Bijlsma, L., Castiglioni, S., Covaci, A., Emke, E., Grabic, R., Voogt, P.De., 2012. Science of the Total Environment Comparing illicit drug use in 19 European cities through sewage analysis. Sci. Total Environ. 432, 432–439. https://doi.org/10.1016/j.scitotenv.2012.06.069.

UNODC. (2008). *Illicit Drug in Central Asia. United Nations Office on Drugs and Crime, Regional Office for Central Asia.* 10.1080/00472336.2019.1597913.

van Nuijs, A.L.N., Lai, F.Y., Been, F., Andres-Costa, M.J., Barron, L., Baz-Lomba, J.A., Ort, C., 2018. Multi-year inter-laboratory exercises for the analysis of illicit drugs and metabolites in wastewater: development of a quality control system. TrAC - Trends Analyt. Chem. 103, 34–43. https://doi.org/10.1016/j.trac.2018.03.009.

Wang, Z., Shao, X.T., Tan, D.Q., Yan, J.H., Xiao, Y., Zheng, Q.Da, Wang, D.G., 2019. Reduction in methamphetamine consumption trends from 2015 to 2018 detected by wastewater-based epidemiology in Dalian, China. Drug Alcohol Depend. 194, 302–309. https://doi.org/10.1016/j.drugalcdep.2018.10.023. November 2018.

Xiao, Y., Watson, M., 2019. Guidance on Conducting a Systematic Literature Review. J. Plann. Educ. Res. 39 (1), 93–112. https://doi.org/10.1177/0739456X17723971.

Yin, F., O'Brien, J.W., Thai, P.K., Hall, W., Chan, G., Bruno, R., Mueller, J.F., 2016. Cocaine, MDMA and methamphetamine residues in wastewater : consumption trends (2009 –2015) in South East Queensland, Australia. Sci. Total Environ. 568, 803–809. https://doi.org/10.1016/j.scitotenv.2016.05.181.

Yong, K., Yin, F., Kim, H., Thai, P.K., Mueller, J.F., Oh, J., 2015. The first application of wastewater-based drug epidemiology in five South Korean cities. Sci. Total Environ. 525, 440–446. https://doi.org/10.1016/j.scitotenv.2015.04.065.

Zhang, X., Huang, R., Li, P., Ren, Y., Gao, J., Mueller, J.F., Thai, P.K., 2019a. Temporal profile of illicit drug consumption in Guangzhou, China monitored by wastewater-based epidemiology. Environ. Sci. Pollution Res. 26, 23593–23602.

Zhang, Y., Duan, L., Wang, B., Du, Y., Cagnetta, G., Huang, J., Yu, G., 2019b. Wastewater-based epidemiology in Beijing, China : prevalence of antibiotic use in flu season and association of pharmaceuticals and personal care products with socioeconomic characteristics. Environ. Int. 125, 152–160. https://doi.org/10.1016/j.envint.2019.01.061. January.

Zheng, Q.Da, Wang, Z., Liu, C.Y., Yan, J.H., Pei, W., Wang, Z., Wang, D.G, 2019. Applying a population model based on hydrochemical parameters in wastewater-based epidemiology. Sci. Total Environ. 657, 466–475. https://doi.org/10.1016/j.scitotenv.2018.11.426.

Zuccato, E., Chiabrando, C., Castiglioni, S., Bagnati, R., Fanelli, R., 2008. Estimating community drug abuse by wastewater analysis. Environ. Health Perspect. 116 (8), 1027–1032. https://doi.org/10.1289/ehp.11022.

Zuccato, E., Chiabrando, C., Castiglioni, S., Calamari, D., Bagnati, R., Schiarea, S., Fanelli, R., 2005. Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Clin. Practice Epidemiol. Mental Health 4 (14), 1–7. https://doi.org/10.1186/Received.