European Monitoring Centre
for Drugs and Drug Addiction

Estimating the size of drug markets in selected European cities using wastewater-derived data on drug and drug metabolite residues

Background paper commissioned by the EMCDDA

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2023

This paper was commissioned by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), to provide background material to inform and contribute to the analysis of EU Drug Markets. This background paper was produced under contract no CT.22.SAS.0048.1.0 and we are grateful for the authors' valuable contributions. The paper is available online for those who would like further information on the topic. The views, interpretations and conclusions set out are those of the authors and are not necessarily those of the EMCDDA or its partners, any EU Member State or any agency or institution of the European Union.

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Abbreviations

ADHD	Attention deficit and hyperactivity disorder
BE	Benzoylecgonine
ECMDDA	European Monitoring Centre for Drugs and Drug Addiction
Ef	Correction factor for excretion
EF	Excretion factor
IWW	Influent wastewater
MDMA	3,4-Methylenedioxymethamphetamine
MW	Molecular weight
PNML	Population-normalised mass load
SCORE	Sewage analysis CORe group Europe
Si	Correction factor for stability
SPM	Solid particulate matter
WBE	Wastewater-based epidemiology
WWTP	Wastewater treatment plant

Executive summary

Wastewater-based epidemiology (WBE) is proving to be a promising tool to back-estimate illicit drug market sizes. Within the framework of the Sewage analysis CORe group Europe (SCORE) network, influent wastewater (IWW) samples were analysed for metabolites and parent compounds of illicit drugs to determine consumption estimates for amphetamine, cocaine, 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine. Between 2015 and 2021 measured concentrations of illicit drugs were translated into amounts of pure compound by considering flow rates, population numbers and most recent excretion factors. WBE-derived concentrations of these stimulants together with other data sources available to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), notably annual average retail purity and price data, or other information such as city-level data from drug checking services, were used to back-estimate illicit drug market sizes. From 2015 to 2021, annual drug estimates of consumed pure and consumed street-level drugs were available for 1 846 and 891 European cities, respectively. However, due to the scarcity of comprehensive information on drug purity and pricing, market size values could be calculated for only 385 locations in this period. This highlights the need for up-to-date and representative information on drug price and purity, and increased standardisation of sampling strategies to obtain more data.

Additionally, this study provides a comprehensive overview of some intrinsic limitations associated with the back-estimation of drug market shares based on WBE data. Since its inception, there has been a large amount of fundamental research conducted within the field of WBE, as well as studies focused on harmonising analytical methodologies. However, there are still some knowledge gaps that require further investigation. Nevertheless, WBE could complement other epidemiological data sources that have been used to calculate drug market sizes (e.g., health interview surveys, seizures, the European Web Survey on Drugs). Finally, this investigation proposes recommendations for future WBE studies aiming to estimate drug market sizes.

Introduction: objectives

The drug market size refers to the quantities of specific illicit drugs available to, or consumed by, a given population during a particular time period (Baker et al., 2011; Udrisard et al., 2022). Understanding the size and nature of illicit drug markets and how they operate is important for planning and prioritising activities to tackle the problems associated with these major global markets, and for having the potential to identify changes in drug markets over time. However, the hidden nature of the illicit drug business makes it difficult to estimate its size and the amount of money it generates. Published estimates are variable, covering different parts of the market and different geographical areas, and furthermore involve many assumptions and associated uncertainties.

Usually, drug market shares are assessed based on two main strategies: a demand-based (bottom-up) and a supply-side (top-down) approach. However, these methods are inherently linked to some limitations (e.g., non-response, misreporting drug use frequency, relying on numerous assumptions

for production estimations, reliance on the efficiency of law enforcement), and, therefore, this study proposes an alternative approach based on wastewater-based epidemiology (WBE) data. Within the WBE approach, concentrations of human metabolic excretion product (biomarkers) of illicit drugs are measured in influent wastewater (IWW) and converted to population-normalised mass loads (PNMLs) by multiplying these with the wastewater flow rate and dividing by the catchment population served by the wastewater treatment plant (WWTP). These PNMLs serve as a proxy for illicit drug use. PNMLs can then be used to further estimate drug market sizes by taking into account data on drug purity and retail prices (see section 'Back calculations'). In particular, WBE could provide complementary information on drug market shares at a high spatial and temporal resolution, and could be employed to rapidly assess changes in illicit drug markets.

Starting from 2011, the SCORE network has coordinated a yearly wastewater monitoring campaign. During this programme, SCORE members collect daily 24-h composite IWW samples over seven consecutive days during a ‘normal’ week (i.e., one without any special events occurring, including festivals and holidays), generally once a year in March or April. This sampling period is chosen to obtain samples representative of drug use in the different (European) cities. The IWW samples are analysed by the participating labs to determine concentrations of excretion products of illicit drugs, e.g., cocaine, amphetamine, methamphetamine and 3,4-methylendioxymethamphetamine (MDMA). The SCORE members use custom validated methods to analyse the IWW samples for these illicit drug biomarkers. To externally validate the results of the monitoring campaign, each laboratory must follow a best-practice protocol and participate in a mandatory annual inter-laboratory exercise. After quality control, the data is disseminated by the EMCDDA and is available online[1]. The data obtained through the yearly wastewater monitoring campaign provides a unique overview of spatio-temporal trends in illicit drug use in the participating cities and countries (EMCDDA, 2022a). Specifically, these figures are used to detect changes in consumption habits, to monitor drug availability on the market, and to highlight potential hotspots.

The goal of this study was to estimate the drug market size in different cities in Europe using a WBE approach to estimate the amount of drugs consumed and considering available price and purity data. This report provides a mathematical framework consisting of three levels for calculating: (i) the amounts of pure drugs consumed (expressed in g/year); (ii) the amounts of street-level drugs consumed; and (iii) drug market size (expressed in Euro/year). Data sources available to EMCDDA, notably annual average purity and price data, city-level data from drug checking services and/or data from the European Web Survey on Drugs, may be factored into the calculations. Additionally, this study will highlight the strengths, limitations and uncertainties of using WBE to calculate market size. Furthermore, the applicability of WBE to investigating geographical patterns in drug market size across different years will be evaluated.

([1]) https://www.emcdda.europa.eu/publications/html/pods/waste-water-analysis_en

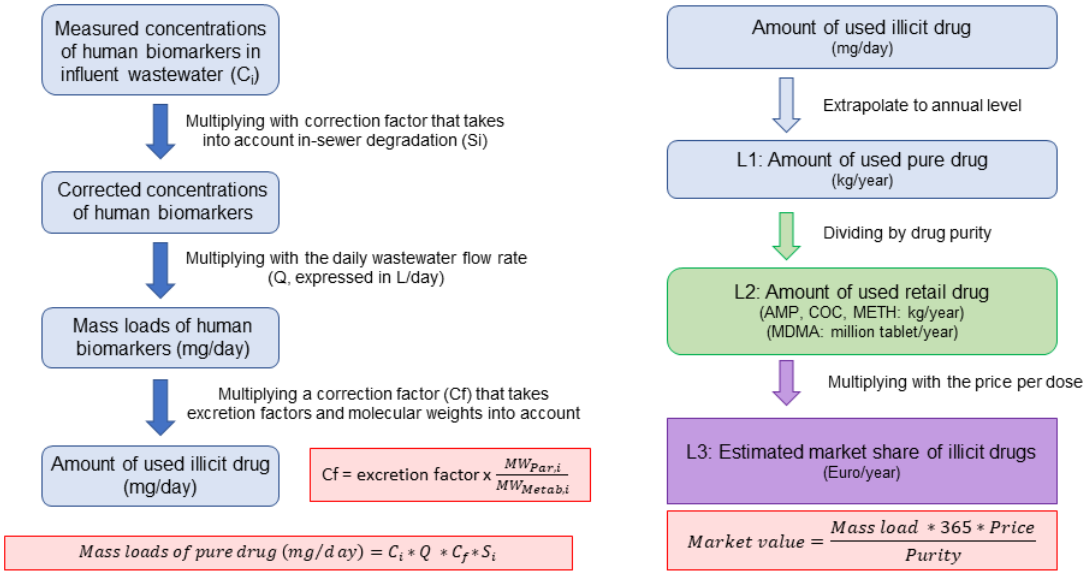
Methodology

Back-calculations

Historical data on the PNML of the biomarkers for illicit drug use are publicly available and can be retrieved from the website of EMCDDA (WBE section) (EMCDDA, 2022b). These were used to further back-calculate market size estimations. From a WBE perspective, a suitable biomarker should meet the following criteria: it should be (i) excreted in sufficient amounts; (ii) stable in wastewater; and (iii) specific for human metabolism. The biomarkers of interest fulfil these requirements.

Figure 1 shows the detailed workflow that was applied to back-calculate drug market size estimates, consisting of three levels. Included in the back-calculation were (L1) amounts of pure drugs used; (L2) amounts of retail drugs used; and (L3) the market size of each drug. It is important to note that drug market size was estimated on a city level, and location-specific drug consumption estimates are not generalisable to the national level (see Section 'Level 2 and 3: Back-calculations to market size of illicit drugs' for more details). The use of cocaine was estimated based on the measurement of its metabolite benzoylecgonine in IWW, whereas amphetamine, MDMA and methamphetamine are estimated based on the excreted parent drug.

FIGURE 1
Back-calculation framework for the estimation of the market share of the different illicit drugs based on measured concentrations in influent wastewater, this calculation is applied at three levels (L1, L2 and L3)



Notes: C_i, biomarker concentration in influent wastewater; Cf, final correction factor; Si, stability correction factor; Q, daily wastewater flow rate.

Table 1 summarises the most recent excretion factors for the biomarkers of interest that were used to refine calculated mass loads.

TABLE 1
Correction factors used in the back-calculation of amphetamine, cocaine, MDMA and methamphetamine

Compound	Correction factor (Ef *Si)	References
Amphetamine	2.77	(Gracia-Lor et al., 2016)
Cocaine (via benzoylecgonine)	3.59	(Castiglioni et al., 2013)
MDMA	4.40	(Gracia-Lor et al., 2016)
Methamphetamine	2.44	(Gracia-Lor et al., 2016)

Abbreviations: Ef, correction factor for excretion; Si, correction factor for stability.

Data sources, inclusion criteria and imputation

Cities for which at least one year of WBE data exist (139 cities in 28 countries) between 2015 and 2021 (https://www.emcdda.europa.eu/data/stats2023/drug-checking_en) were included in this study.

Locations and years with PNMLs missing for more than one day (out of seven) were excluded to ensure a representative weekly mean. Population data from the original submission files (WBE data, SCORE, internal communication) were used for normalising the PNML to account for yearly changes in the population size.

Retail price and purity data were obtained from the *Statistical bulletin 2022* (EMCDDA, 2022b). Price and purity data had not yet been published for 2021, so in general no market size estimation could be performed for that year. The published retail price data had already been corrected for inflation, making temporal comparison possible. Furthermore, it was noted that multiple study results were reported for the same drug and year. Since it was not possible to discriminate between multiple studies based on value, as no definitions were provided with the study/data, the arithmetic mean was taken in this case.

Missing values were imputed based on two approaches:

(i) A one- or two-year missing data gap was imputed based on the previous and next year. This was only done if the variability between the years was considered low, with $\frac{|year_1 - year_2|}{mean(year_1, year_2)} \leq 15\%$ used as the criterion. No values from 2020 and 2021 were used for gap imputation due to the large and uncertain COVID-19 pandemic changes. In the results, gap imputation was performed for 24 price and two purity values.

(ii) For purity data, as a last option, values from drug checking services (EMCDDA, internal communication, including 2021 data) were used for the imputation (n = 16) of city-based PNML. Drug checking values were not extrapolated to country level.

Because of missing purity and/or price data, it was not possible to perform any level-3 market size estimation for 11 countries (AT, CH, DE, EE, FI, FR, IS, LV, RS, SI and UK). However, data on the amounts of pure drug are still available (level 1).

Data processing and visualisation was performed in R using the Tidyverse and sf package (R Core Team, 2022; Wickham et al., 2019; Pebesma, 2018).

Retrospective analysis per drug

FIGURE 2
Annual amount of pure parent drug in 2020. Expressed in kg/year

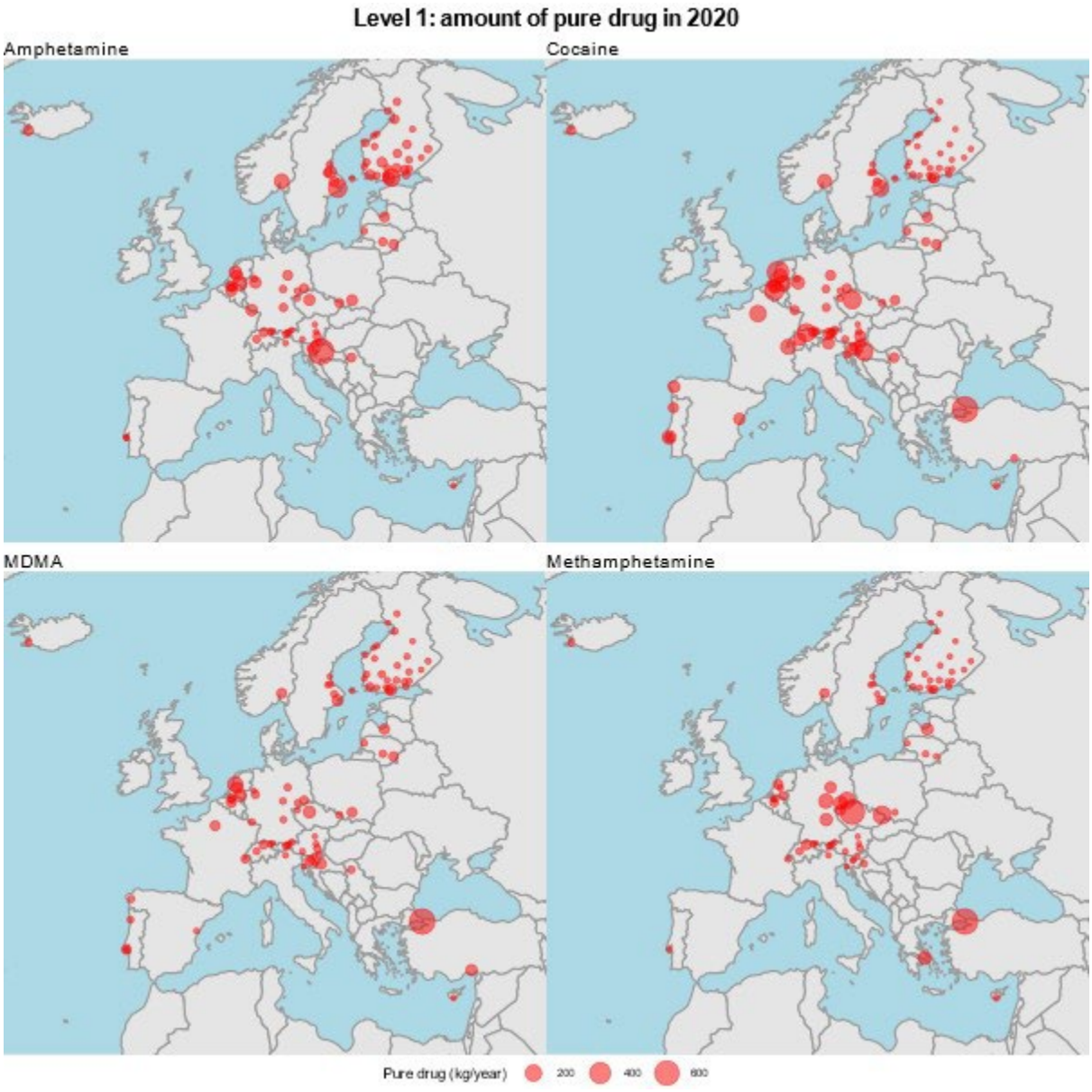


FIGURE 3

Annual amount of street-level drug in 2020. For amphetamine, cocaine and methamphetamine expressed in kg/year; MDMA is expressed in million tablets/year

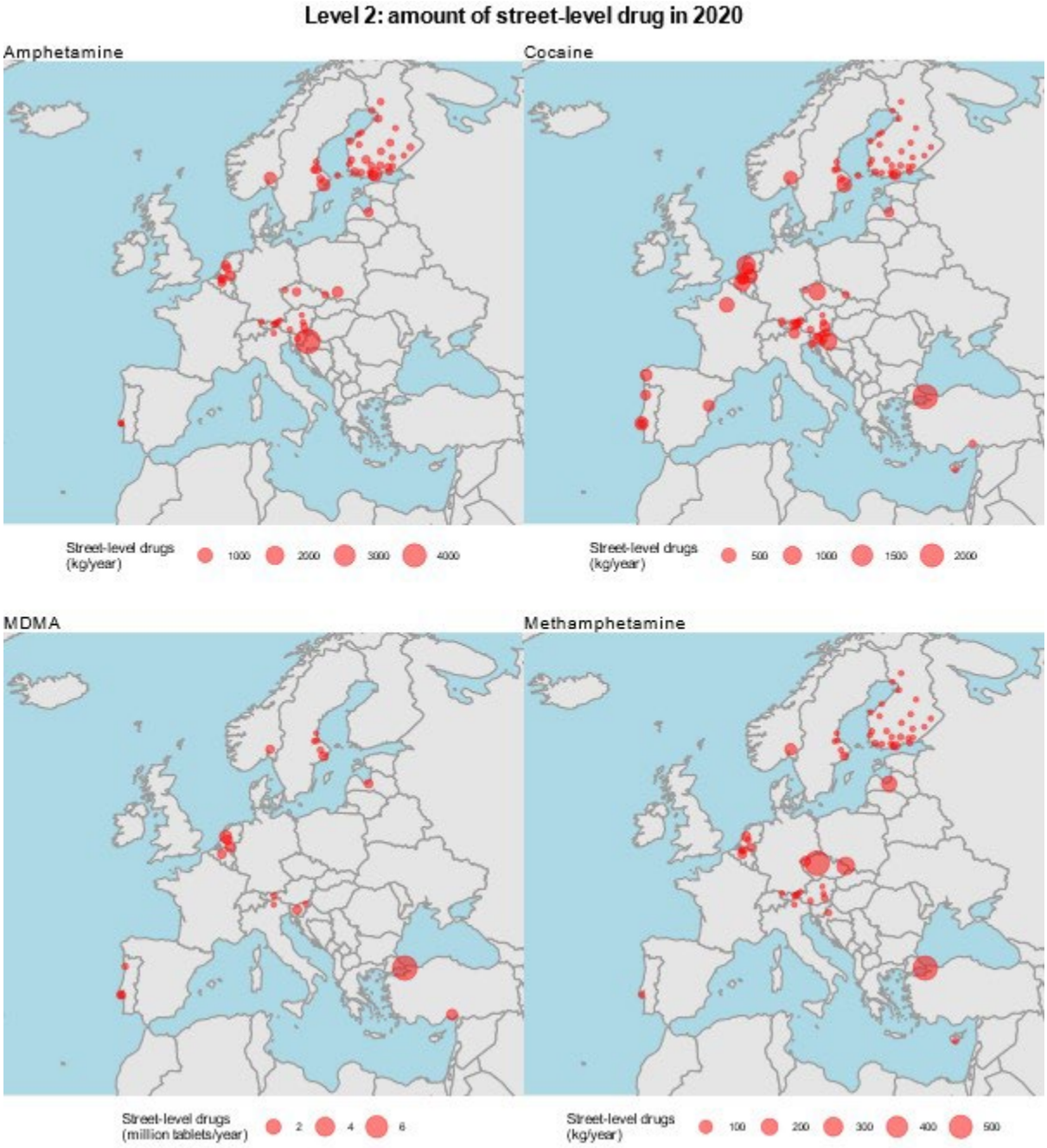
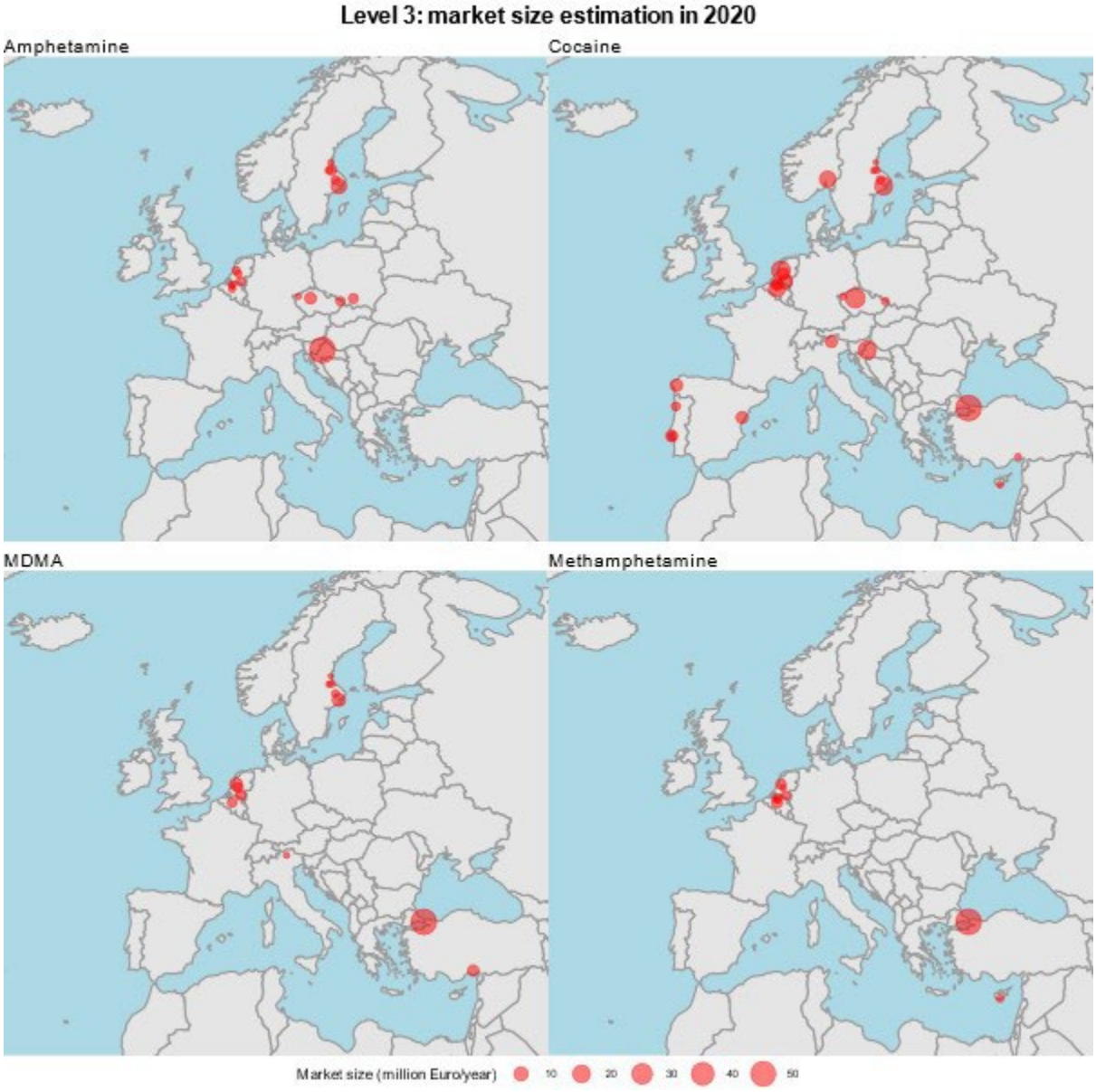


FIGURE 4
Estimated drug market size in 2020. Expressed in Euro/year



Figures 2–4 spatially visualise the different levels of back-calculation for the year 2020, showing: Level 1, amount of pure drug consumed; Level 2, amount of street-level drug consumed; and Level 3, drug market size. For a select number of cities and countries in 2020, sufficient metadata (e.g., wastewater, purity, price) were available for the calculation of market sizes. However, at that time, the drug market in some countries was influenced by the COVID-19 countermeasures, as indicated in the EMCDDA-EUROPOL joint report (EMCDDA and Europol, 2020). This is shown in Tables 2–5 for the compounds amphetamine, cocaine, MDMA and methamphetamine, respectively.

TABLE 2

Amphetamine consumption in 2020 in a select number of countries and cities. Countries were selected based on the high availability of metadata

Country	City	Population	Level 1 (g/year)	Level 2 (g/year)	Level 3 (€/year)
BE	Antwerp Zuid	130 218	45 651	89 163	641 974
BE	Boom	30 600	7 693	15 025	108 179
BE	Brussels	953 987	54 008	105 485	759 489
PT	Almada	138 685	153	655	(b)
PT	Lisbon	426 964	1 981	8 501	(b)
PT	Porto	150 000	(a)	(a)	(a)
SE	Gävle	85 000	71 349	165 929	3 318 574
SE	Sandviken	28 000	15 610	36 302	726 047
SE	Söderhamn	14 500	5 483	12 752	255 036
SE	Stockholm	860 800	287 177	667 853	13 357 060
SE	Uppsala	200 000	35 049	81 509	1 630 175

Abbreviations: (a) not detected in influent wastewater, (b) missing price and/or purity data.

TABLE 3

Cocaine consumption in 2020 in a select number of countries and cities

Country	City	Population	Level 1 (g/year)	Level 2 (g/year)	Level 3 (€/year)
BE	Antwerp Zuid	130 218	200 470	249 341	13 115 352
BE	Boom	30 600	16 728	20 805	1 094 364
BE	Brussels	953 987	592 775	737 283	38 781 063
PT	Almada	138 685	42 368	85 593	2 784 328
PT	Lisbon	426 964	204 657	413 449	13 449 503
PT	Porto	150 000	64 832	130 973	4 260 557
SE	Gävle	85 000	11 533	17 744	1 543 698
SE	Sandviken	28 000	2 906	4 471	388 998
SE	Söderhamn	14 500	1 128	1 735	150 961
SE	Stockholm	860 800	364 705	561 084	48 814 318
SE	Uppsala	200 000	24 830	38 200	3 323 401

The countries were selected based on the high availability of metadata.

TABLE 4

MDMA consumption in 2020 in a select number of countries and cities. Countries were selected based on the high availability of metadata

Country	City	Population	Level 1 (g/year)	Level 2 (tablets/year)	Level 3 (€/year)
BE	Antwerp Zuid	130 218	16 601	(b)	(b)
BE	Boom	30 600	1 182	(b)	(b)
BE	Brussels	953 987	34 137	262 596	1 376 002
PT	Almada	138 685	3 840	36 573	(b)
PT	Lisbon	426 964	30 641	291 821	(b)
PT	Porto	150 000	5 138	48 937	(b)
SE	Gävle	85 000	4 377	26 856	375 980
SE	Sandviken	28 000	826	5 069	70 967
SE	Söderhamn	14 500	343	2 105	29 470
SE	Stockholm	860 800	55 223	338 790	4 743 058

SE	Uppsala	200 000	6 541	40 126	561 765

Abbreviations: (b) missing price and/or purity data.

TABLE 5
Methamphetamine consumption in 2020 in a select number of countries and cities

Country	City	Population	Level 1 (g/year)	Level 2 (g/year)	Level 3 (€/year)
BE	Antwerp Zuid	130 218	4 524	8 976	897 568
BE	Boom	30 600	27	55	5 454
BE	Brussels	953 987	9 676	19 198	1 919 835
PT	Almada	138 685	(a)	(a)	(a)
PT	Lisbon	426 964	1 431	3 586	(b)
PT	Porto	150 000	(a)	(a)	(a)
SE	Gävle	85 000	393	473	(b)
SE	Sandviken	28 000	19	23	(b)
SE	Söderhamn	14 500	28	33	(b)
SE	Stockholm	860 800	10 709	12 902	(b)
SE	Uppsala	200 000	267	321	(b)

Countries were selected based on the high availability of metadata.

Abbreviations: (a) not detected in influent wastewater, (b) missing price and/or purity data.

Limitations and uncertainties

Despite the progress made in more than a decade of research, there are a number of intrinsic uncertainties inherent in WBE with regard to biomarker stability, possible sorption of the analytes of interest to the sewer system and/or suspended solids, pharmacokinetic information, metabolic pathway overlap, and direct disposal of unused drugs. Additionally, uncertainties are introduced by the quantitative chemical analysis to the back-calculation of PNMLs, including the analytical and instrumental uncertainties and differences in sampling practices across laboratories (i.e., sampling mode, period and frequency). Furthermore, estimation of the market value of the substances of interest requires knowledge of drug purity and drug price; but often there is a limited amount of spatio-temporal information available.

In the following sub-section, we will provide an in-depth discussion of the main uncertainties associated with the estimation of drug market sizes based on WBE estimates. Table 6 gives an overview of the general uncertainties encountered in the estimation of market values.

TABLE 6
Summary of uncertainties associated with estimating drug market size through a wastewater-based epidemiologic approach

Uncertainty	Problem	Consequence	Risk mitigation
Level 1: Back-calculations to annual amounts of pure drug			
Biomarker stability: in-sewer	Biomarkers may degrade in sewer	Consumption may be underestimated	Accounted for through appropriate correction factors

Biomarker stability: in-sample	Biomarkers may degrade in sample (after collection)	Consumption may be underestimated	Storage at a low temperature (<-20°C) and addition of preservatives
Sorption to the sewer system or to suspended solids	Biomarkers may sorb to solid particulate matter and biofilm	Consumption may be underestimated	The analytes of interest for this study do not require any correction factor due to limited sorption
Information on pharmacokinetics	Metabolism and excretion may differ between and within individuals	Consumption may be under- or overestimated	Most up-to-date excretion factors (EFs) are used (see Table 1)
Metabolic pathway overlap	Metabolic pathways of WBE biomarkers can overlap	Currently used WBE biomarkers could potentially not distinguish between the use of some compounds	Compound-specific metabolites for AMP and METH are not routinely measured
Influence of licit drug use	Measured concentrations of WBE biomarkers originate from both legal and illegal use	WBE measures total consumption, trends can only be assigned to changes in both legal and illegal settings	Proportion of licit compared to illicit drug use should be evaluated
Direct disposal of parent compound	Direct disposal of unused drugs can contribute to the measured loads in IWW	Consumption may be overestimated	If available, human metabolites are measured to estimate human consumption. Additionally, aberrant PNML levels that deviate from the historical pattern were discarded
Chemical and instrumental uncertainty	Chemical and instrumental uncertainty within and between different laboratories	Consumption may be under- or overestimated	A validated method and common practice protocol are followed by the participating laboratories. The applied method was validated based on international guidelines and laboratory performance was ensured by an external quality control study
Sampling mode and frequency	Various sampling modes and frequencies influence the ability to compare different mass loads	Consumption may be under- or overestimated	Only flow-corrected concentrations are taken into consideration. An autosampler device should be available for the compilation of 24-h composite IWW samples
Level 2: Back-calculations to annual amount of sold retail drug			

Temporal and spatial variations in illicit drug use	Consumption rates might be different from the sampled period due to seasonal and weekly variations	Consumption may be under- or overestimated	A 'normal' week (no special events occurring) was chosen to assess baseline consumption
Drug purity	Data are based on a limited number of seizures or studies, or are not available	Consumption may be under- or overestimated	Improve data gathering. Impute when appropriate
Level 3: Back-calculations to market size valuation			
Drug price	Data are based on a limited number of studies or are not available	Consumption may be under- or overestimated	Improve data gathering. Impute when appropriate
Spatial differences in the locality where a drug is sold and excreted in the wastewater system	Drug market size is estimated based on the assumption that the drug is sold and excreted in the same geographical area	Consumption may be under- or overestimated	The extent of this issue should be evaluated through external data sources (e.g., surveys) to better understand consumption patterns

Level 1: Back-calculations to mass loads of illicit drugs

In-sewer and in-sample biomarker stability

Several investigations have been carried out to better understand the in-sample and in-sewer transformation/fate of the human biomarkers for illicit drugs (Ramin et al., 2017; Li et al., 2019). The addition of preservatives to the samples (e.g., hydrochloric acid) and storage at a low temperature (<−20°C) are appropriate ways to minimise in-sample biomarker loss. Freezing the samples after collection in the WWTP is guaranteed when participating in the SCORE monitoring campaign. The use of preservatives is recommended but not required. Additionally, preservatives can only be added during sample collection, and therefore do not prevent in-sewer degradation. Human biomarkers could potentially be degraded by biological and chemical processes that occur during the in-sewer transport to the WWTP (Ramin et al., 2017). In-sewer loss of biomarkers could be substantial in the presence of sewer biofilms. In general, a higher ratio of biofilm area to bulk water volume, higher wastewater temperatures, and a longer hydraulic retention time increase biomarker transformation in the sewers (O'Brien et al., 2017). Several studies have demonstrated a high stability of the compounds of interest in IWW for at least 24-h at pH 7.5 and 20°C (van Nuijs et al., 2012; Gao et al., 2019). The correction factors presented in Table 1 take into account possible degradation in the sewers.

Sorption to the sewer system or to suspended solids

For some chemicals, sorption to solid particulate matter (SPM) and/or biofilm can also result in higher uncertainty, as highlighted by the WBE methodology, especially for analytes with high log Kow values. The log Kow value is a measure of the distribution of a chemical substance between octanol and water – the higher the value, the higher the affinity for the octanol and by proxy solid phase (Baker et al., 2011; Ramin et al., 2017). Within the SCORE monitoring campaign, quantification of biomarker concentrations in the filtered aqueous phase is common practice and chemicals sorbed to particulates will not be measured. However, it has been indicated that the sorption of all targeted biomarkers is less than 9 %, and, therefore, underestimation of biomarker concentration due to adsorption to SPM is relatively limited (Baker et al., 2011).

Information on pharmacokinetics

Metabolism and the excretion of illicit drugs are known to differ between individuals and even within individuals under different conditions (e.g., state of health). Excretion factors (EFs) used in WBE are mostly derived from limited pharmacokinetic information which might not correspond with the average excretion profile in the different catchment populations (Kato, 1975; Yasuda et al., 2008; Boogaerts et al., 2021a). Additionally, these EFs do not provide fully accurate estimates, since they are only based on urinary excretion. However, the IWW matrix also contains excretion products from other human matrices such as faeces, blood, saliva and sweat. For this reason, considerable efforts are being made to refine the EFs of different drugs (Gracia-Lor et al., 2016; Boogaerts et al., 2021a). In this context, the latest comprehensive analysis to propose refined correction factors for the biomarkers of interest has been produced (Castiglioni et al., 2013; Gracia-Lor et al., 2016). These correction factors (see Table 1) were used for the refinement of back-calculations to doses, and, subsequently, to reduce uncertainty with regard to the estimated market size.

Metabolic pathways overlap and influence of licit drug use

Metabolic pathways may overlap, i.e., a common metabolite may be formed from different parent drugs. Measured biomarker concentrations could thus be the result of the consumption of different parent drugs (Guirguis, 2010; Bettington et al., 2018). This is particularly relevant for methamphetamine, which is partially metabolised to amphetamine. Measured loads of amphetamine in IWW can therefore be the result of both amphetamine and methamphetamine consumption. At this time, compound-specific metabolites for amphetamine are not routinely measured within the SCORE monitoring campaign.

Additionally, a small proportion of the amphetamine measured in IWW could be the result of legally prescribed medication for the treatment of attention deficit and hyperactivity disorder (ADHD). However, amphetamine is only given to a limited number of such patients, when treatment with methylphenidate is clinically unsatisfactory (BCFI, 2023). For this reason, the high PNMLs measured in IWW are assessed as being mainly the result of illicit amphetamine use. Since this study includes many different locations, the contribution of licit use varies across different countries and should be investigated.

Specific biomarkers for crack cocaine are not routinely measured for the SCORE monitoring programme, and benzoylecgonine (BE) is formed by both cocaine HCl and crack cocaine use. While the indications are that the use of crack cocaine is low to negligible in Western Europe (including Belgium, Ireland, Italy, the Netherlands, Portugal and Spain), there have been recent signs that its use may be rising (EMCDDA, 2022c). However, currently, it can be concluded from other drug market indicators that measured concentrations of BE are mainly the result of cocaine HCl use. Correction factors used in the back-calculations assume that measured loads of BE in wastewater are derived exclusively from cocaine HCl (Table 1).

Direct disposal of illicit drugs

The disposal of unused drugs directly into the sewer system can increase the level of uncertainty (Guirguis, 2010; Bettington et al., 2018). This is an issue if the parent drug itself is measured, which is the case in this study for amphetamine, MDMA and methamphetamine (Petrie et al., 2015). For cocaine, a human metabolite is measured (i.e. BE), and the detected loads in IWW are therefore not influenced by the deliberate discharge of cocaine (Boogaerts et al., 2021a). Ideally, metabolites should be selected as WBE biomarkers instead of parent compounds. However, metabolic candidates that fulfil the selection criteria for biomarkers cannot always be identified, and parent drugs, such as amphetamine, MDMA and methamphetamine, have been used in multiple applications (Gonzalez-Marino et al., 2020).

To minimise this uncertainty, only WBE data retrieved from a ‘normal’ week were taken into consideration. Experience shows that the dumping of even small amounts of parent drug into the sewage system results in aberrant PNML levels that deviate from the historical pattern, requiring them to be excluded from the data analysis (Emke et al., 2014; Boogaerts et al., 2021b). For example, several notable dumping events were found in the Netherlands and these outliers were not published by EMCDDA, and therefore also not taken into consideration in the determination of the market size (Gonzalez-Marino et al., 2020). Different analytical approaches are available to identify the potential dumping of parent drugs, as discussed by Petrie et al. (2016) and Quireyns et al. (2022).

Not all residues of drugs found in IWW are the result of consumption, and identifying intentional or accidental disposal is crucial in wastewater-based epidemiology to ensure the accuracy of observed spatio-temporal trends in consumption patterns. So far, only a limited number of studies have provided analytical evidence for the direct disposal of illicit drugs or pharmaceuticals. Additionally, only minimal standardisation in the workflow is employed to distinguish direct disposal from consumption.

Chemical and instrumental uncertainty

A validated method and common practice protocols are followed by the participants of SCORE to reduce analytical uncertainties. Laboratory performance is ensured through multi-year participation in an external quality control study and in-house quality assurance and quality control measures (Castiglioni et al., 2013; van Nuijs et al., 2018). Only results from laboratories that fulfil the criteria of this inter-laboratory exercise are included for market size estimation. Additionally, validation of the

various in-house methods employed is carried out based on international guidelines for method validation, in order to ensure high levels of accuracy and precision in the analytical methods used to quantify the biomarkers of interest from the IWW matrix (European Medicines Agency, 2011; U.S. Department of Health and Human Services Food and Drug Administration, 2018).

Sampling mode and frequency

Only flow-corrected concentrations (= mass loads) are taken into consideration for the back-calculation of market size. To participate in the SCORE monitoring campaign, an autosampler device should be present in the WWTP for the compilation of 24-h composite IWW samples. Flow-proportional sampling is recommended, but not always possible for logistical reasons (Ort et al., 2014). Therefore, volume- or time-proportional sampling modes were also applied during the SCORE monitoring campaign. In this case, the application of a high sampling frequency is recommended to compile the daily IWW samples and to accurately capture average biomarker concentrations over the 24-h period. To minimise inter-laboratory uncertainty, a best-practice protocol describes the sampling approach to which all SCORE participants must adhere.

Level 2 and 3: Back-calculations to market size of illicit drugs

Temporal and spatial variations in illicit drug use

A mere one week of data at each location was considered for the calculation of the total mass load in one year. Throughout the year, consumption rates might be different from the sampled period due to seasonal and weekly variations. For example, seasonal variability for cocaine and MDMA were noted in earlier studies (Ort et al., 2014; Tscharke et al., 2016; Boogaerts, 2021b). Extrapolating the findings from one week to yearly use will inevitably include an additional degree of uncertainty, and potentially significant underestimation since festive periods are excluded. Furthermore, the selection of a ‘normal’ week may not always be identical across different participating laboratories and/or locations for logistical reasons.

It is possible that sold drugs may not be consumed by the buyer, or the location of excretion could be different to that of sale due to commuting. Currently, drug market sizes are estimated based on the assumption that drugs are consumed and sold within the same geographical area, but this remains uncertain, potentially resulting in an over- or underestimation of illicit drug use.

At this point, limited wastewater-based information is available on the consumption of illicit drugs in Eastern European countries. In the future, it would be prudent to include additional locations to increase the coverage of the SCORE monitoring programme.

Temporal trends in the size of the illicit drugs market might also stem from demographic changes in the population contributing to a WWTP. At this stage, market values are not standardised for the population present in the WWTP catchment area at specific times. Therefore, differences in the drug market may be the result of population movements in and out the catchment area (e.g., as result of tourism and commuting). It is well known that the types of drug consumed and the amounts taken are very different among different demographics (Boogaerts et al., 2022). The government-imposed

lockdowns as a result of the coronavirus pandemic partially coincided with the study period and were characterised by a decrease in the mobility of the catchment population. For this reason, it is difficult to verify whether the fluctuations in market share during these times were due to variations in population size or changes in consumption behaviour. Additionally, the phenomenon of 'drug tourism', where people buy drugs in a certain city and consume them elsewhere, cannot be taken into account.

Drug purity and price

Limited, country-dependent, data are available on retail drug pricing and purity. These data come from a wide range of different sources, and the comparability between these different datasets is not always known. For example, there are considerable inter-country differences in the types of information systems (e.g., police sources, health interview surveys among drug users) and sampling strategies used to compile data. For example, seizure-based estimates of drug purity rely heavily on the assumption that the efficiency of law enforcement in seizing illicit substances is relatively constant. However, law enforcement strategies and efforts may vary significantly over the years in different countries due to priorities set nationally or even locally. Additionally, data are also not available on a city-based level. If the drug market is not comparable between specific locations in terms of price and purity, national averages are not an ideal basis for back-calculating city-based estimates of drug market values.

It should also be noted that data are submitted to the EMCDDA as average national yearly estimates. However, issues of representativeness may arise from this extrapolation. In some instances, data are obtained from local rather than national monitoring systems, and/or from ad hoc studies. Furthermore, different methods are employed to calculate the averages (i.e., weighted versus simple means). In terms of drug prices, however, the data obtained for this study are corrected for inflation rates to ensure reliable interpretation.

Another source of uncertainty is that information on the retail prices and purity of drugs is not always recorded on a yearly basis. Therefore, temporal changes in drug prices could result in differences in market size estimates. Furthermore, despite thresholds determining what seized quantity constitutes retail use being agreed at EU level, some countries deviate from the reporting protocol.

Figure 5 gives an overview of the available data on back-estimated mass loads, drug purity and drug retail pricing. As shown by this chart, back-calculated mass loads of illicit drugs were available for most locations and time points, making it possible to calculate the amount of pure parent drug consumed. However, information on drug purity and pricing is often scarce or unavailable for specific countries and years, which complicates the calculation of the value of the drugs consumed. As discussed in Section 3.2, imputation of missing values was possible in some cases. However, for many data points this was not possible due to the lack of representative data on drug purity and retail prices.

FIGURE 5

Overview of data available to EMCDDA on drug consumption (WBE), purity and prices

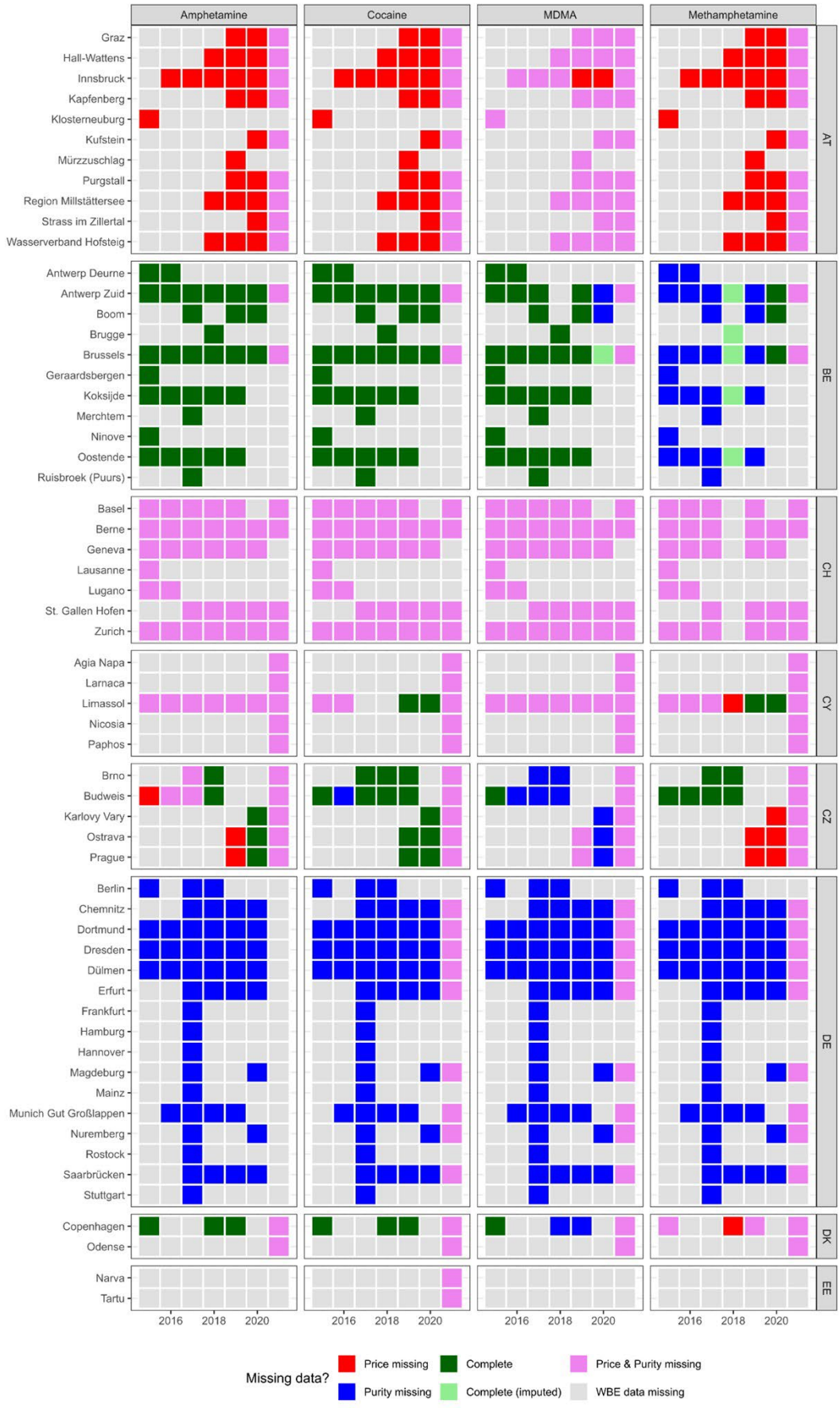
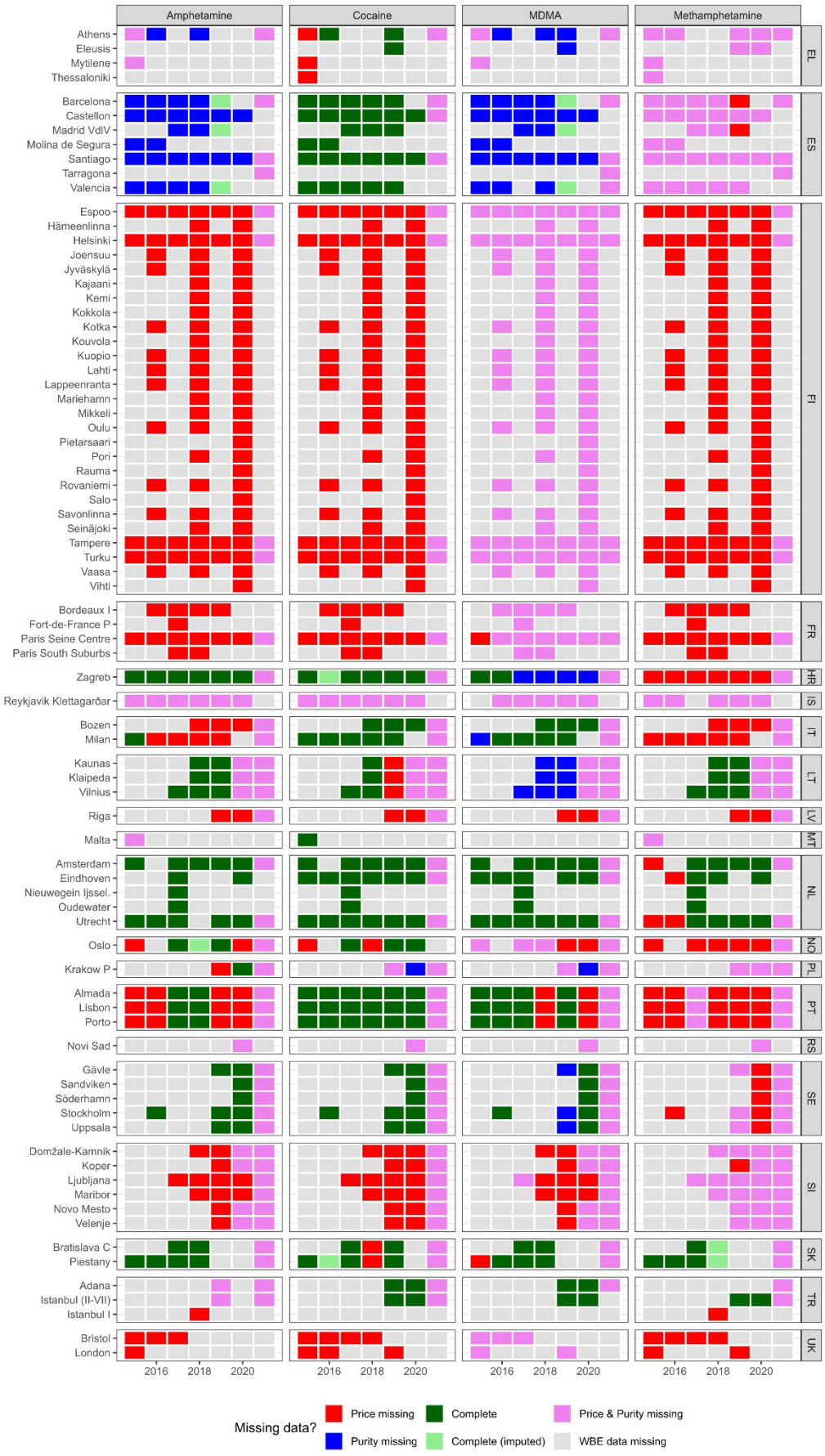


Figure 5, continued.



Recommendations for future WBE studies on estimating city-level drug market size

WBE could be employed as a complementary information source to monitor spatio-temporal changes in the drug market. Although WBE is a promising tool for the estimation of market sizes, this approach involves some intrinsic uncertainties. Over the last decade, a great deal of fundamental research on the methodological uncertainties of WBE has been performed, with a view to further optimising and streamlining its application to monitoring illicit drug consumption at a local level. To minimise the limitations of this methodology, specific criteria are provided by the SCORE network for participation in the yearly monitoring campaigns. This includes taking part in the annual inter-laboratory exercise and compliance with a best-practice protocol to ensure the production of sound and reliable data.

For logistical reasons, only wastewater data from one ‘normal’ week are included each year per location to provide a baseline for illicit drug use. However, the extent to which special events (e.g., festivals, holidays, concerts) impact drug market size should be further explored. Additionally, seasonal variations in illicit drug use should be further investigated to test the validity of this sampling scheme for the estimation of drug market sizes. To obtain the full picture of drug market shares in Europe, the SCORE network could be extended to include more cities (e.g., in Eastern European countries) to achieve a more inclusive pan-European coverage.

Extensive knowledge regarding the parameters used in back-calculations is required for a reliable interpretation of the drug market estimations. More detailed information on drug purity and pricing is needed to back-calculate market size estimates based on WBE mass loads. At present, the lack of up-to-date information on drug price and purity is creating a bottleneck. The limitations of the currently used methods for compiling data on drug purity and pricing include a lack of spatial specificity, lags in data acquisition and the infrequency of data reporting (i.e., data are often not compiled on a yearly basis). Additionally, some of these figures have issues in terms of representativeness (i.e., they are often based on non-repeated case studies, or have a limited number of data points and poor spatial coverage). The imputation of missing values is also complicated by the dynamic nature of the illicit drug market. Furthermore, data on drug purity and pricing are often derived from a wide range of information sources, and the comparability between these different datasets is frequently uncertain. Therefore, there is a need to harmonise the sampling and reporting strategies across different countries and national focal points. Furthermore, national focal points should review data on drug purity and pricing more rigorously to check if they are representative of their country.

References

Baker, D. R. and Kasprzyk-Hordern, B. (2011), 'Multi-residue determination of the sorption of illicit drugs and pharmaceuticals to wastewater suspended particulate matter using pressurised liquid extraction, solid phase extraction and liquid chromatography coupled with tandem mass spectrometry', *Journal of Chromatography A*, 1218(44), pp. 7901–7913.

BCFI (2023), 'Gecommentarieerd Geneesmiddelenrepertorium – Zenuwstelsel – Middelen Bij ADHD En Narcolepsie – Lisdexamfetamine', January 19, https://www.bcfi.be/nl/chapters/11?frag=8902082.

Bettington, E., Spinks, J., Kelly, F., Gallardo-Godoy, A., Nghiem, S. and Wheeler, A. J. (2018), 'When is a medicine unwanted, how is it disposed, and how might safe disposal be promoted? Insights from the Australian population', *Australian Health Review*, 42(6), pp. 709–717.

Boogaerts, T., Ahmed, F., Choi, P. M., Tscharke, B., O'Brien, J., De Loof, H., Gao, J. et al. (2021a), 'Current and future perspectives for wastewater-based epidemiology as a monitoring tool for pharmaceutical use', *Science of the Total Environment*, Vol. 789, October 1, 2021, p. 148047.

Boogaerts, T., Jurgelaitiene, L., Dumitrascu, C., Kasprzyk-Hordern, B., Kannan, A., Been, F., Emke, E., de Voogt, P., Covaci, A. and van Nuijs, A. L. N. (2021b), 'Application of wastewater-based epidemiology to investigate stimulant drug, alcohol and tobacco use in Lithuanian communities', *Science of the Total Environment*, 777, p. 145914.

Boogaerts, T., Quireyns, M., De Prins, M., Pussig, B., De Loof, H., Matheï, C., Aertgeerts, B. et al. (2022), 'Temporal monitoring of stimulants during the COVID-19 pandemic in Belgium through the analysis of influent wastewater', *International Journal of Drug Policy*, 104, p. 103679.

Castiglioni, S., Bijlsma, L., Covaci, A., Emke, E., Hernández, F., Reid, M., Ort, C. et al. (2013), 'Evaluation of uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers', *Environmental Science & Technology,* 47(3), pp. 1452–1460.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) (2022a), *European drug report 2022: trends and developments*, Publications Office of the European Union, Luxembourg.

EMCDDA (2022b), *Statistical bulletin 2022 – price, purity and potency*, https://www.emcdda.europa.eu/data/stats2022/ppp_en

EMCDDA (2022c), *Wastewater analysis and drugs – a European multi-city study*, https://www.emcdda.europa.eu/publications/html/pods/waste-water-analysis_en

EMCDDA and Europol (2020), *EU drug markets: impact of COVID-19*; Publications Office of the European Union, Luxembourg

Emke, E., Evans, S., Kasprzyk-Hordern, B. and de Voogt, P. (2014), 'Enantiomer profiling of high loads of amphetamine and MDMA in communal sewage: a Dutch perspective', *Science of the Total Environment*, 487, pp. 666–672.

European Medicines Agency (2011), *Guideline on Bioanalytical Method Validation*, EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2, 21 July 2011.

Gao, J., Li, J., Jiang, G., Shypanski, A. H., Nieradzik, L. M., Yuan, Z., Mueller, J. F., Ort, C. and Thai, P. K. (2019), 'Systematic evaluation of biomarker stability in pilot scale sewer pipes', *Water Research*, 151, pp. 447–455.

Gonzalez-Marino, I., Baz-Lomba, J. A., Alygizakis, N. A., Andres-Costa, M. J., Bade, R., Bannwarth, A., Barron, L. P. et al. (2020), 'Spatio-temporal assessment of illicit drug use at large scale: evidence from 7 years of international wastewater monitoring', *Addiction,* 115(1), pp. 109–120.

Gracia-Lor, E., Zuccato, E. and Castiglioni, S. (2016), 'Refining correction factors for back-calculation of illicit drug use', *Science of the Total Environment*, 573, pp. 1648–1659.

Guirguis, K. (2010), 'Medications collected for disposal by outreach pharmacists in Australia', *Pharmacy World & Science*, 32(1), pp. 52–58.

Kato, R. (1975), 'Sex-related differences in drug metabolism', *Drug Metabolism Reviews*, 3(1), pp. 1–32.

Li, J., Gao, J., Thai, P. K., Shypanski, A., Nieradzik, L., Mueller, J. F., Yuan, Z. and Jiang, G. (2019), 'Experimental investigation and modeling of the transformation of illicit drugs in a pilot-scale sewer system', *Environmental Science & Technology*, 53(8), pp. 4556–4565.

O'Brien, J. W., Banks, A. P. W., Novic, A. J., Mueller, J. F., Jiang, G., Ort, C., Eaglesham, G., Yuan, Z. and Thai, P. K. (2017), 'Impact of in-sewer degradation of pharmaceutical and personal care products (PPCPs) population markers on a population model', *Environmental Science & Technology*, 51(7), pp. 3816–3823.

Ort, C., Eppler, J. M., Scheidegger, A., Rieckermann, J., Kinzig, M. and Sörgel, F. (2014), 'Challenges of surveying wastewater drug loads of small populations and generalizable aspects on optimizing monitoring design', *Addiction*, 109(3), pp. 472–481.

Pebesma, E. (2018), 'Simple features for R: standardized support for spatial vector data', *The R Journal,* 10(1), pp. 439–446.

Petrie, B., Barden, R. and Kasprzyk-Hordern, B. (2015), 'A review on emerging contaminants in wastewaters and the environment: current knowledge, understudied areas and recommendations for future monitoring', *Water Research*, Vol. 72, Occurrence, Fate, Removal and Assessment of Emerging Contaminants in Water in the Water Cycle (from Wastewater to Drinking Water), April 1, pp. 3–27.

Petrie, B., Youdan, J., Barden, R. and Kasprzyk-Hordern, B. (2016), 'New framework to diagnose the direct disposal of prescribed drugs in wastewater – a case study of the antidepressant fluoxetine', *Environmental Science & Technology*, 50(7), pp. 3781–3789.

Quireyns, M., Boogaerts, T., Van Wichelen, N., Covaci, A. and van Nuijs, A. L. N. (2022), 'State-of-the-art analytical approaches and strategies to assess disposal of drugs for wastewater-based epidemiology', *WIREs Forensic Science*, 5(1), p. e1469.

R Core Team (2022), *R: a language and environment for statistical computing*, R Foundation for Statistical Computing, Vienna.

Ramin, P., Brock, A. L., Causanilles, A., Valverde-Pérez, B., Emke, E., de Voogt, P., Polesel, F. and Plósz, B. Gy. (2017), 'Transformation and sorption of illicit drug biomarkers in sewer biofilms', *Environmental Science & Technology*, 51(18), pp. 10572–10584.

U.S. Department of Health and Human Services Food and Drug Administration (2018), *Bioanalytical Method Validation Guidance for Industry*.

Tscharke, B. J., Chen, C., Gerber, J. P. and White, J.M. (2016), 'Temporal trends in drug use in Adelaide, South Australia by wastewater analysis', *Science of the Total Environment*, 565, pp. 384–391.

Udrisard, R., Esseiva, P. and Zobel, F. (2022), I*mproving the estimation of the size of the European drug market*, Addiction Suisse, Lausanne

van Nuijs, A. L. N., Abdellati, K., Bervoets, L., Blust, R., Jorens, P. G., Neels, H. and Covaci, A. (2012), 'The stability of illicit drugs and metabolites in wastewater, an important issue for sewage epidemiology?', *Journal of Hazardous Materials*, 239–240, pp. 19–23.

van Nuijs, A. L. N., Lai, F. Y., Been, F., Andres-Costa, M. J., Barron, L., Baz-Lomba, J. A., Berset, J. D. et al. (2018), 'Multi-year inter-laboratory exercises for the analysis of illicit drugs and metabolites in wastewater: development of a quality control system', *TrAC-Trends in Analytical Chemistry*, 103, 2018, pp. 34–43.

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L.D., François, R., Grolemund, G. et al. (2019), 'Welcome to the Tidyverse', *Journal of Open Source Software*, 4(43), p. 1686.

Yasuda, S., Zhang, L. and Huang, S.-M. (2008), 'The role of ethnicity in variability in response to drugs: focus on clinical pharmacology studies', *Clinical Pharmacology & Therapeutics*, 84(3), pp. 417–423.