TITLE: Wastewater based epidemiology for the surveillance of illicit drug and substance of abuse use in prison settings: a critical review

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Abstract

People held in prison suffer from drug use disorders, with important health and safety implications. In order to design strategies to reduce drug consumption and for provision of services, reliable data is necessary. In this study, a review of published works that have applied wastewater-based epidemiology (WBE) in prison settings was performed, in order to evaluate its utility. The study also explored future options of WBE in correctional settings.

A search of MEDLINE was conducted using the following PubMed query terms: ("Wastewater" OR "Sewage") AND ("Prisons" OR "Health Care Correctionals") AND ("Abuse, substance" OR "illicit drugs") since 2005 (first report of WBE applied to illicit drug consumption) to February 26, 2025. Then, it was complemented by a Google Scholar citation analysis.

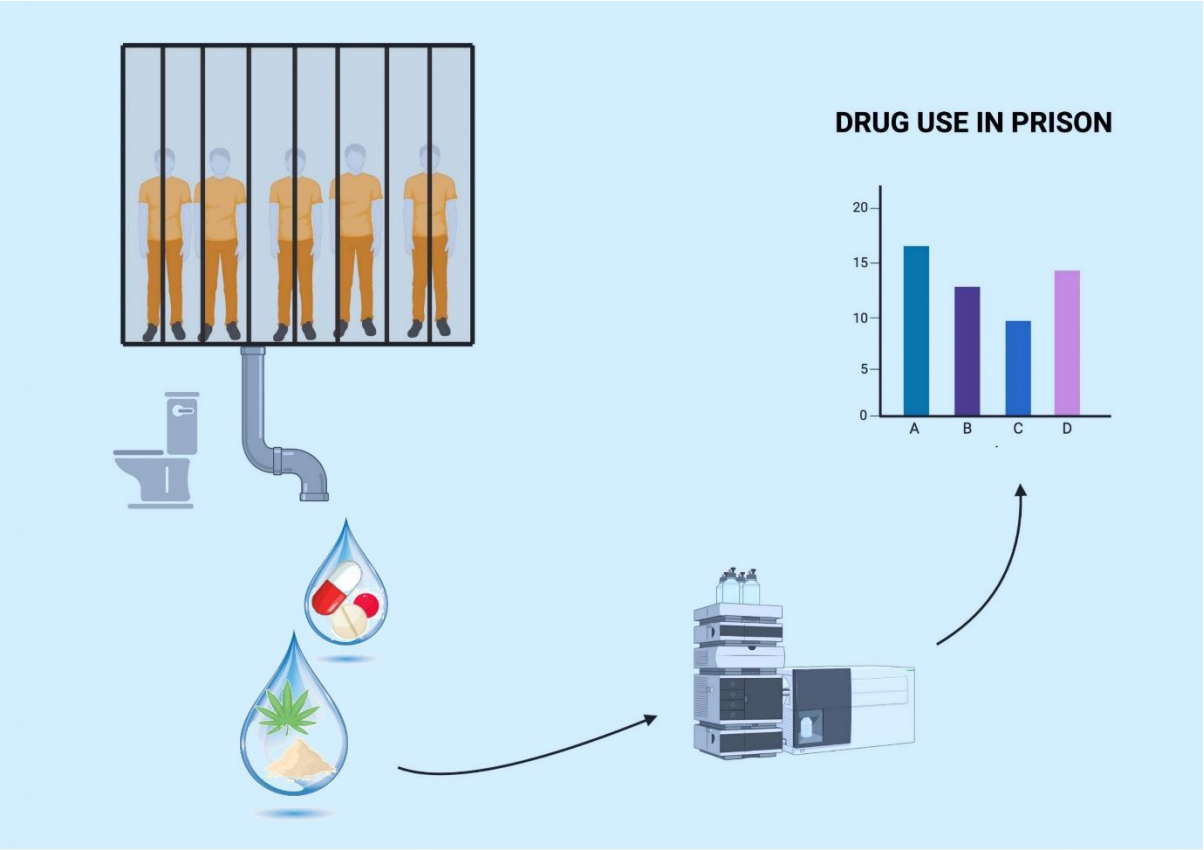
We found 8 studies, half of which have been conducted is Australia. Cocaine, cannabis, methamphetamine and methadone have been the most widely monitored substances (5 studies). Different studies have also monitored various new psychoactive substances (NPS). So far, estimation consumption in prison settings has generally been lower than in the community, with the exception of cannabis and cocaine in French prisons.

WBE has proven to be a valuable complementary tool to inform drug consumption in prison settings, as it can offer objective data. However, the number of publications is still limited. Studies focusing on

gabapentinoids, synthetic cannabinoids, or enantiomeric profiling should be considered in future research. Additionally, the use of WBE to monitor the effectiveness of interventions offers also a great potential.

Keywords: Wastewater surveillance; prison; drugs of abuse; prescription misuse; illicit drugs; wastewater analysis

Graphical/Visual Abstract



Wastewater based epidemiology can result useful in the surveillance of illicit drug and substance of abuse use in prison settings

1. INTRODUCTION

People held in prison suffer high levels of sexual health problems, suicide attempts, self-harm, and substance use, including alcohol, tobacco, and illicit drug use disorders (Enggist, 2014, Australian Health & Welfare, 2022). For example, according to a recent survey about Health and Drug Use in the Prison Population in Penitentiary Institutions conducted by the Spanish Observatory of Drugs and Drug Addiction (ESDIP, 2022), the consumption of all illegal drugs is higher among the prison population in the 12 months prior to their admission to prison than in the general population (ESDIP, 2022). Furthermore, 75.1% of the incarcerated population has consumed some illegal drug before being imprisoned. Similarly, in Australia and in the United States of America (USA) more than 50% of prison entrants reported using illicit drugs in the previous 12 months (Australian Health & Welfare, 2022; (Sawyer & Wagner, 2023).

Additionally, there is a high prevalence of mental illness among inmate population. For example, 34.8% of the Spanish prison population reports having been diagnosed with a mental or emotional disorder at some time in their lives (ESDIP, 2022). Additionally, reported prevalence of comorbidity of mental health and substance use disorders in prison settings is high (EMCDDA, 2021; Vicens et al., 2011, Casares-López et al., 2011). The most common mental health disorders among people who use drugs in Spanish prisons include personality disorders (such as antisocial personality disorder), major depression and psychotic illnesses such as schizophrenia, schizophreniform disorder, maniac episodes and delusional disorder (Arroyo & Ortega, 2009; Vicens et al., 2011). A study carried out in London showed that the prevalence of psychosis in incarcerated population was more than 20 times higher than that of the

general community, and that around 70% of people in prison had more than one mental health disorder (Bebbington et al., 2017). Mental health problems are also prevalent in prisons. For instance, in Australia more than a half of prison entrants reported mental health issues at some stage in their lives (Australian Health & Welfare, 2022). A similar pattern can be seen in prisons in the USA (U.S. Department of Justice, 2016).

The abuse of drugs has important health and safety/security implications in prisons. It is frequently associated with increasing violence and harassment (Kevin, 2005); impedes rehabilitation goals (MacPherson, 2004); increases transmission of blood-borne viruses (human immunodeficiency virus (HIV) and hepatitis C virus (HCV)) by sharing used injection equipment (ECDC, 2018); contributes to prison overdose deaths; and can exacerbate prisoners' mental health and social problems (Dolan et al., 2007). Additionally, upon release, ex-inmates who abuse substances are at increased risk of criminal behavior, relationship instability, unemployment, an increased risk of fatal overdose (Nunn et al., 2009) and transmission of infectious diseases such as tuberculosis, HCV and HIV (EMCDDA., 2012).

Often, it is in prison where prevention, treatment, and harm reduction services are provided to drug users (provision of drug information and drug prevention, opioid replacement treatment programs, psychosocial interventions, preparation for release and social reintegration, etc.), whom community health services consider hard to reach, in order to address their drug use and drug-related problems (EMCDDA., 2021). Substance abuse continues when people is incarcerated, as e.g. in Spanish prisons, 16.8% of inmates reported having consumed (in the last 30 days) illegal drugs while being incarcerated

(ESDIP, 2022). Similarly, approximately 2 out of 5 prison dischargees reported using illicit drugs in Australian prisons (Australian Health & Welfare, 2022). In fact, 18% of the prison population is incarcerated for crimes such as drug possession and trafficking, only surpassed by robbery crimes (32%) in Europe (EMCDDA, 2021). According to a meta-analysis conducted by Bennet et al. (2008), there is a substantial correlation between drug use and crime, with drug users committing crimes around 3 times more frequently than non-drug users. Crack users are six times more likely to commit a crime, followed by heroin users (3 times more) and cocaine users (2.5 times more probable) (Bennet et al., 2008).

In order to design effective strategies to reduce drug consumption and for the proper planning and provision of services that can improve the health conditions and social well-being of people in prison, it is necessary to ensure the availability of reliable (and comparable) data. Examples of improvements in this field include the EMCDDA methodological framework for monitoring drugs in European prisons (EMCDDA., 2021).

In 2001, Christian Daughton, a former directive of the United States Environmental Protection Agency, proposed a, at that time, revolutionary idea: using wastewater samples at the entrance to wastewater treatment plants (WWTPs), in order to estimate consumption of drugs, exposure to contaminants or the presence of certain pathogens in a population (Daughton, 2001). These samples collected the urine and feces of thousands of people in an aggregated and anonymous manner. In 2005, Zuccato et al. used this approach to estimate the use of the illegal drug cocaine in Italy for the first time. Since then, this methodology, currently known as wastewater-based epidemiology (WBE) or sometimes

wastewater/sewage surveillance, has been widely applied by several authors to estimate the consumption of illicit drugs across the world (Huizer et al., 2021; Thomas et al., 2012; Gonzalez-Mariño et al., 2020).

Apart from municipal WWTP inlets, this technique is also valid for other more localized settings like prisons (Hassard et al., 2022). WBE can be a complement to existing methods as it provides a more objective and representative approach, given that prisons are enclosed environments with a defined population and their wastewater discharges into a specific sewer system. It is a relatively low-cost, fast and easy-to-implement reliable method, and allows for comparison between sampled sites. It also enables frequent measurements, making it possible to sample different time periods and observe temporal changes in consumption. Although WBE avoids certain ethical and privacy concerns by providing anonymity, the application of WBE to specific settings like prisons has led to the development of ethical guidelines (Prichard et al., 2014).

Since the first study applying this tool in a prison in 2011 in a penitentiary center in Girona, northeastern Spain (Postigo et al., 2011), some further studies were developed. However, the full potential of WBE for monitoring drug use among inmates is still to be examined.

In this study, we performed a systematic review of published works that have applied WBE in prison settings, in order to evaluate the utility of WBE as a complementary method to measure the type and amount of legal and illegal substances consumed in prisons. Furthermore, we explored if implementing WBE in the monitoring and assessment of illicit drug/substance of abuse in prison settings could be

useful. Last but not least, current research gaps are addressed and results are carefully discussed with the aim of improving effectiveness in prevention measures.

2. METHODS

The PRISMA guideline for elaborating systematic reviews was followed to perform the study (Page et al., 2021).

2.1 Search strategy

We performed a systematic review of the literature on illicit drug/substance of abuse use, wastewater, and prison settings. A systematic search of MEDLINE was conducted using the following PubMed query terms: ("Wastewater" OR "Sewage") AND ("Prisons" OR "Correctional facilities") AND ("Abuse, substance" OR "illicit drugs"). Search was performed since 2005 (first published report of WBE applied to illicit drug consumption (Zuccato et al., 2005)) to March 2024. The search was originally performed on 12 March 2024 and updated during the peer review process on 26 February 2025.

2.2 Inclusion/exclusion criteria

We included studies that: a) applied WBE to estimate illicit drug and substance of abuse in prison/correctional settings b) No language, time or geographical restrictions were applied.

We excluded studies that: a) did not refer to substance abuse (both legal and illegal) in prison settings; b) Applied grab sampling (i.e: no 24 h composite sampling was performed); c) No flow-rate was estimated; And d) studies that did not allow to estimate consumption in prison/correctional settings (not

possible to define a population and their wastewater discharges into a specific prison sewer system). Characteristics of these excluded studies can be consulted as supplementary material (Table S1).

With regards to consumption of illicit drugs and substance of abuse, all retrieved data, when possible, were converted to the same units: i.e: mg/day/1000 inh., as detailed below (see Data Extraction and Homogenization section).

2.3 Selection process

Four authors (IE, VA, MN and UL) independently evaluated the titles and abstracts of each of the studies to assess whether they meet the inclusion criteria. Subsequently, the reference list of the selected articles was used to look for new articles. Furthermore, we utilized Google Scholar to conduct a citation analysis of the chosen studies and scrutinized the content of the retrieved citations. To reduce bias, the researchers reviewed manuscripts autonomously, without having maintained contact with the authors or having participated in their development. Discrepancies were resolved through critical discussion with the rest of the authors until agreement was reached. Afterwards, each author individually evaluated the full text of the articles and studies that did not meet the inclusion criteria were excluded. A flowchart of the search strategy can be consulted as supplementary material (Figure S1).

2.4 Data extraction and homogenization

Four authors (IE, VA, MN and UL) after manually revising every article, independently extracted data from each program into custom tables in Microsoft Excel, including the following data: a) publication year; b) country; c) setting (inmate population); d) sampling (period of the year, number of samples,

sampling method) and analytical method; e) list of monitored substances; f) load of substance; g) applied correction factors.

Population-normalized loads data were directly obtained from each study, or back-calculated from consumption estimation data using the correction factors detailed in each study (Table S2). Subsequently, to allow comparability among different works and settings, they were again converted to consumption data (in mg/day/1000 inh.) by using the most updated correction factors compiled by Wang et al (Wang et al., 2023). Although several correction factors are proposed in the literature, the use of this single factor allows for comparability, while as being the most recent one, it compiles data and consensus from the former literature.

Three authors (VA, XGG, and UL) performed all these calculations. In the case of cocaine, cannabis (Δ9- tetrahydrocannabinol, THC), methadone, morphine and ketamine consumption back-calculations were based on the population-normalized loads of their metabolites, viz.: benzoylecgonine, 11-nor-9-carboxy-Δ9- tetrahydrocannabinol (THC-COOH), 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), 6-monoacetylmorphine (6-MAM) and norketamine, respectively.

Daily consumption of illicit drugs (cannabis, methamphetamine and cocaine) collected in prison settings were then compared with the regional (community) average consumption for every country measured with WBE. For that purpose, we looked for studies that showed illicit and substance of abuse consumption in the same region and time period. The same procedure of unifying back-calculation of drug use using the correction factor proposed by Wang et al (Wang et al., 2023) was performed.

All the metadata compiled and calculation performed are presented in detail in the Supporting Information as an excel file (File S1).

2.5 Methodological quality assessment

To evaluate the methodological quality of each study, we designed an ad-hoc questionnaire based of available WBE recommendations and guidelines (Castiglioni et al., 2013; EMCDDA, 2013). Results of the applied questionnaire can be consulted in Table S3.

3 RESULTS AND DISCUSSION

3.1 Characteristics of the WBE studies in prison settings

The 6 published studies that have used WBE and passed the quality threshold to inform drug abuse (illicit and pharmaceuticals) in prison settings are shown in Table 1.

Table 1. Main characteristics of wastewater based epidemiology (WBE) studies in prison settings to estimate the use of illicit drug/substance of abuse.

STUDY	COUNTRY	PRISON SIZE POPULATION	NUMBER OF DRUGS/ METABOLITES MEASURED	SAMPLING DETAILS	MAIN OBSERVATIONS
Postigo et al., 2011	Spain	3500	19	24-hour composite flow-proportional samples for 10-11 consecutive days (July, September,	• First study applying WBE in penitentiary setting, which also included festivity dates as sampling days. • Among illicit drugs, cannabis and cocaine appeared in all the samples.

				December) and other specific samples (Christmas, New Year`s Eve) in 2008-2009 for a total of **42 samples**	• Cocaine was consumed more on weekends and reached the maximum consume on Christmas' Eve. • Occasional detection of LSD and heroin probably due to direct dumping.
van Dyken et al., 2014	Australia	400	6	24-hour composite volume proportional samples for 7 consecutive days (January) in 2013 for a total of **7 samples**	• First study applying WBE in penitentiary centers of Australia. • Prescription data of methadone was also collected in the study. • The study also analyzed ketamine, although traces were detected.
van Dyken et al., 2016	Australia	390	30	24-hour composite volume proportional samples for 12 consecutive days (May, July) in 2013 for a total of **24 samples**	• For the first time, buprenorphine levels were analyzed and misuse of this drug was detected. • Some new psychoactive substances (mephedrone, methylone) were analyzed and detected occasionally.
Brewer et al., 2016	United States of America	2083	3	24-hour composite samples for 28 days (July, August) and hourly samples of three days in 2011 for a total of **100 samples**	• Random urinalyses were performed over 28 days for a total of 243 samples, that served to compare the 2 methodologies' results. • Metamphetamine appeared in all the hourly composite samples.

Néfau et al., 2017	France	Not provided	13	24-hour composite flow proportional samples in 2015 for a total of **3 samples**	• 3 French penitentiary facilities were sampled, but only data of 2 establishments is provided because of issues with flow measurement. • Massive endemic cannabis use was detected.
Wang et al., 2023	Australia	>500	27	24-hour composite flow proportional samples (March-December) in 2019 for a total of **65 samples**	• Long-term monitoring of drug use in a penitentiary. • Consumption of buprenorphine and methamphetamine (most frequently detected drug) declined after increasing the restrictions for the prison access during COVID-19 pandemics. • Prescription consumption was estimated for buprenorphine, methadone, morphine, tramadol and oxycodone.

SD: Lysergic acid diethylamide; COVID-19: Coronavirus disease 2019

Two studies were not considered WBE studies, and were excluded as capable of providing drug use estimates. Yet, they are considered within the discussion on this review as regards detection or non-detection of particular substances. The study carried out in Northern Ireland (Davies et al., 2023) did not perform composite sampling, nor did measure flow-rate, so consumption (or even normalized load) data could not be obtained. On the other hand, in the Mexican study, it was not possible to define a population and their wastewater discharges into a specific prison sewer system, so we could not obtain consumption data for correctional settings (Cruz-Cruz et al., 2019). Characteristics and main results provided in these 2 studies can be consulted in Table S1.

Of the remaining 6 studies, 4 of them are considered to present low risk of bias, while one study in Australia (van Dyken et al., 2014) and the one in France (Néfau et al., 2017) pose medium and higher bias risk, respectively (Table S3) due to uncertainties in sampling and measurement of flow rates.

As regards their characteristics, studies have been performed across prisons of all sizes: from small prisons, around 400-500 inmates (van Dyken et al., 2014; van Dyken et al., 2016), to big prisons with 3500 inmates (Postigo et al., 2011). All included studies performed 24 h composite sampling (volume or flow proportional). All studies share the analytical technique; solid phase extraction is used to concentrate the samples while liquid chromatography combined with mass spectrometry to analyze them.

The country in which more studies have been conducted is Australia, with 3 publications (van Dyken et al., 2014; van Dyken et al., 2016, Wang et al., 2023). There are also studies from: France (Néfau et al.,

2017), Spain (Postigo et al., 2011) and the USA (Brewer et al., 2016). French and Australian studies also provided dispensing data for prescribed drugs (methadone, codeine, buprenorphine).

Cocaine and cannabis, methamphetamine and methadone have been the most widely monitored substances (5 studies). 3,4-methylenedioxymethamphetamine (MDMA) has been monitored 4 times, while codeine and buprenorphine have been monitored in 3 studies. Two benzodiazepines, alprazolam and oxazepam, have been monitored once each. Different studies have also monitored various new psychoactive substances (NPS). However, so far, none of them has considered licit drugs, namely alcohol and tobacco. A complete list of all monitored substances and the average estimated consumption can be consulted in Table 2.

Table 2. Average estimated consumption (mg/1000 inhabitants/day) ± standard deviation of illicit drug and substance of abuse based on WBE in penitentiary settings, calculated as detailed in Data Extraction and Homogenization section. Details on the back-calculations presented in File S1.xls.

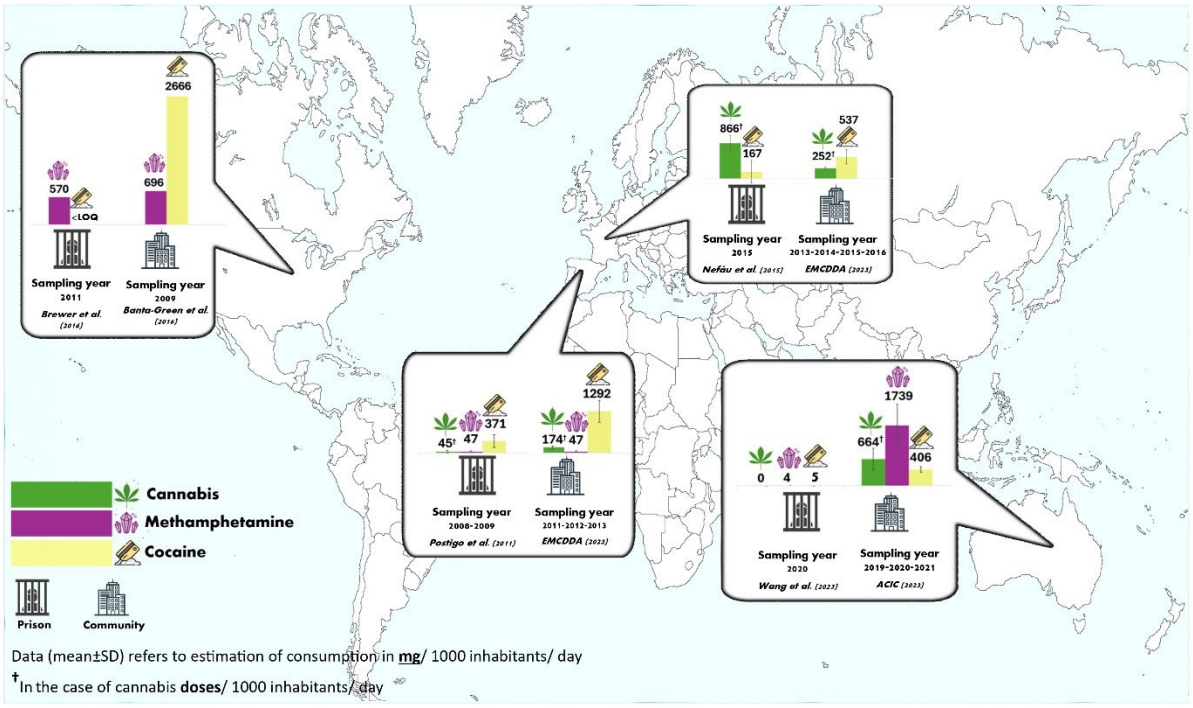
Drug group	Drug (metabolite)	*Postigo et al., 2011*	*van Dyken et al., 2014*	*van Dyken et al., 2016*	*Brewer et al., 2016*	*Néfau et al., 2017*	*Wang et al., 2023*
Stimulants	Cocaine	371 ± 194*	-	<LOQ	<LOQ	167 ± 59.1	4.9
	Amphetamine	57.5 #	19.0 ± 6.5	-	-	-	15 ± 12
	Methamphetamine	47.3 #	118 ± 64 *	132 ± 187	570 *	-	4.4 ± 5.0
	Ephedrine	1167 ± 869 *	-	-	-	-	<LOQ
Ecstasy	MDMA[a]	80	-	<LOQ	-	-	2.5 ± 7.2
	MDA[b], MDEA[c]	-	-	<LOQ	-	-	<LOQ
Opioids	Morphine	-	739.7 ± 100.5	-	-	<LOQ	
	Heroin	1135 ± 667#	-	-	-	<LOQ	540 ± 430
	Methadone	4339.9 ± 1072.1 *	724 ± 158	396 ± 283	-	226 ± 145	210 ± 87
	Codeine	-	4767 ± 866*	2948 ± 1882	-	-	3900 ± 1500
	Oxycodone	-	-	-	-	-	450 ± 220
	Tramadol	-	-	-	-	-	1400 ± 290
	Buprenorphine	-	-	608 ± 277	-	160	100 ± 70
	Fentanyl	-	-	-	-	-	<LOQ
Cannabis	THC[d]	4530 ± 2,031	1175 ± 1266#	<LOQ	-	86684 ± 18770	<LOQ
Benzodiazepines	Alprazolam	131 ± 34*	-	-		-	-

Drug group	Drug (metabolite)	*Postigo et al., 2011*	*van Dyken et al., 2014*	*van Dyken et al., 2016*	*Brewer et al., 2016*	*Néfau et al., 2017*	*Wang et al., 2023*
	Oxazepam	-	-	-	-	-	-
LSD[j]	LSD[e]	*Possibly thrown into the sewage*[#]	-	-	-	-	-
NPS[i]	Ketamine	-	60.0 ± 22.8	-	-	-	<LOQ
	Mepherdrone	-	-	<LOQ	-	<LOD	<LOQ
	Methylone	-	-	<LOQ	-	-	<LOQ
	4-MEC[f]	-	-	-	-	<LOD	-

*****Detected in all the samples; **#**Detected in only few samples; **<LOQ**: under limit of quantification; **<LOD**: under limit of detection**; [a]MDMA**: 3,4-methylenedioxymethamphetamine; **[b]MDA**: 3,4-methylenedioxyamphetamine; **[c]MDEA**: 3,4-methylenedioxy-N-ethylamphetamine; **[d]THC**: tetrahydrocannabinol; **[e]LSD**: lysergic acid diethylamide; **[f]4-MEC**: 4-metilethcatinone.

3.2 WBE-estimated use of drugs in prisons

The consumption in prison settings was compared with the estimation of consumption in the community (Figure 1). As it can be observed, there are important differences in the amount and pattern of illicit drug and substance of abuse measured in different settings, which will be subsequently discussed below. Data used to estimate drug consumption in the community was obtained from WBE studies corresponding to similar years to those than the corresponding prison studies, as compiled into Table S4 (details in File S1).



3.2 1 Stimulants

Cocaine (measured as it metabolite, benzoylecgonine) has been one of the most frequently monitored substance in WBE studies in prisons. Higher average consumption in France (Néfau et al., 2017) and Spain (Postigo et al., 2011) has been reported (167 and 371 mg/day/1000 inh., respectively), compared with Australia (van Dyken et al., 2014; van Dyken et al., 2016, Wang et al., 2023), and the USA (Brewer et al., 2016), where consumption vary between under limit of quantification (<LOQ) to 0.8 mg/day/1000 inh. This partially reflects the higher use of cocaine in Europe also among the general population, when compared to Australia. However, estimated cocaine consumption among prisoners in those studies are lower than what it has been reported in the general population (EMCDDA, 2023c). For example, the estimated amount of cocaine consumed per person in a Spanish prison (371 mg/day/1000 inh.) was lower to the estimated consumption in Barcelona in the period 2011-2013. (EMCDDA, 2023c). This is also the case in Australia, were cocaine use in the community (Queensland) in the period 2019-2021 (ACIC 2023, ACIC 2022, ACIC 2021) was much higher than in the prison. Information from surveys show that 1.3% of the Spanish prison population reported having consumed powder cocaine within the prison in the last 30 days, administered through different routes such as sniffing, smoking, or injecting. It is noteworthy that 1% of users acknowledged starting to use powder cocaine while in prison (ESDIP, 2022).

Amphetamine, and specially metamphetamine, have also been monitored in several studies. The highest in-prison methamphetamine use was reported in the USA (Brewer et al., 2016), with an estimated consumption in the range of 180-960 mg/day/1000 inh., which is similar to the consumption reported in the Northwest region of the USA, where the studied prison is located (Banta-Green et al.,

2009). A similar amount was estimated in the Australian National reports for the last 5 years (1000-2350 mg/day/1000 inh.) (Australian Criminal Intelligence Commission 2023), and several countries in Northern Europe (EMCDDA, 2023c) or Mexico (1817 day/1000 inh. in Culiacán) (Cruz-Cruz et al., 2019). However, metamphetamine consumption in Australian prisons is lower than in the community. Interestingly, the study of Wang et al., 2023 showed that metamphetamine use decreased when no visitors were allowed during the COVID-19 pandemic (Wang et al., 2023). Methamphetamine consumption is lower in Spain, both in the general population (Spanish national average, 51.2 mg/day/1000 inh.) (Bijlsma et al., 2021), and in prisons where “sporadical use” was reported (Postigo et al., 2011).

Several studies have monitored MDMA in prison wastewater, showing very low consumption in general (Postigo et al., 2011; van Dyken et al., 2016; Néfau et al., 2017; Wang et al., 2023). Some studies have also measured 3,4-methylenedioxy-N-ethylamphetamine (MDEA) and 3,4-methylenedioxyamphetamine (MDA) (van Dyken et al., 2016; Wang et al., 2023). Both MDEA and MDA can be an impurity in “ecstasy” tablets (Cheng et al., 2006), while MDA is also a MDMA metabolite.

Ephedrine was also monitored in the Spanish study, showing an average consumption of 1167 mg/day/1000 inh. (Postigo et al., 2011), while it was monitored but not detected in any of the samples in Australia (Wang et al., 2023). This substance has illicitly been used as stimulant, appetite suppressant and concentration aid, but also as a prescription drug to treat various diseases (asthma, hypotension).

3.2 2 Opioids

Several opioids have been monitored in prison´s wastewater. Both methadone (through its metabolite EDDP) and buprenorphine, which are frequently used for opioid use disorder, have been the most frequently monitored substances. The consumption estimated using WBE seems to correlate well with dispensed methadone. Methadone is a maintenance therapy with a good record and a low probability of non-medical use, so it could potentially be used as a quality control marker in WBE implementation. On the contrary, non-prescribed buprenorphine use has been reported in prison settings (Gryczynski et al., 2021). In particular, the use of WBE to measure actual use of buprenorphine and compare it with prescription data has shown that this drug is indeed being diverted in Australian prisons. (Van Dyken et al., 2016, Wang et al., 2023). Furthermore, buprenorphine use decreased during the COVID-19 pandemic, probably due to a reduction in drug trafficking (Wang et al., 2023). Sublingual buprenorphine is easier to infiltrate into (drug smuggling) and transfer within the prisons without being detected (Bi-Mohammed et al., 2017, Norman, 2022). For that reason, there is now a recommendation to use subcutaneous buprenorphine (Royal College of Psychiatrists, 2023).

In the study published by Wang et al., 2023 the average daily consumption of codeine (estimated by WBE) was approximately 6-times higher than pharmacy dispensing data. The authors discussed that this could be because of non-prescribed codeine use or direct disposal of the substance into the sewer system (Wang et al., 2023).

Other prescription opioids that have been monitored in prisons include: morphine, tramadol and oxycodone. The WBE analysis carried out by Wang et al. showed no evidence of abuse of these

substances in prison (Wang et al., 2023). Up to now, two studies have tried to detect fentanyl in prison wastewater, but it has not been detected (Wang et al., 2023; Davies et al., 2023).

3.2 3 Cannabis

One of the most important conclusions in the study of Néfau et al. was the “massive or, indeed, endemic cannabis use in the prison setting”. Even if taking into account technical constraints, a daily average use of 86.69 ± 18.77 g of THC /day/1000 inh. was reported (Néfau et al., 2017). This consumption is around 3.5 times higher than in the general population in the area of Paris for the period 2013-2016 (EMCDDA, 2023c).

The Spanish study showed a lower cannabis use (around 4.5 g of THC/day/1000 inh.), but still, higher than reported in other countries (i.e: Australia and USA). Nevertheless, this cannabis consumption is almost 4 times lower than what was reported for Barcelona in 2011-2013 (EMCDDA, 2023c). According to the Survey on Health and Drug Consumption in the inmate population in Correctional Institutions (ESDIP, 2022), cannabis was the most consumed illegal drug in Spanish prisons in 2022, with 11.2% of the inmate population reporting having consumed this substance in the last 30 days within the prison.

3.2 4 Benzodiazepines

The study of Postigo et al. was the first to monitor benzodiazepines in prison´s wastewater. In particular, they monitored alprazolam (Postigo et al., 2011). They did not provide pharmacy dispensing data, so no comparison with WBE estimation can be performed. The study of Néfau et al. monitored oxazepam, but acknowledged that it was not possible to estimate consumption because this substance is a metabolite of several different benzodiazepines (Néfau et al., 2017). Davies et al. also monitored

alprazolam, which was not detected, and oxacepam which appeared in some samples (Davies et al., 2023).

3.2 5 New psychoactive substances

NPS have earned growing attention from a public healthcare perspective (Simão et al., 2022). The study of van Dyken et al. was the first to monitor an NPS via WBE in a prison, showing traces of ketamine and mephedrone (4-methylmethcathinone or 4-MMC) (van Dyken et al., 2014). Two years later, they monitored the stimulants MDEA and MDA. All of them were below the limit of quantification (van Dyken et al., 2016). The study carried out by Wang et al. (Wang et al., 2023) monitored MDEA, MDA, mephedrone, methylone, norketamine and ketamine. All of them remained undetected throughout the study. Finally, Davies et al. (Davies et al., 2023) monitored several NPS but could not detect any. Indeed, detection of NPS in wastewater is a challenging task, as their use is normally marginal compared to other drugs, they have a largely unknown metabolism and their presence in the illicit market is very volatile. Yet, there are still open possibilities, which are discussed below.

3.3 Urinalysis controls

Analysis of wastewater in prisons has also been compared with random urinalysis, which has been traditionally used in this setting to obtain information about substance abuse (Brewer et al., 2016; van Dyken et al., 2016). In the study of Brewer et al., urinalysisis were only positive for the presence of methamphetamine on 6 out of 243 samples within one month. On the contrary, wastewater analysis revealed methamphetamine excretion every day and every hour (Brewer et al., 2016), which may

indicate that inmates are able to evade urine testing, while WBE would provide a more representative situation of drug use.

3.4 Limitations

As any other drug use indicator, WBE has its limitations. On the one hand, it only provides aggregate consumption information, so it does not offer information about individual use. A major limitation that should be considered results from WBE studies is that, depending on the sewer system, it may not be able to discriminate prisoner use from workers or visitor use; thereby data interpretation needs to be taken with caution. While still achievable, obtaining representative composite samples can be a challenging task, especially in small prisons, and measuring flow-rates can be difficult, since a flow-meter needs to be fitted in the sampling point.

Additionally, there are ethical considerations, particularly when studying smaller populations especially in specific study settings like prisons (EMCDDA, 2016; Prichard et al., 2014; Ort et al., 2014; Hall et al., 2012). Although these are less concerning than urinanalyses or cell searches, since data will be aggregated, data communication requires considering such ethical issues in particular to avoid stigmatization.

From the point of view of the processes used to review the articles, we were not able to find a good guideline criteria about the quality of studies linked with WBE. So we have made our own model to determine the quality of the performed studies (Table S3). This model might not be suitable for other reviews about this topic.

3.5 Additional monitoring studies

In this paper, we have reviewed and discussed all the available reports in which drug abuse has been measured by means of WBE in prisons to date. However, as shown above, the number of publications is rather limited. Based on what is already known about both WBE and drug use in prisons, we believe that this methodology has great and unexplored potential for monitoring drugs and designing further preventive interventions. In the following lines, we explore some examples of patterns of psychoactive substance use and aspects that might be relevant to consider.

3.5 1. Gabapentin & pregabalin (gabapentinoids)

Both pregabalin and gabapentin are used recreationally due to their ability to produce sedative effects accompanied by a pleasant sense of euphoria, leading to what is known as "pharming" or "pharm party," which is becoming increasingly common in correctional settings (Royal College of psychiatrists, 2019). Gabapentinoids can also enhance the euphoric effects of other drugs like opioids due to increased absorption when taken simultaneously with them (Soni & Walters, 2019). A systematic review on gabapentinoid abuse concluded that abuse or misuse of gabapentinoids occurs especially in patients in opioid substitution programs or with opioid dependence, with misuse observed in up to one in every three or four patients in this population (Mathieson et al., 2020). Given the high prevalence of patients in opioid substitution programs or with opioid dependence in prisons, as well as the increasingly common use of pharming or recreational drug use, pregabalin and gabapentin are two drugs to consider for understanding their real consumption within correctional facilities. Pregabalin has been specifically reported as one of the most troublesome prescribed medicines abused and diverted in prison settings (Royal College of Psychiatrists, 2019, Soni & Walters, 2019). So far, none of the available studies have

measured gabapentin or pregabalin consumption using WBE in a prison, even though these substances have already been successfully monitored in municipal wastewater treatment plants (Choi et al., 2014, Kannan et al., 2023). Future studies may try to apply WBE to monitor the abuse of these compounds.

3.5.2 Pyrolytic byproducts

Previous studies have measured cocaine´s pyrolytic products derived from its smoked consumption (crack) in wastewater (González-Mariño et al., 2019; Steenbeek et al., 2022). The analysis of these products (anhydroecgonine and/or anhydroecgonine methyl ester) can help to discriminate the route of administration of the drug. For example, the aforementioned study of González-Mariño et al., 2019 showed different consumption patterns including different administration routes between Spain and Brazil.

Some prescribed pharmaceuticals are consumed smoked. In particular, there are reports of abuse of smoked: quetiapine (Haridas et al., 2010), buprenorphine (Horyniak et al., 2011), gabapentin/pregabalin (Evoy et al., 2017) and buthyl-escopolamine (hyoscine) (Jalali et al., 2014).

Techniques to measure pyrolytic products of other substances such as heroin, methamphetamine, amphetamine, fentanyl, and synthetic cannabinoids have been developed or are being studied with promising results, (Bell & Nida, 2015). It would be interesting to explore if the monitoring of these pyrolytic byproducts in wastewater can help to show if drugs are indeed abused this way (smoked) in correctional settings. However, methodological complexities need to be addressed.

3.5.3 Synthetic cannabinoids and other NPS

Synthetic cannabinoid abuse in prisons is frequently reported in the literature (Abbott et al., 2023; EMCDDA, 2023b; Giorgetti et al., 2022, Vaccaro et al., 2022). The abuse of these NPS has been recognized as a particular challenge in recent years by the EMCDDA (EMCDDA, 2023a). The issue with synthetic cannabinoids in prison is that they are easily accessible and perceived as difficult to identify (Abbott et al., 2023). The main entry routes include visitors, staff members, and inmates entering or returning from leave. Another entry route is the use of paper sheets invisibly impregnated with synthetic cannabinoids, which are used as postal correspondence for inmates (Vaccaro et al., 2022; Abbott et al., 2023).

A study carried out in 31 major cities in China monitoring 16 different synthetic cannabinoids in wastewater showed that these substances were used in a significant number of cities (Fan et al., 2022). Synthetic cannabinoids have only been monitored once, in a prison from Northern Ireland (Davies et al., 2023). This study, that used grab sampling, could not detect any of the several synthetic cannabinoid monitored.

Additionally, the illicit market of NPS is rapidly evolving, therefore, the use of screening methods based on chromatography coupled to high-resolution mass spectrometry should also be considered (Bade et al., 2021; Salgueiro-Gonzalez et al., 2022; Bade et al., 2023).

3.5.4 Alcohol and tobacco

The consumption of alcohol decreases significantly while in prison according to surveys (e.g: from 54.5% to 2% in the Spanish prison population (ESDIP, 2022)), likely because it is not possible to acquire this substance in prison since its sale is prohibited, and there are difficulties in its introduction from the

outside due to its high volume (Enggist, 2014). However, incarcerated persons also show disproportionally high levels of alcohol and tobacco use disorders (Australian Health & Welfare, 2022; Barry et al., 2010; EMCDDA, 2023a). Even if alcohol consumption is usually forbidden in correctional settings, there are reports of prison-made illicit alcohol (pruno, moonshine) in the literature (CDC, 2012; Walters et al., 2015). Alcohol use has also been widely studied by WBE (Lopez-García et al., 2020; Ryu et al., 2016; Rodriguez-Alvarez et al., 2015) and therefore, the technique could be easily implemented.

Similarly, tobacco (nicotine) consumption has been widely measured with WBE (Asadi et al., 2023; Montes et al., 2020). There are also improved methods to differentiate tobacco (e.g. by measuring the alkaloids anabasine and/or anatabine) use form nicotine use (Zheng et al., 2023). As far as we are concerned, so far, there is no study reporting nicotine or alcohol use using WBE in prison settings. Detecting tobacco use with WBE could be interesting, considering that there are tobacco bans implemented across prisons in several places, like some regions in Australia and the United Kingdom (Australia Health & Welfare, 2002; Perret et al., 2022), or the fact that tobacco is in many cases the most consumed legal substance by inmates within prisons. In fact, for instance, 74.0% of the Spanish prison population declared having smoked tobacco in the last 30 days (ESDIP, 2022) compared with 37.2% in the general population (Observatorio, Español de las Drogas y las Adicciones, 2023). Smoking plays a complex role in the lives of inmates, as they smoke for various reasons, not just because of the addictive nature of nicotine. Tobacco also relieves stress and boredom and can serve as an important form of currency (Enggist, 2014).

However, in the case of both alcohol and tobacco, unless there is a clear separation of sewers, the results need to be considered with particular caution, given that both substance use may be prevalent among prison staff, as mentioned in 3.4 above.

3.5.5. Enantiomeric analysis

Enantiomeric analysis has resulted useful in source determination of amphetamine like-substances, helping to differentiate between disposal and consumption of prescription versus illicit drug use (Estévez-Danta et al., 2021; Verovšek et al., 2022; Sharfudeen et al., 2023; Mwenesongole et al., 2023). Therefore, this could be particularly relevant in prison setting, where prescriptions are very well controlled and many prescription drugs are normally enantiomerically pure, e.g. lisdexanfetamine, leading to amphetamine, is prescribed as the S-enantiomer whereas illicit amphetamine is normally racemic (Estévez-Danta et al., 2021).

3.5.6 Using WBE in prison settings for prevention and treatment policies

As already discussed above, illicit drug and substance abuse is a relevant problem among incarcerated people (EMCDDA, 2021). WBE may offer relevant information about which substances are the most frequently abused, or which are experiencing an increase in their consumption and as such, may be a valid and complementary element for decision-making on drug addiction prevention and treatment policies within prison.

Interventions for prisoners suffering from substance abuse can be divided in two groups: psychosocial and pharmacological. These interventions are aimed to reduce both consumption and related problems through harm reduction programs (EMCDDA, 2021). Among psychological interventions, cognitive-

behavioral therapy has proven to be useful in reducing recidivism (Beaudry et al, 2021), while motivational interviewing has shown to be effective in reducing consumption. (De Andrade, 2018). A Cochrane database systematic review found that treatment with opioid agonists or naltrexone were not effective in reducing consumption or criminal activity compared to non-pharmacological interventions (Perry et al., 2015). However, a more recent study has shown that opioid substitution treatment is able to reduce opioid consumption (Boksán et al., 2023).

Still, both types of interventions (psychosocial and pharmacological) need more research to reach more robust conclusions.

We envision that WBE may be a useful tool for evaluating the effectiveness of psychosocial interventions and their combination with pharmacological interventions, by establishing experimental designs that consider them as an additional source of verification of the decrease in drug consumption in the inmate population undergoing treatment. It might also be a reliable measure of the success of initiatives to reduce health-related harm in general, such as those that work to lower HIV or HCV infections, needle and syringe exchanges, condom use and an overall decrease in hazardous sexual activity.

Figures, Video, Audio and Tables

Table 1. Main characteristics of wastewater based epidemiology (WBE) studies in prison settings to estimate the use of illicit drug/substance of abuse.

Table 2. Average estimated consumption (mg/1000 inhabitants/day) ± standard deviation of illicit drug and substance of abuse based on WBE in penitentiary settings, calculated as detailed in Data Extraction and Homogenization section. Details on the back-calculations presented in File S1.xls.

Figure 1. Comparison of WBE calculated consumption figures of cannabis (as THC), methamphetamine and cocaine in prison setting and among the general community. Data presented as average ± standard deviation (whenever available) in mg/ 1000 inhabitants/day (methamphetamine and cocaine) or mg/day /100 inh. (THC).

SUPLEMMENTARY MATERIAL

Table S1: Characteristics of excluded studies

Table S2: Correction factors applied in prison WBE

Table S3: Methodological quality prison WBE studies

Table S4: Community consumption of cocaine, methamphetamine and cannabis

File S1. Metadata and back-calculations on drug use from each prison and community population WBE study. (Presented as a separate Excel file).

Figure S1: Flowchart of the search strategy

Wastewater based epidemiology and substance abuse in prison settings:

- Eight studies have applied WBE to estimate drug use in prison settings.

- Cocaine, cannabis, methamphetamine and methadone have been the most monitored substances.
- WBE has proven to be a valuable tool to inform drug consumption in prison settings.
- Studies focusing on gabapentinoids, synthetic cannabinoids, or enantiomeric profiling have been detected as research gaps and should be considered in future studies.

Conclusion

In conclusion, WBE has proven to be a valuable tool to inform illicit drug and substance of abuse consumption in prison settings. WBE offers objective data that can complement or even outperform the information obtained with other methods such as surveys and urinalysis and it is a relatively cheap and fast technology. However, the number of publications is still rather limited, and several research gaps and potential application have been pinpointed in this work. Studies focusing on gabapentinoids, synthetic cannabinoids, or enantiomeric profiling should be considered in future studies. Additionally, the use of WBE to monitor the effectiveness of interventions offers also a great potential.

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Wastewater based epidemiology for the surveillance of illicit drug and substance of abuse use in prison settings: a systematic review

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SUPLEMMENTARY MATERIAL

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Table S1. Characteristics of excluded articles.

STUDY	COUNTRY	PRISON SIZE/ POPULATION	NUMBER OF SUBSTANCES MEASURED	SAMPLING METHOD	OBSERVATIONS
Cruz-Cruz et al. 2019	México	Unknown	9	24-hour composite time-proportional samples for 1 day (beginning, during and at the end of the daily working hours of the sites) at every sampling site for a total of **378 samples (not all from prisons)**	• 31 Wastewater Treatment Plants (WWTPs) and other 95 sites (38 schools, 42 addiction treatment units and 15 social rehabilitation centers) in 13 states of the country were sampled. • Cocaine (benzoylecognine), amphetamine, methamphetamine, MDMA[a], heroin (6-MAM[b], morphine) and THC-COOH[c] were analyzed. • Highest THC-COOH[c], cocaine and benzoylecgonine concentrations detected in social rehabilitation centers. • Highest concentration of methamphetamine detected at schools; more than double the concentration detected in the other category sites. • The study was excluded because there is no estimation of consumption in penitentiaries.
Davies et al. 2023	Northern Ireland	1940 (300 inmates per house)	37	Grab samples of 7 manholes, each corresponding to a particular in-mate house. for a total of **7 samples**	• 37 new psychoactive drugs (NPS) were analyzed. • Only benzoylecognine detected in all samples. Methadone, buprenorphine, oxazepam, morphine, codeine and nordiazepam detected in some samples. No other NPS detected. • The sampling methodology is not representative and thereby no estimation of consumption performed.

[a]**MDMA**: 3,4-methylenedioxymethamphetamine; [b]**6-MAM**: 6-monoacetylmorphine; [c]**THC-COOH**: 11-nor-9-carboxy-Δ9- tetrahydrocannabinol

Table S2. Corrections factors applied in prison WBE studies.

SUBSTANCE	Biomarker	Postigo et al., 2011	van Dyken et al., 2014	van Dyken et al., 2016	Néfau et al.,2017	Wang et al., 2023	CF used in this review
Cocaine	**Cocaine**	2.3	-	-	-	13.3	Not used
Cocaine	**Benzoylecognine**	-	-	-	2.2	2.9	2.9
THC	**THC-COOH**	36.4	166.7	-	166.7 & 36.4	166.7	166.7
Methadone	**Methadone**	-	-	-	4.34	4.5	Not used
Methadone	**EDDP**	3.6	3.6	3.6	3.6	2	2
Heroin	**6-MAM**	86.9	-	-	-	76.9	76.9
Ephedrine	**Ephedrine**	1.3	-	-	-	1.3	1.3
MDMA	**MDMA**	3.9	-	-	1.53	4.44	4.44
Amphetamine	**Amphetamine**	3.3	-	3.3	3.3	2.53	2.53
Methamphetamine	**Methamphetamine**	2.3	2.56	2.56	2.3	2.3	2.3
Alprazolam	**Alprazolam**	5	-	-	-	-	5
Codeine	**Codeine**	-	10	10	-	3.3	3.3
Morphine	**Morphine**	-	10	-	2.38	1.28	1.28
Ketamine	**Norketamine**	-	62.5	62.5	-	-	62.5
Buprenorphine	**Buprenorphine**	-	-	20	1.05	9.61	9.61
Methylone	**Methylone**	-	-	4.92	-	-	Not used

Table S3. Methodological quality of WBE prison studies

STUDY	ITEM 1	ITEM 2	ITEM 3	ITEM 4	ITEM 5	ITEM 6	RISK OF BIAS
Postigo et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Low
van Dyken et al., 2014	Yes	Yes	No	Yes	Yes	Yes	Medium
van Dyken et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Low
Brewer et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Low
Néfau et al., 2017	No	Yes	No	Yes	No	Yes	High
Wang et al., 2023	Yes	Yes	Yes	Yes	Yes	Yes	Low

Item 1. Does the study present an appropriate estimation of the analyzed population using one of the following methodologies: mobile phone data, census data, wastewater biomarkers (biological oxygen demand, total nitrogen, and ammonia nitrogen)?

Item 2. Does the study distinguish the sources of wastewater used for sampling (e.g. samples are taken in the influent of a wastewater treatment plant exclusive for the prison setting, samples are taken from manhole collecting the wastewater of a specified zone)?

Item 3. Does the sampling methodology feasible to give representative data taking in to account the following criteria: sampling period, number of samples, sampling mode (e.g. grab samples, flow-proportional)?

Item 4. Are the analyzed substances suitable to perform a wastewater based epidemiology back-calculation (e.g. derived from human use only, stability in sewage water)?

Item 5. Does the estimation of flow is good for data interpretation (e.g. flowmeter type, flow defined by water consumption)?

Item 6. Is the analytical method suitable for providing reliable results at the expected concentration level (e.g. validating and quality control/assurance data provided)?

Table S4. Community consumption of cocaine, methamphetamine and cannabis (mg/day/1000 inh.)

REGION	Sampling year	Reference	Cocaine	Methamphetamine	Cannabis
Queensland, Australia	2019-2020-2021	Australian Criminal Intelligence Commission 2019, 2020, 2021	406 ± 70	1739 ± 533	26975 ± 8217
Paris, France	2013-2014-2015-2016	EMCDDA, 2023c	537 ± 181	0	25176.2 ± 4228.2
Barcelona, Spain	2011-2012-2013	EMCDDA, 2023c	1292.2 ± 337.1	47.6 ± 21.1	17405.3 ± 4672.8
Northwestern United States	2009	Banta-Green et al., 2009	2667	696	-

Medline search (https://pubmed.ncbi.nlm.nih.gov/) ON March 2024

("Wastewater" OR "Sewage") AND ("Prisons" OR "Correctional Facilities") AND ("Substance abuse" OR "illicit drug"

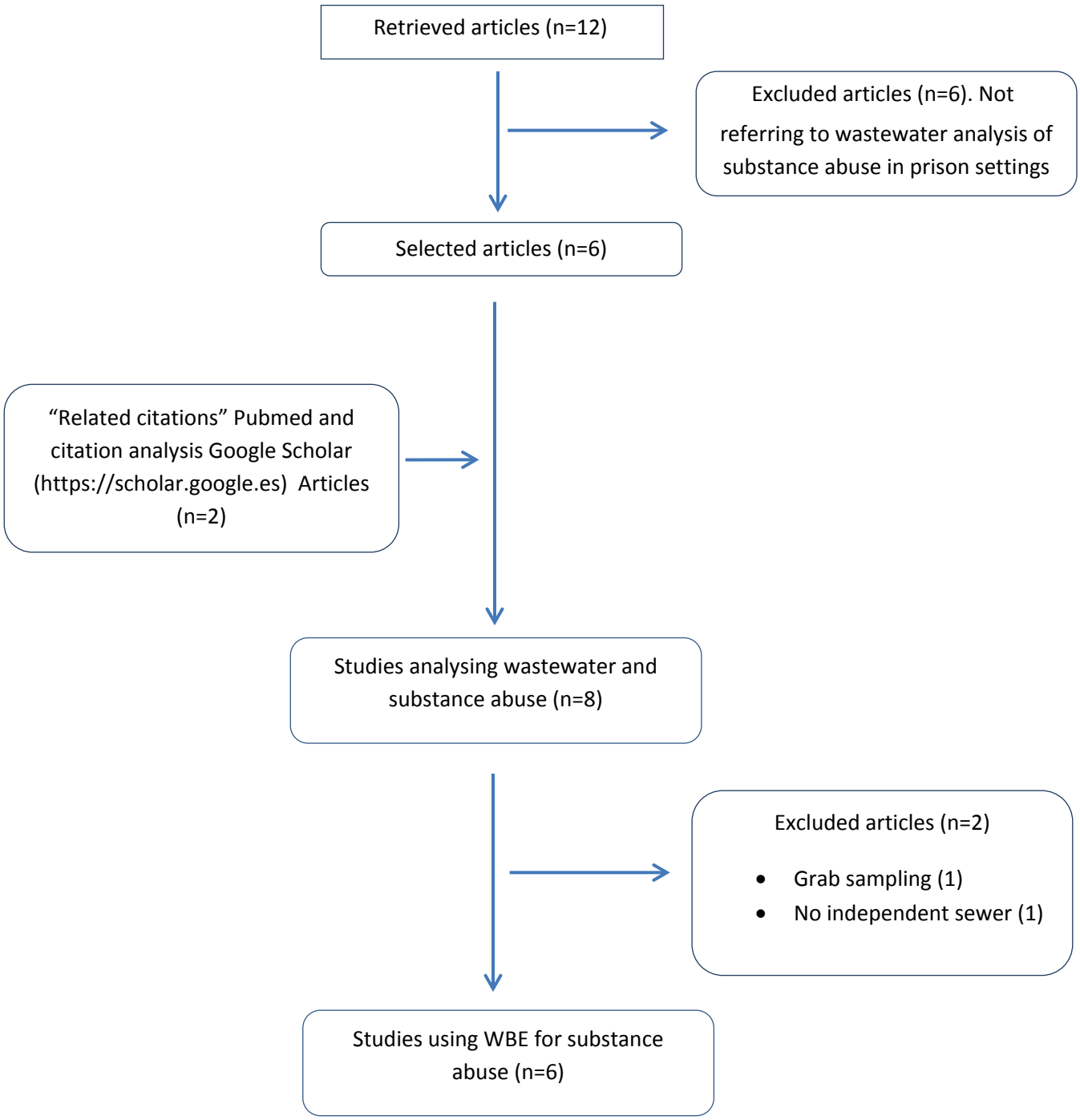

Figure S1. Flowchart of the search strategy

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6

Topic	No.	Item	Location where item is reported
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Does not apply
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Does not apply
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Supplementary material, Table S3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Does not apply
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6

Topic	No.	Item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Does not apply
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Does not apply
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Does not apply
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Does not apply
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Supplementary material, Figure S1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary material, Table S1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Does not apply

Topic	No.	Item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Does not apply
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Does not apply
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Does not apply
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Does not apply
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Does not apply
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Does not apply
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Does not apply
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 8-11
	23b	Discuss any limitations of the evidence included in the review.	Page 11
	23c	Discuss any limitations of the review processes used.	Page 11

Topic	No.	Item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Section 4, Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Does not apply
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Does not apply
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 15
Competing interests	26	Declare any competing interests of review authors.	Page 15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 1

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org