

Information Bulletin

WASTEWATER-BASED EPIDEMIOLOGY FOR MONITORING DRUG USE



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EXECUTIVE SUMMARY

The Hemispheric Drug Strategy (HDS) directs the Inter-American Drug Abuse Control Commission (CICAD, by its Spanish-language acronym) to foster scientific research to generate, collect, organize, analyze, and disseminate information to support evidence-based drug policies and strategies. Similarly, the OAS Hemispheric Plan of Action on Drugs, 2021-2025 advises member states to: “Contribute to the Early Warning System of the Americas (SATA, by its Spanish acronym) to gather the available national alerts and disseminate them to member states, so they can respond in the shortest possible time to new threats.” To that end, CICAD’s Inter-American Observatory on Drugs (OID, by its Spanish-language acronym) develops research protocols, manuals, guidelines, and training materials for a broad range of areas.

The CICAD Executive Secretariat (ES-CICAD) and its member states assign increasing importance to research, prevention, and control measures that can mitigate the problem of synthetic drugs, including new psychoactive substances (NPS), fentanyl and other synthetic opioids, and illicit pharmaceuticals in the Americas. According to CICAD’s March 2023 Information Bulletin “North American Trends in Fentanyl Use, Production, and Supply,” Fentanyl was linked to 86% of the 7,560 apparently opioid-related overdose deaths that occurred in Canada in 2021. Similarly, in the United States, the annual number of fentanyl-related overdose deaths nationwide increased from 5,544 in 2014 to 56,516 in 2020 (and 70,404 provisionally in 2021), an increase of 919%. Although less data is available for Mexico, the latest information suggests that opioid use – and particularly fentanyl – may be increasing there as well, especially near the U.S. border.

While member states have made progress in data collection and analysis, obtaining a complete picture of the drug use situation in any country or population is a complex task. CICAD’s OID has been working with OAS member states to update epidemiological approaches to data gathering, with an aim to identify low-cost research methods. While population-based epidemiology research has been considered the best approach for drug use studies in key populations for many years, national surveys are not always possible on a regular basis. National population studies can be expensive and have statistical limitations concerning low-prevalence drugs. Given these challenges, a multi-indicator approach is essential when assessing drug use among communities and populations.

The wastewater-based epidemiology approach has been proven to be a valuable complementary tool to build a more comprehensive analysis of drug use. Since 2005, this method has been developed and optimized through international collaboration between researchers in various disciplines (chemistry, physiology, sewage engineering, statistics and drug epidemiology, and others). Their work has contributed to the development of knowledge on wastewater-based epidemiology

(WBE) and best practices.¹ Using a standardized procedure has improved the credibility and reliability of the studies and facilitated comparisons between data from different sources. The worldwide application of WBE for the monitoring of drugs has demonstrated its potential for monitoring the use of common drugs such as cocaine, cannabis, amphetamine, methamphetamine, methylene-dioxy-methamphetamine (MDMA), other synthetic drugs, opioids, and NPS.

¹ van Nuijs 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-Trend Anal Chem* 103: 34-43.

Figure 1. Key points for the WBE approach

1 What is required at the WWTP?

- Sampling point prior to treatment
- Wastewater flowrate at the sampling point
- Knowledge of the size of the population served by the treatment plant
- Refrigerator and/or freezer space to store samples after collection
- Information about the sewage network and special circumstances

5 What is wastewater-based

Wastewater-based epidemiology (WBE) assesses the presence or quantity of markers (chemical or biological) in wastewater collected at a wastewater treatment plant, to gain information on the population served by the plant, more specifically here, their drug consumption.

2 What is required at the laboratory?

- Refrigerator and/or freezer space to store samples after reception
- Labeled drugs to spike in the samples
- Equipment (filtration and solid phase extraction system) to prepare wastewater samples
- Analytical instruments: liquid chromatograph coupled to mass spectrometry
- Scientists

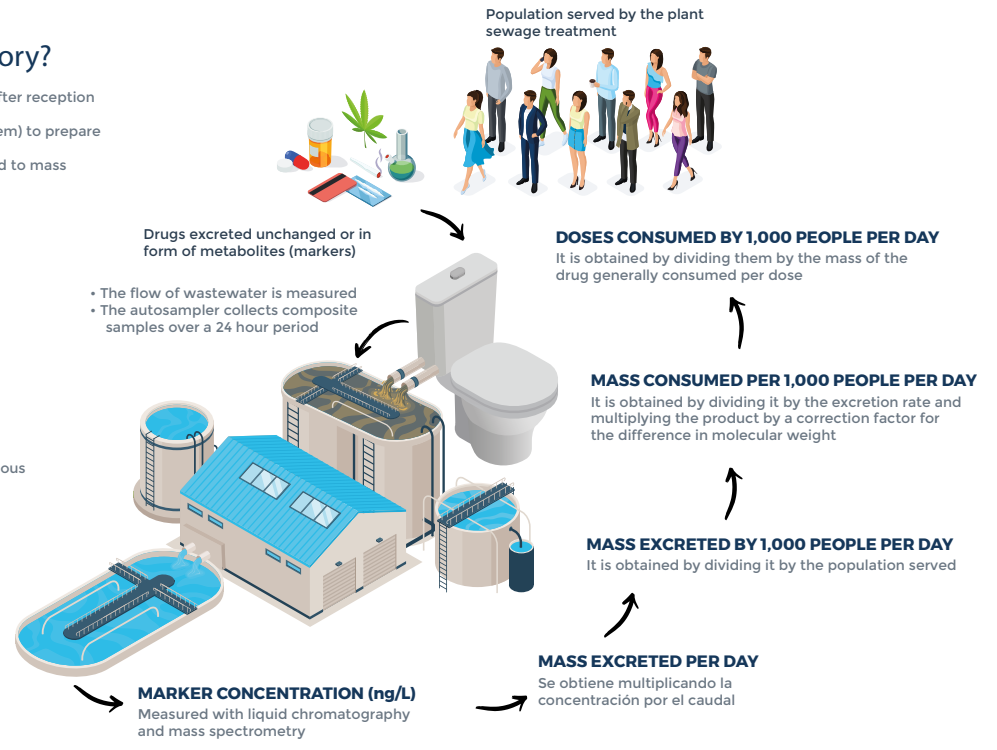
3 What are the ethical considerations?

Considering the risks of consequences for vulnerable groups, WBE study must:

- Consider the socio-political context of the study
- Determine the need to anonymize data
- Develop a communication plan
- Identify and understand the expectations of the various

4 Who are the key stakeholders?

- Regional/National Institutions involved in drug monitoring
- Local authorities in charge of sewage treatment
- Wastewater professionals
- Scientists
- Law enforcement agents
- Public health practitioners
- Policy makers



What are the advantages and limitations?

Method Features	Conventional methods	Epidemiología basada en aguas residuales
Respondent bias	(-) Yes	(+) No
Geographic resolution	(-) Low	(+) High
Real-time estimates	(-) No	(+) Yes
Study cost	(-) High	(+) Low
Retrospective data analysis	(-) It's not possible	(+) Possible, depending on the way the data is obtained
Data on frequency and consumption patterns	(+) Yes	(-) No
Detection of pattern changes in a short period	(-) It's not possible	(-) Possible
Mode of drug consumption	(+) Yes	(-) No
Consumer characteristics	(+) Yes	(-) No
Information on the purity of the drugs	(+) Yes	(-) No
Identification of new drugs	(+/-) Possible, but difficult	(+) Yes

While WBE is a useful tool for filling in the gaps of other epidemiological research, it has certain limitations. For example, WBE does not provide information on prevalence and frequency of use, routes of administration, purity of the drugs, the number of users or their characteristics, and estimates of the size of the population served by wastewater treatment plants are often uncertain. Therefore, WBE is proposed as a complement to established monitoring tools rather than as a replacement. In this context, future WBE studies should aim to better integrate this method with existing epidemiological indicators. Indeed, one can better understand drug use patterns and obtain information to design effective interventions and strategies through successful integration and close collaboration between wastewater specialists, epidemiologists, and authorities responsible for public health, drug enforcement, and drug intervention.

This objective of the document is to provide information to our member states who have expressed an interest in learning more about WBE as a tool for monitoring drug consumption. It lays out the basic steps to developing a WBE study on drug use, providing basic technical guidance to researchers planning wastewater-based drug studies. While WBE can be used to monitor several biomarkers of population health (e.g., SARS-Cov-2, polio, and diet, exposure to contaminants, etc.), this document focuses solely on the use of WBE for monitoring drug use. This document first describes the elements of the WBE approach for estimating drug use among communities and populations, then identifies what physical and human resources are required to conduct such studies, while emphasizing the stakeholders and other important considerations. Finally, this document reviews the published studies that have been previously conducted in OAS member states.²

² A systematic literature review identified published WBE studies from the following OAS member states: Barbados, Brazil, Canada, Colombia, Costa Rica, Mexico, United States, and Uruguay.

WHAT IS WASTEWATER-BASED EPIDEMIOLOGY (WBE)?



Wastewater-based epidemiology (WBE), also called wastewater surveillance, is a tool to assess the presence or quantity of chemical or biological markers in untreated (raw) wastewater collected from a wastewater treatment plant (WWTP). It is used to gain information on the health of the community or population served by a WWTP, and, more specifically for this document, the level of drug use. This approach is based on the principle that the individuals in a community or population that are exposed to or consuming substances excrete them unchanged or as metabolites in urine and/or feces, and these substances ultimately end up in wastewater.³ By measuring target residues, termed “markers” in raw wastewater, it is possible to estimate the exposure or use of these substances in a community or population.

The first study that described the WBE approach was conducted in Italy, and measured cocaine and its metabolites in raw wastewater and then calculated cocaine consumption by a population.⁴ WBE expanded rapidly in Europe, leading to the creation of the Sewage Analysis CORE group Europe (SCORE), initially to harmonize the approach and, more recently, to further develop wastewater-based epidemiology as an innovative tool to improve human health on a global scale (SCORE 2022). Over the years, researchers from non-European Union (EU) countries also joined the SCORE network, producing data estimates and comparisons of drug use over time in 120 cities in 37 countries worldwide. The results from WBE studies generally agree with prevalence data derived from conventional methods, demonstrating the value of the WBE approach as a complement to conventional socio-epidemiological methods such as population surveys and questionnaires, medical records, crime statistics, and seizure data.^{5,6} Most WBE studies focus on estimates of population consumption based on samples of raw wastewater collected repeatedly from centralized municipal WWTPs, which is the main focus of this document. Still, an increasing number of studies have used this approach to estimate drug use in specific communities (e.g., educational institutions and prisons) and during special events (e.g., music festivals, sporting events, and holidays).⁷

Although WBE has been used for almost two decades to estimate drug use, new applications for this technique have been developed more recently. Considering that most of the chemicals entering our body through what we consume (eating, drinking, smoking) are excreted unchanged or as a mixture of metabolites in our urine and feces, these compounds ultimately end up in municipal wastewater. WBE can thus be applied to biomarkers to estimate alcohol use,⁸ as well as tobacco and

³ Bijlsma, L., A. M. Botero-Coy, R. J. Rincon, G. A. Penuela and F. Hernandez (2016). “Estimation of illicit drug use in the main cities of Colombia by means of urban wastewater analysis.” *Sci Total Environ* 565: 984-993.

⁴ Zuccato, E., C. Chiabrando, S. Castiglioni, D. Calamari, R. Bagnati, S. Schiarea and R. Fanelli (2005). “Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse.” *Environ Health* 4: 1-7.

⁵ Zuccato, E., C. Chiabrando, S. Castiglioni, R. Bagnati and R. Fanelli (2008). “Estimating community drug abuse by wastewater analysis.” *Environ Health Perspect* 116(8): 1027-1032.

⁶ van Nuijs, A. L., S. Castiglioni, I. Tarcomnicu, C. Postigo, M. Lopez de Alda, H. Neels, E. Zuccato, D. Barcelo and A. Covaci (2011). “Illicit drug consumption estimations derived from wastewater analysis: A critical review.” *Sci Total Environ* 409(19): 3564-3577.

⁷ Verovsek, T., I. Krizman-Matasic, D. Heath and E. Heath (2020). “Site- and event-specific wastewater-based epidemiology: Current status and future perspectives.” *Trends Environ Anal* 28: e00105

⁸ Ryu, Y., D. Barcelo, L. P. Barron, L. Bijlsma, S. Castiglioni, P. de Voogt, E. Emke, F. Hernandez, F. Y. Lai, A. Lopes, M. L. de Alda, N. Mastroianni, K. Munro, J. O’Brien, C. Ort, B. G. Plosz, M. J. Reid, V. Yargeau and K. V. Thomas (2016). “Comparative measurement and quantitative risk assessment of alcohol consumption through wastewater-based epidemiology: An international study in 20 cities.” *Sci Total Environ* 565: 977-983

NPS.⁹ Other applications include the measurement of 8-iso-prostaglandin F2 α as a biomarker of oxidative stress, i.e., an imbalance between oxidants and antioxidants, which might be caused by exposure to various compounds¹⁰ and analysis of water-soluble vitamins as indicators of diet.¹¹ More recently, WBE has been widely used to estimate the prevalence of SARS-CoV-2.¹² This approach can also be used to estimate the prevalence of a range of communicable diseases, such as polio.¹³

1.1. Advantages and limitations of WBE

WBE is now widely recognized as a tool that is complementary to conventional methods for assessing drug use.^{14,15} Table 1 summarizes the main advantages and limitations of both WBE and the conventional approaches. One of the main advantages of WBE in comparison with survey methods is that wastewater analysis is not affected by respondent bias and does not rely on individual recollection or knowledge about the types and quantities of drugs used (i.e., “recall bias”). In addition, considering that WBE captures the whole population served by a WWTP, it is possible to assess drug use at a higher geographic resolution than surveys and at a lower cost. It also has the potential to provide near-real-time estimates and temporal trends, considering that a shorter time is required to obtain the results. The analysis of wastewater can thus be a useful tool in monitoring both temporal and geographical trends.

However, WBE cannot entirely replace the existing methods, such as self-reported surveys, overdose/toxicological reports, treatment demand, and drug-related crime statistics. For instance, the analysis of wastewater cannot provide information on the prevalence and frequency of use, the routes of administration, or purity of the drugs and cannot be used to estimate the numbers of users nor the characteristics or demographics of the users of the drugs (EMCDDA 2016).¹⁶

⁹ Bade, R., J. M. White, M. Gheta, S. Adiraju, S. Adhikari, L. Bijlsma, T. Boogaerts, D. A. Burgard, S. Castiglioni, A. Celma, A. Chappell, A. Covaci, E. M. Driver, R. U. Halden, F. Hernandez, H. J. Lee, A. L. N. van Nuijs, J. E. Oh, M. A. P. Castro, N. Salgueiro-Gonzalez, B. Subedi, X. T. Shao, V. Yargeau, E. Zuccato and C. Gerber (2022). “A taste for new psychoactive substances: Wastewater Analysis study of 10 countries.” *Environ Sci Tech Let* 9(1): 57-63.

¹⁰ Ryu, Y., M. J. Reid and K. V. Thomas (2015). “Liquid chromatography-high resolution mass spectrometry with immunoaffinity clean-up for the determination of the oxidative stress biomarker 8-iso-prostaglandin F2 α in wastewater.” *J Chromatogr A* 1409: 146-151.

¹¹ Tsuji, T., T. Fukuwatari, S. Sasaki and K. Shibata (2010). “Urinary excretion of vitamin B1, B2, B6, niacin, pantothenic acid, folate, and vitamin C correlates with dietary intakes of free-living elderly, female Japanese.” *Nutr Res* 30(3): 171-178.

¹² CWN. (2020). “Ethics and communications guidance for wastewater surveillance to inform public health decision-making about COVID-19.” Retrieved October 16, 2022, from <https://cwn-rce.ca/wp-content/uploads/COVID19-Wastewater-Coalition-Ethics-and-Communications-Guidance-v4-Sept-2020.pdf>.

¹³ Duintjer Tebbens, R. J., M. Zimmermann, M. A. Pallansch and K. M. Thompson (2017). “Insights from a Systematic Search for Information on Designs, Costs, and Effectiveness of Poliovirus Environmental Surveillance Systems.” *Food Environ Virol* 9(4): 361-382.

¹⁴ Castiglioni, S., L. Bijlsma, A. Covaci, E. Emke, F. Hernández, M. Reid, C. Ort, K. V. Thomas, A. L. N. van Nuijs, P. de Voogt and E. Zuccato (2013). “Evaluation of uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers.” *Environ Sci Technol* 47(3): 1452-1466.


¹⁵ European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) (2016). *Assessing illicit drugs in wastewater: Advances in wastewater-based drug epidemiology*, Publications Office of the European Union.

¹⁶ van Nuijs, A. L., S. Castiglioni, I. Tarcomnicu, C. Postigo, M. Lopez de Alda, H. Neels, E. Zuccato, D. Barcelo and A. Covaci (2011). “Illicit drug consumption estimations derived from wastewater analysis: A critical review.” *Sci Total Environ* 409(19): 3564-3577

Table 1. Summary of the main advantages and limitations of WBE and the conventional epidemiological approaches (adapted from (EMCDDA 2016))

Method features	Conventional approaches	Wastewater-based epidemiology
Respondent bias	(-) Yes	(+) No
Geographical resolution	(-) Low	(+) High
Estimates in near real-time	(-) No	(+) Yes
Cost of the study	(-) High	(+) Low
Retrospective analysis of the data	(-) Not possible	(+) Possible, depending on how the data are collected
Data on frequency and patterns of use	(+) Yes	(-) No
Detection of changes in patterns over a short period of time	(-) Not possible	(-) Possible
Mode of drug consumption	(+) Yes	(-) No
User characteristics	(+) Yes	(-) No
Information on the purity of the drugs	(+) Yes	(-) No
Identification of new drugs	(+/-) Possible, but difficult	(+) Yes

Based on the complementarity of WBE with conventional methods, the combination of data from wastewater analysis with data obtained through conventional means provides a superior set of data for understanding the extent and causes of drug use. The addition of WBE to the toolset can provide timely results and can also serve as an early warning tool (van Nuijs et al. 2011).



**WHAT IS
REQUIRED TO
IMPLEMENT
WBE AS A TOOL
TO MONITOR
DRUG USE?**

Conducting a wastewater-based epidemiology study involves four phases: planning, sampling, analysis, and interpretation. Each phase has different requirements, as briefly summarized in the following paragraphs. Additional details about the requirements for conducting a WBE study are presented in subsections 2.1 to 2.4.

At the **planning phase**, it is essential to determine the study's objective and identify the stakeholders (see section 2.1) who should be involved over the course of the study. Once the study's objective is clearly defined, it is possible to identify the relevant geographical resolution, select the wastewater treatment plants and determine the required approvals. It is also important at this stage to identify appropriate biomarkers to monitor for the drugs in the wastewater. Biomarkers should be ones that are stable in the sewer system, specific to humans, for which there are pharmacological data on metabolism and excretion at levels sufficient to generate detectable concentrations in wastewater. It is also important at this stage to develop adequate strategies to disseminate the results, taking into account the objective of the study and ethical considerations (see section 3).

At the **sampling phase**, a suitable sampling method must be implemented, using best practices for collecting, manipulating, and storing the samples (see section 2.2). All procedures must be well documented. For example, any unusual situations about the population (holidays, events, etc.) and the sewage network (repairs, modifications, new connections, rain events, etc.), must be noted for later interpretation of the results.

At the **analysis phases**, there must be access to analytical instruments able to quantify compounds at trace levels (ng/L), and qualified personnel must be available for the chemical analysis to obtain reliable results. Analytical methods must be validated for the selected markers. Adequate quality control/quality assurance (QA/QC) measures must be implemented to ensure the robustness of the process. The procedures to prepare the samples and the laboratory infrastructure required to conduct a WBE study are described in section 2.3.

At the **interpretation phase**, the concentrations measured in the wastewater are used to estimate the drug use within the community or population in units of mg consumed per day per 1,000 inhabitants. Estimates of the specific load of drug excreted require reliable data on the wastewater flow rate (m³ per day) and the population served by the WWTP. Pharmacological data on the percentage of each drug or its metabolite excreted in urine are also required. Then, to estimate the number of daily doses per 1,000 inhabitants, the average dose (mg) would have to be known. Note that drug purity may be a complicating factor in making these estimates.

2.1. Key stakeholders

The key stakeholders for WBE studies generally include:^{17,18}

- Regional/National Institutions involved in drug monitoring
- Local authorities in charge of sewage treatment
- Wastewater professionals
- Scientists
- Law enforcement agents
- Public health practitioners
- Policy makers

For some aspects of WBE, Yargeau, and Werschler identified additional qualified personnel who could contribute to the research. These include statisticians to develop best practices for the sampling strategies, professionals with expertise in biostatistics and pharmacokinetics to determine the excretion rates and correction factors required for the estimates, as well as survey statisticians for integrating the WBE results with conventional data on drug use.

2.2. Infrastructure required at the wastewater treatment plant to conduct WBE studies

Wastewater sampling is the first step conducted at the WWTP and requires access to a **sampling point prior to treatment, other than screening and grit removal**. In order to perform the calculations required to estimate drug use, the wastewater flow rate at or close to the sampling point must be continuously measured over the entire period of sample collection. There are two possible approaches to sampling: **composite sampling** and **passive sampling**.

¹⁷ Gunnar, T. and A. Kankaanpää (2019). "The practical implications of wastewater-based illicit drug epidemiology." *Curr Opin Environ Sci Health* 9: 49-57.

¹⁸ Yargeau, V. and T. Werschler (2019). "Wastewater-based epidemiology as an input to national statistics on recreational drug use: A Canadian pilot study." *Acc Sym Ser* 1319: 137-153.

Figure 2. Schematic of wastewater-based epidemiology (WBE) approach

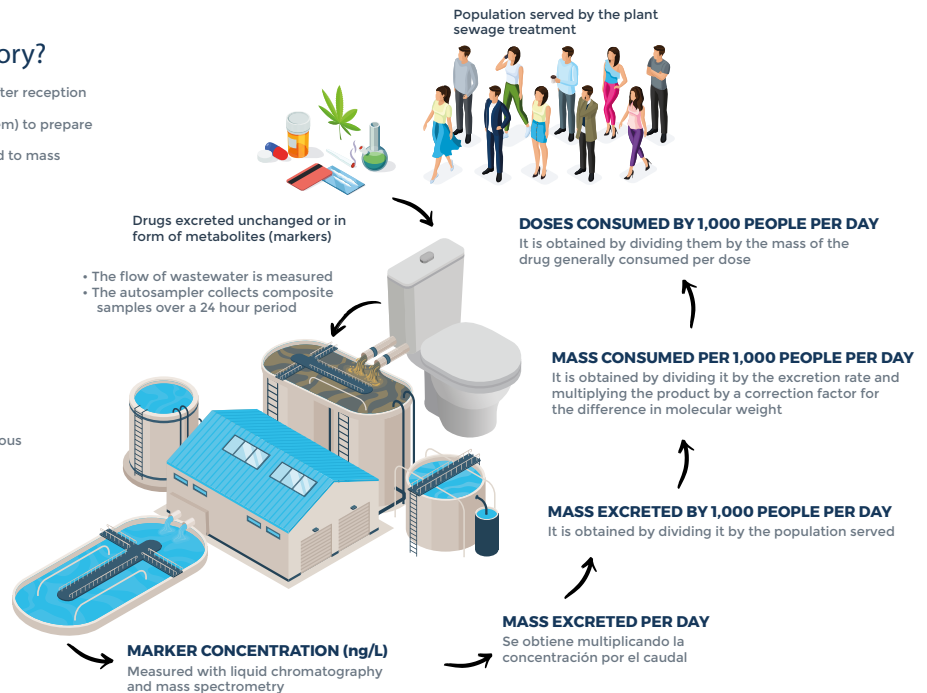
- 1** What is required at the WWTP?
- Sampling point prior to treatment
 - Wastewater flowrate at the sampling point
 - Knowledge of the size of the population served by the treatment plant
 - Refrigerator and/or freezer space to store samples after collection
 - Information about the sewage network and special circumstances

- 5** What is wastewater-based
- Wastewater-based epidemiology (WBE) assesses the presence or quantity of markers (chemical or biological) in wastewater collected at a wastewater treatment plant, to gain information on the population served by the plant, more specifically here, their drug consumption.

- 2** What is required at the laboratory?
- Refrigerator and/or freezer space to store samples after reception
 - Labelled drugs to spike in the samples
 - Equipment (filtration and solid phase extraction system) to prepare wastewater samples
 - Analytical instruments: liquid chromatograph coupled to mass spectrometry
 - Scientists

- 3** What are the ethical considerations?
- Considering the risks of consequences for vulnerable groups, WBE study must:
- Consider the socio- political context of the study
 - Determine the need to anonymize data
 - Develop a communication plan
 - Identify and understand the expectations of the various

- 4** Who are the key stakeholders?
- Regional/National Institutions involved in drug monitoring
 - Local authorities in charge of sewage treatment
 - Wastewater professionals
 - Scientists
 - Law enforcement agents
 - Public health practitioners
 - Policy makers



In composite sampling, raw wastewater is collected as a **24-hour composite sample** using a flow- or volume-proportional sampling strategy rather than a time-proportional sampling strategy. Sampling intervals should not exceed 10 min, and for small catchments or institution locations such as schools or prisons, shorter time intervals (e.g., 1 min) are recommended (Castiglioni et al. 2013). This recommendation is also part of the SCORE guidelines that propose collecting 100 small samples per day to be combined to obtain a representative daily sample.¹⁹ Such sampling strategies are required because of the high temporal fluctuations in the concentrations of drugs in wastewater due to diurnal variations in wastewater flows and in drug loads (EMCDDA 2016). Inadequate sampling strategies may lead to substantial sampling artefacts, which can result in both over- and underestimation of drug use estimates (EMCDDA 2016).^{20,21} The protocols developed in 2010 by members of the SCORE group recommend collecting the samples in silanized glass or polyethylene terephthalate (PET) containers in a refrigerated sampling device at 4°C (EMCDDA 2016).

¹⁹ SCORE. (2022). "Bringing experts and knowledge about wastewater-based epidemiology together." Retrieved October 16, 2022, from <https://score-network.eu>

²⁰ Ort, C., M. G. Lawrence, J. Reungoat and J. F. Mueller (2010a). "Sampling for PPCPs in wastewater systems: comparison of different sampling modes and optimization strategies." *Environ Sci Technol* 44(16): 6289-6296.

²¹ Ort, C., M. G. Lawrence, J. Rieckermann and A. Joss (2010b). "Sampling for pharmaceuticals and personal care products (PPCPs) and illicit drugs in wastewater systems: are your conclusions valid? A critical review." *Environ Sci Technol* 44(16): 6024-6035.

While composite sampling is the most frequently used approach, some studies have used **passive samplers** such as the Polar Organic Chemical Integrative Sampler (POCIS) to estimate the quantity of the drugs in raw wastewater.^{22,23} Passive samplers are devices deployed in water for an extended period of time to allow the accumulation of the compounds in the adsorbent within the sampler. This is used along with calibration data to estimate a time-weighted average of the compound monitored in the water. These samplers are easy to use and do not require power. The drawback to passive samplers is that because they are typically deployed for an extended period, generally about 2 weeks, the information they provide is less time specific. The use of passive samplers to estimate concentrations in wastewater also requires data on the sampling rates of the sampler for each compound monitored. Calibrated sampling rates need to be corrected for different exposure conditions, such as temperature and turbulence, which poses some challenges.²⁴

After collection, the samples should be stored in a **refrigerator at 4°C** until they are transported to the lab or in a **freezer at -20°C** if the samples will not be processed within 12 hours of collection. If frozen, the volume of wastewater in the container should be reduced to allow for expansion during freezing.

To ensure that the relevant information is systematically gathered, researchers should apply a **standardized questionnaire** to characterize the catchment and monitoring information (e.g., population size, exfiltration of wastewater, special events) and to assess the sampling conditions (e.g., flow variations, sampling mode, and frequency). This questionnaire is accessible as supplementary material published in the 2013 paper by Castiglioni et al.

²² Yargeau, V., B. Taylor, H. X. Li, A. Rodayan and C. D. Metcalfe (2014). "Analysis of drugs of abuse in wastewater from two Canadian cities." *Sci Total Environ* 487: 722-730.

²³ Hahn, R. Z., C. A. do Nascimento and R. Linden (2021). "Evaluation of illicit drug consumption by wastewater analysis using polar organic chemical integrative sampler as a monitoring tool." *Front Chem* 9: 596875.

²⁴ Harman, C., I. J. Allan and E. L. Vermeirssen (2012). "Calibration and use of the Polar Organic Chemical Integrative Sampler - A critical review." *Environ Toxicol Chem* 31(12): 2724-2738.

2.3. Laboratory infrastructure required to conduct WBE studies

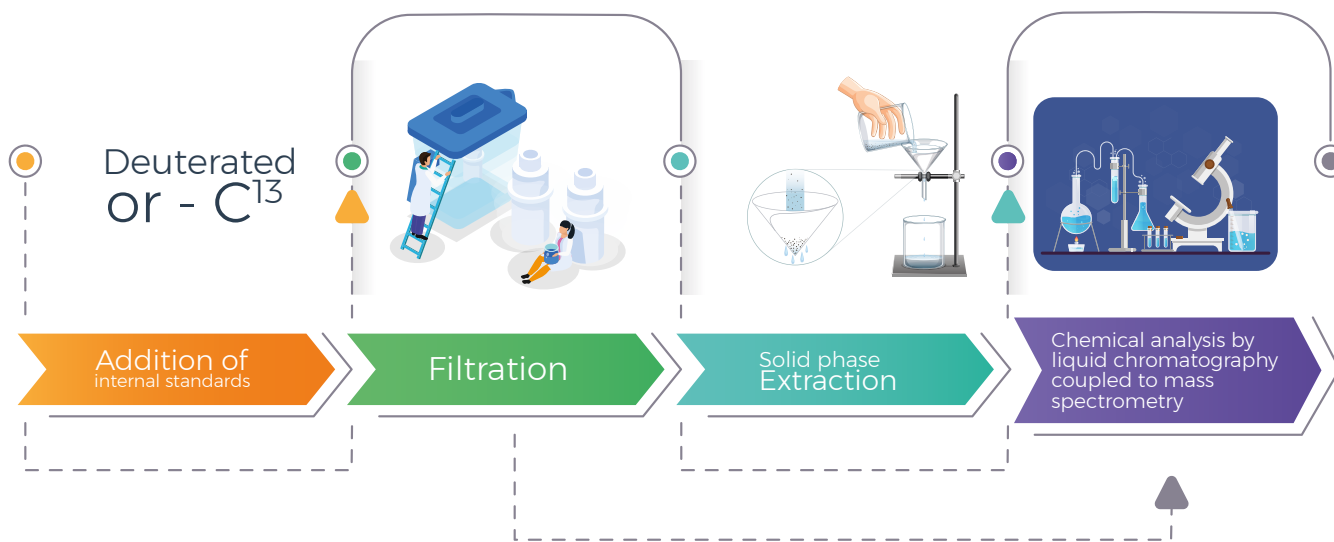
Figure 3 summarizes the process to be followed once the samples are received at the lab. The infrastructure required at the laboratory consists of the following:

- **Refrigerator space (4 °C) or freezer space (-20 °C)** to store samples if the analysis is not done within 12 hours of sample collection. (Castiglioni et al. 2013)
 - The internal standards are used to quantify any degradation during storage, recovery during extraction, and matrix effects during analysis. It is now common practice to spike the sample matrix prior to extraction and analysis with an analog of each compound monitored labeled with stable isotopes (i.e., compounds labelled with deuterium and/or ¹³C) to obtain more accurate quantification data (EMCDDA 2016).
- **Filtration equipment** to remove the suspended solids in the raw wastewater samples and a **solid phase extraction (SPE) system**: A variety of SPE sorbents can be used to optimize the extraction of different target analytes. Alternatives to SPE, such as on-line solid-phase extraction (Postigo et al. 2008) and large-volume direct injection, have been used to automate or streamline the preparation of samples prior to analysis.²⁵
- **Analytical instruments**: The analytical technique of choice for analyzing drugs in a wastewater matrix is liquid chromatography coupled with mass spectrometry (Castiglioni et al., 2013). Chromatographic separations can be conducted using either a high-pressure liquid chromatograph (HPLC) or an ultra-high pressure liquid chromatograph (UHPLC). Different mass spectrometry instruments have been used to determine the concentrations of drugs in wastewater, including tandem mass spectrometry (MS/MS), time of flight mass spectrometry (TOF-MS), and high-resolution mass spectrometry (HRMS) with an Orbitrap mass spectrometer. The analytical system must be capable of detecting residues of the target analytes in raw wastewater at low part per trillion (i.e., ng/L) concentrations. Note that the complex matrix of raw wastewater reduces the sensitivity of the instruments.

In addition to the equipment mentioned above, it is essential to have qualified analytical chemists to perform the sample preparation rigorously, develop and validate the analytical methods required for each biomarker, operate the analytical instrument, and perform the analysis of the analytical data. The quantification of the target drug residues is difficult, considering their low concentrations (ng/L) and the complexity of the raw wastewater matrices, which may hamper sensitivity and reliability.

²⁵ Berset, J. D., R. Brenneisen and C. Mathieu (2010). "Analysis of illicit and illicit drugs in waste, surface and lake water samples using large volume direct injection high performance liquid chromatography--electrospray tandem mass spectrometry (HPLC-MS/MS)." *Chemosphere* 81(7): 859-866.

Figure 3. Schematic of the sample preparation and analysis at the laboratory



Source: Photos of equipment taken from antiteck.com and emdmillipore.com

2.4. Information required to interpret the results of WBE studies

The back-calculations to obtain estimates of drug use requires pharmacokinetic data to determine the percentage of the dose of the target drug or its metabolite that is excreted in urine. In addition, a correction factor must be applied to account for the molecular mass ratio of the parent drug to the metabolite when the parent drug is not the target marker (Zuccato et al. 2008). Different correction factors have been reported in various studies, and are used to determine the data and the differences in excretion rates between the various dosing methods (e.g., oral, injection, nasal insufflation, etc.). There is still a need to harmonize and standardize the approach used to perform this part of the calculations.²⁶ As a result, in some studies, only the load (i.e., mg/day/1000 people) of the measured target drug is reported, and no attempt is made to estimate the drug consumption in terms of doses (i.e., doses/day/1000 people).

The calculations to obtain estimates of consumption also requires information about the size of the population served by the treatment plant. The most common methods are based on collections of census data or analysis of hydrochemical parameters in wastewater.²⁷ Population size estimates using wastewater parameters are preferable in cases where there is great uncertainty about the flow.^{28,29} Parameters such as biological oxygen demand, chemical oxygen demand,

²⁶ Reedman, L. and A. Brennan. (2019). "Estimating cannabis consumption using markers in wastewater: Methodological paper." Retrieved January 16, 2022, from <https://www150.statcan.gc.ca/n1/en/catalogue/13-605-X201900100006>.

²⁷ de Campos, E. C., E. C. P. De Martinis and B. S. De Martinis (2022). "Forensic analysis of illicit drugs and novel psychoactive substances in wastewater a review of toxicological, chemical and microbiological aspects." *Braz J Anal Chem* 9(34): 15-34.

²⁸ Lai, F. Y., C. Ort, C. Gartner, S. Carter, J. Prichard, P. Kirkbride, R. Bruno, W. Hall, G. Eaglesham and J. F. Mueller (2011). "Refining the estimation of illicit drug consumptions from wastewater analysis: co-analysis of prescription pharmaceuticals and uncertainty assessment." *Water Res* 45(15): 4437-4448.

²⁹ O'Brien, J. W., P. K. Thai, G. Eaglesham, C. Ort, A. Scheidegger, S. Carter, F. Y. Lai and J. F. Mueller (2014). "A model to estimate the population contributing to the wastewater using samples collected on census day." *Environ Sci Technol* 48(1): 517-525

and nitrogen and phosphorus levels can be used as hydrochemical parameters to estimate population size. Researchers have also tested the accuracy of data on the ammonia concentrations in wastewater.³⁰ Additional methods obtain more reliable estimates of population size using specific excreted substances, such as creatinine, cotinine, pharmaceuticals, coprostanol, and hormones as anthropogenic markers (EMCDDA 2016).³¹ In cities with a significant number of commuters, the numbers that are absent from the population during the day or night should be evaluated when estimating the population size based on census data.

2.5. Summary of WBE best practices for drug monitoring

The previous sections provided details about the required infrastructure and best practices to conduct WBE studies. Table 2 provides a summary of the requirements and best practices discussed in these previous sections.

Table 2. Summary of the requirements and best practices for the different phases involved in a WBE study to estimate drug use

Study phase	Requirements and best practices
Planning	<p>Define clear study objectives</p> <p>Identify stakeholders and ethical considerations</p> <p>Obtain required approvals</p> <p>Select appropriate markers</p>

³⁰ Been, F., L. Rossi, C. Ort, S. Rudaz, O. Delemont and P. Esseiva (2014). "Population normalization with ammonium in wastewater-based epidemiology: application to illicit drug monitoring." *Environ Sci Technol* 48(14): 8162-8169

³¹ Daughton, C. G. (2012). "Real-time estimation of small-area populations with human biomarkers in sewage." *Sci Total Environ* 414: 6-21.

<p>Sampling</p>	<p><i>Sampling point:</i> wastewater influent (prior to treatment), with flow monitoring</p> <p><i>Sampling mode:</i> 24-h composite samples collected using flow-proportional or volume proportional sampling, or time-proportional when there are only small flow variations. Samples collected in sampler at 4°C. Passive samplers (e.g., POCIS) may also be used if data on sampling rates are available.</p> <p><i>Sampling frequency:</i> depends on concentrations of markers and catchment size, but generally at intervals <10 min.</p> <p><i>Sampling container:</i> silanized glass or polyethylene terephthalate (PET)</p> <p><i>Storage after collection:</i> Store at 4°C if samples are processed within 12 hours; otherwise freeze (-20°C) immediately after collection</p> <p><i>Collection of relevant data:</i> layout of sewer catchment, flow data, unusual changes in the sewage network, special events, type of influent and additional conventional parameters or wastewater quality as well as temperature and pH</p>
<p>Analyzing</p>	<p><i>Sample preparation:</i> use stable isotope labeled internal standards</p> <p><i>Analytical quality:</i> use of quality controls, determination of limits of detection and quantification. Ideally, participation in interlaboratory study (ILS) to determine laboratory performance</p> <p><i>Qualified analytical chemists:</i> to develop and validate method, operate instrument, and perform data analysis</p>
<p>Interpreting</p>	<p><i>Back-calculations of consumption:</i> collection of information on excretion rates and correction factors for the selected markers</p> <p><i>Estimates of population size:</i> collection of data to obtain estimates from hydrochemical parameters and/or census data</p>



**ETHICAL
CONSIDERATIONS
OF WBE**

As the number of applications of WBE has grown, so have the discussions about the ethics of using wastewater for monitoring population health or drug use. Until recently, the application of WBE had not raised notable ethical issues considering that individuals are not identified using this approach and because the results can contribute to improving public health.³² Results can lead to an increased level of stigma toward vulnerable groups. Reports of drug use in specific districts could increase discrimination against populations in that area or result in changes in policing strategies that can impact the community.³³ Therefore, some level of caution is required when reporting and disseminating results. These risks are even more significant when the results of a WBE study are site-specific (e.g., schools, prisons, workplaces, indigenous or racialized communities, during events, etc.).

To minimize the risks of negative consequences for vulnerable groups and to ensure the continued development of best practices in the WBE field, researchers have started to develop guidelines to promote an ethical culture among research teams or when using WBE as a public health surveillance tool, especially in the context of wastewater-based monitoring of COVID-19 (CWN 2020).^{34,35} These guidelines should be considered in addition to any laws and regulations in effect and to research protocols already existing in research institutions.

Most mitigation strategies regarding research ethics should be identified and implemented during the planning phase of a WBE study. The study's design must consider how the findings could be interpreted within the socio-political context of the study, determine the need to anonymize the data, and develop a communication plan based on these factors. In some research institutions, seeking approval of a human research ethics committee might also be required, especially for site-specific studies. Identifying and understanding the expectations of the various stakeholders involved in the study also can facilitate the management of ethical risks and the identification of mitigation measures.

³² Hall, W., J. Prichard, P. Kirkbride, R. Bruno, P. K. Thai, C. Gartner, F. Y. Lai, C. Ort and J. F. Mueller (2012). "An analysis of ethical issues in using wastewater analysis to monitor illicit drug use." *Addiction* 107(10): 1767-1773.

³³ Prichard, J., W. Hall, P. de Voogt and E. Zuccato (2014). "Sewage epidemiology and illicit drug research: the development of ethical research guidelines." *Sci Total Environ* 472: 550-555.

³⁴ Prichard, J., W. Hall, E. Zuccato, P. De Voogt, N. Voulvoulis, K. Kummerer, B. Kasprzyk, A. Barbato, A. Parabiaghi, F. Hernandez, J. van Wel, K. V. Thomas, K. Fent, M. Mardal and S. Castiglioni (2016). *Ethical research guidelines for wastewater-based epidemiology and related fields*. S. Network.

³⁵ EMCDDA. (2022). "Wastewater analysis and drugs – a European multi-city study." European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal Retrieved October 16, 2022, 2022, from https://www.emcdda.europa.eu/publications/html/pods/waste-water-analysis_en#section4.



OVERVIEW OF WBE STUDIES CONDUCTED IN THE AMERICAS

Table 3. provides a summary of the WBE studies conducted in OAS member states for monitoring drugs. The WBE studies conducted in other countries or conducted to monitor for other indicators of population health have not been included.

Table 3. WBE published studies conducted in OAS member states 2008-2022

Barbados (1 study)

Study 1 - Barbados

Reference

Edwards, Q. A., T. Sultana, S. M. Kulikov, L. D. Garner-O'Neale, V. Yargeau and C. D. Metcalfe (2018). Contaminants of emerging concern in wastewaters in Barbados, West Indies. *B Environ Contam Tox* 101(1): 1-6.

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Amphetamine, Methamphetamine, Cocaine, Benzoyllecgonine, MDMA, MDA, Morphine, Methadone, EDDP, Codeine, Tramadol, Oxycodone, Ketamine, Fentanyl

Key findings

- 16 drugs were detected in the wastewater.
- The levels of amphetamine and methamphetamine at <LOQ indicates low consumption of these drugs in Barbados.
- Cocaine, MDA and MDMA were present at the highest concentrations.
- Drug consumption could not be estimated considering the use of grab samples and the lack of information on the population size and wastewater flow rates.

Brazil (10 studies)

Study 1 - Brazil

Reference

da Silva, K. M., J. B. Quintana, I. Gonzalez-Marino, R. Rodil, A. D. Gallassi, L. C. Arantes and F. F. Sodre (2018). Assessing cocaine use patterns in the Brazilian capital by wastewater-based epidemiology. *Int J Environ an Ch* 98(15): 1370-1387

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Cocaine, Benzoyllecgonine, Cocaethylene

Key findings

- Reported a different cocaine/benzoyllecgonine ratio possibly linked to a different alcohol co-consumption lowering the excretion of benzoyllecgonine.
- Provided further evidence that refrigerated autosampler is required, especially in warm climates.
- A comparison of results with drug seizure data suggests that only 3% of cocaine was seized during the period of the study.

Study 2 - Brazil

Reference

de Campos, E. G., E. C. P. De Martinis and B. S. De Martinis (2022). "Forensic analysis of illicit drugs and novel psychoactive substances in wastewater a review of toxicological, chemical and microbiological aspects." *Braz J Anal Chem* 9(34): 15-34

Markers and # sites monitored (*metabolites are identified in italics*)

- Review paper

Key findings

- Review of the forensic, toxicological, chemical, and microbiological aspects of the monitoring of common drugs of abuse and novel psychoactive substances (NPS) in wastewater.

Study 3 - Brazil

Reference

Ferreira, A. P. (2019). Drugs of abuse and metabolites in urban wastewater: A case study, Rio De Janeiro municipality, Brazil. *World J Avd Res Rev* 9(4): 14-19

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Cocaine, Cannabis

Key findings

- Concentrations were similar to data from Colombia and Europe but lower than those found in another Brazilian study.
- Drew attention to potential environmental effects of these drugs.

Study 4 - Brazil

Reference

Ferreira, A. P. (2020). Illicit drugs in wastewater treatment plants utilization of wastewater-based epidemiology in a Brazilian regional city. *World J Avd Res Rev* 06(01): 006-018

Markers and # sites monitored (*metabolites are identified in italics*)

- Four (4) WWTPs
- Cocaine, Benzoylcegonine, Amphetamine, Methamphetamine, Cannabis (THC-COOH)

Key findings

- The most consumed drug was cocaine.
- Provided additional evidence about geographical particularities in the area included in the study.
- Drew attention to potential environmental effects of these drugs.

Study 5 - Brazil

Reference

Ferreira, A. P. and M. J. Cruz-Hernández (2022). Plantas de tratamiento de aguas residuales: Estimación del consumo de drogas ilícitas en la zona oeste, Rio de Janeiro. Revista Eletrônica Acervo Saúde 15(2): 1-9

Markers and # sites monitored (*metabolites are identified in italics*)

- Three (3) WWTPs
- Amphetamine, Methamphetamine, MDMA, Cannabis (THC-COOH), Cocaine

Key findings

- Emphasized the non-homogeneous drug use in the study area.

Study 6 - Brazil

Reference

Hahn, R. Z., M. F. Bastiani, L. D. F. Lizot, I. C. D. Moreira, and F. Meireles, A. Schneider, C. A. do Nascimento y R. Linden (2021). Determination of a comprehensive set of drugs of abuse, metabolites, and human biomarkers in wastewater using passive sampling followed by UHPLC-MS/MS analysis. Microchem J 172: 106960

Markers and # sites monitored (*metabolites are identified in italics*)

- One (1) WWTP
- Cotinine, Caffeine, OH-COT, MDA, Cocaine, Benzoyllecgonine, AEME, Amphetamine, Methamphetamine, MDMA, THC-COOH

Key findings

- Reported the detection of these drugs over 392 consecutive days of monitoring using POCIS samplers.
- Highest concentrations were found for caffeine, benzoyllecgonine and 11-nor-9-carboxy- Δ^9 -THC.
- First study to include all SCORE priority drugs in a WBE study using POCIS-based sampling strategy.

Study 7 - Brazil

Reference

Hahn, R. Z., C. A. do Nascimento and R. Linden (2021). Evaluation of illicit drug consumption by wastewater analysis using polar organic chemical integrative sampler as a monitoring tool. Front Chem 9: 596875

Markers and # sites monitored (*metabolites are identified in italics*)

- Review paper

Key findings

- Provided a review of the use of POCIS for the monitoring of drugs in wastewater as well as target compounds, markers, excretion rates, and correction factors.

Study 8 - Brazil

Reference

Maldaner, A. O., L. L. Schmidt, M. A. F. Locatelli, W. F. Jardim, F. F. Sodre, F. V. Almeida, C. E. B. Pereira and C. M. Silva (2012). Estimating cocaine consumption in the Brazilian Federal District (FD) by sewage analysis. *J Brazil Chem Soc* 23(5): 861-867

Markers and # sites monitored (*metabolites are identified in italics*)

- Six (6) WWTPs
- Cocaine, Benzoylecgonine

Key findings

- First report of cocaine and its metabolite in wastewater in Brazil.
- Evaluated the impact of drug purity when estimating use.
- Indicated that in most developing countries, the lack of sanitation or the decentralized approach to wastewater treatment can impair implementation of WBE, considering that sewage collection often covers only a small portion of a given population and generally from higher income neighborhoods.

Study 9 - Brazil

Reference

Sodré, F. F., R. S. Feitosa, W. F. Jardim and A. O. Maldaner (2018). Wastewater-based epidemiology of cocaine in the Brazilian Federal District: Spatial distribution, weekly variation and sample preservation strategies. *J Brazil Chem Soc* 29(11): 2287-2298

Markers and # sites monitored (*metabolites are identified in italics*)

- Eight (8) WWTPs
- Cocaine, Benzoylecgonine

Key findings

- Results indicated differences in consumption between the regions, and higher consumption over the weekend.
- Identified that acidification to pH 2.0 is required prior to sample transportation.

Study 10 - Brazil

Reference

Sodré, F. F., D. d. J. Soares Freire, D. Barbosa Alcântara and A. O. Maldaner (2022). Understanding illicit drug use trends during the carnival holiday in the Brazilian capital through wastewater analysis. *Front Anal Sci* 2: 930480.

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- THC-COOH, cocaine, benzoylecgonine, cocaethylene

Key findings

- Reported a higher cocaine consumption during the Carnival and a higher consumption of cannabis during the holiday.
- An unusual low consumption was noticed immediately after the Carnival holiday, possibly linked to lower demand or supply issues.
- First investigation by WBE on cannabis use in Brazil.

Canada (3 studies)

Study 1 - Canada

Reference

Metalfe, C., K. Tindale, H. Li, A. Rodayan and V. Yargeau (2020). Illicit drugs in Canadian municipal wastewater and estimates of community drug use. *Environ Pollut* 158(10):3179-3185

Markers and # sites monitored (*metabolites are identified in italics*)

- Three (3) WWTPs
- Cocaine, Benzoylcegonine, Amphetamine, Methamphetamine, MDMA, MDA

Key findings

- Cocaine was the most widely used illicit drug for the three cities.
- Methamphetamine use was highest in the largest city and cocaine use was lowest in the smallest city.

Study 2 - Canada

Reference

Yargeau, V., B. Taylor, H. X. Li, A. Rodayan and C. D. Metcalfe (2014). Analysis of drugs of abuse in wastewater from two Canadian cities. *Sci Total Environ* 487: 722-730

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Cocaine, Benzoylcegonine, Amphetamine, Methamphetamine, MDA, MDMA, Ephedrine, THC-COOH, 6-MAM, Ketamine, Fentanyl, Morphine, 6-acetylmorphine, Methadone, EDDP, Heroin, Acetylcodeine, Dihydrocodeine, Codeine, Tramadol, oxycodone

Key findings

- Identified differences between a small community and a large urban center.
- Demonstrated the potential use of the Polar Organic Chemical Integrative Sampler (POCIS) as a monitoring tool.
- The most widely used drug was cocaine.
- Use of amphetamine, ephedrine, methamphetamine, and cocaine was greater in the large urban center, but oxycodone was used more in the smaller city.
- MDMA use peaked on the weekend.
- First report of ketamine in North America.

Study 3 - Canada

Reference

Yargeau, V. and T. Werschler (2019). Wastewater-based epidemiology as an input to national statistics on recreational drug use: A Canadian pilot study. *Acs Sym Ser* 1319: 137-153.

Markers and # sites monitored (*metabolites are identified in italics*)

- Fifteen (15) WWTPs
- Cocaine, benzoylcegonine, amphetamine, methamphetamine, MDMA, THC-COOH, 6-MAM, Ketamine, Fentanyl, Morphine, Heroin, Acetylcodeine, Codeine

Key findings

- Reported variations in consumption generally unexpected at the population level.
- Identified significant differences in consumption in cities across the country.
- Demonstrated the sensitivity of the results to the excretion rate applied.
- Recommended a multidisciplinary approach, including statisticians.
- First study of fentanyl consumption using WBE

Colombia (3 studies)

Study 1 - Colombia

Reference

Bijlsma, L., A. M. Botero-Coy, R. J. Rincon, G. A. Penuela and F. Hernandez (2016). Estimation of illicit drug use in the main cities of Colombia by means of urban wastewater analysis. *Sci Total Environ* 565: 984-993

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Cocaine, cannabis, amphetamine, methamphetamine, MDMA, heroin, ketamine

Key findings

- First WBE study in Colombia.
- Identified a high use of cocaine, while the use of cannabis, MDMA and ketamine was low. Residues of 6-MAM (heroin), methamphetamine and amphetamine were not detected.
- Estimates were mostly in agreement with information obtained by conventional means
- Supported the need for proper quality control and inter-lab comparisons.

Study 2 - Colombia

Reference

Botero-Coy, A. M. (2016). Applications of LC-MS/MS in the determination of pesticide residues and drugs of abuse in samples from Latin America. Emphasis on the analytic problem of glyphosate. PhD Thesis, Universitat Jaume I, Castellón de la Plana, Spain

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs in Colombia but the thesis includes two cities in Spain, as well
- Cocaine, benzoylecgonine, amphetamine, methamphetamine, THC-COOH, ketamine, 6-MAM, MDMA

Key findings

- Cocaine and benzoylecgonine were the most used drugs, followed by cannabis.
- Several comparisons were made with consumption in European cities.

Study 3 - Colombia

Reference

Gonzalez-Marino et al. (2020). "Spatio-temporal assessment of illicit drug use at large scale: evidence from seven years of international wastewater monitoring." *Addiction* 115(5): 994-996

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTTPs in Colombia, but the paper includes 143 WWTTPs
- Amphetamine, methamphetamine, MDMA, benzoylecgonine, THC-COOH

Key findings

- Little evidence of methamphetamine consumption in Colombia.
- Several comparisons between cities over the 7-year period of the study.
- Estimates of drug consumption based on WBE globally correspond to prevalence and seizure data.



Costa Rica (1 study)

Study 1 - Costa Rica

Reference

Causanilles, A., C. Ruepert, M. Ibanez, E. Emke, F. Hernandez and P. de Voogt (2017). "Occurrence and fate of illicit drugs and pharmaceuticals in wastewater from two wastewater treatment plants in Costa Rica." *Sci Total Environ* 599: 98-107

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Cocaine, benzoylecgonine, THC, THC-COOH, OH-THC, codeine, morphine, 6-MAM, MDMA, amphetamine, methamphetamine, oxazepam, diazepam, temazepam, nordazepam

Key findings

- First application of WBE in Central America.
- Cocaine and cannabis were found to be the most used drugs.
- Moderate presence of the opioids, codeine, and morphine observed.
- Commonly used psychoactive substances of abuse (synthetic phenethylamines such as amphetamine, methamphetamine, MDMA (Ecstasy), and benzodiazepines) were not detected.

Mexico (1 study)

Study 1 - Mexico

Reference

Cruz-Cruz, C., V. Yargeau, D. Vidana-Perez, A. Schilmann, M. A. Pineda, M. Lobato, M. Hernandez-Avila, J. A. Villatoro and T. Barrientos-Gutierrez (2021). "Opioids, stimulants, and depressant drugs in fifteen Mexican cities: A wastewater-based epidemiological study." *Intern J Drug Policy* 88

Markers and # sites monitored (*metabolites are identified in italics*)

- Fifteen (15) WWTPs in different Mexican cities
- Amphetamine, methamphetamine, MDMA, ketamine, THC-COOH, 6-MAM, norfentanyl, benzoylecgonine

Key findings

- Increased presence of drugs observed on known drug traffic routes.
- First report of fentanyl, norfentanyl, and ketamine in wastewater in Mexico.
- Drugs with highest levels were cannabis, methamphetamine, and cocaine.
- The highest levels of methamphetamine and amphetamine were observed in cities closed to the US border.
- Use of heroin, MDMA, ketamine, and fentanyl increased during weekends while use stayed constant for cannabis, cocaine, and amphetamine.

United States of America (15 studies)

Study 1 - United States of America

Reference

Banta-Green, C. J., J. A. Field, A. C. Chiaia, D. L. Sudakin, L. Power and L. de Montigny (2009). "The spatial epidemiology of cocaine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) use: a demonstration using a population measure of community drug load derived from municipal wastewater." *Addiction* 104(11): 1874-1880

Markers and # sites monitored (*metabolites are identified in italics*)

- 96 municipalities
- Benzoylecgonine, methamphetamine, MDMA

Key findings

- Higher loads in urban areas and below detection in many rural areas.
- Methamphetamine was present in all municipalities.
- MDMA was at quantifiable levels in fewer than half the communities.

Study 2 - United States of America

Reference

Bishop, N., T. Jones-Lepp, M. Margetts, J. Sykes, D. Alvarez and D. E. Keil (2020). "Wastewater-based epidemiology pilot study to examine drug use in the Western United States." *Sci Total Environ* 745: 140697

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) populations

- Amphetamine, methamphetamine, MDA, MDMA, morphine, 6-MAM, methadone, EDDP, codeine, benzoylecgonine, hydrocodone, hydromorphone, oxycodone, noroxycodone, ketamine, fluoxetine, tramadol, ritalinic acid

Key findings

- Consistently measured at detectable concentration levels, and present at both sites.
- The small urban community demonstrated greater collective excretion rates (CER) than the rural community, except for amphetamine and methamphetamine.

Study 3 - United States of America

Reference

Brewer, A. J., C. J. Banta-Green, C. Ort, A. E. Robel and J. Field (2016). "Wastewater testing compared with random urinalyses for the surveillance of illicit drug use in prisons." *Drug Alcohol Rev* 35(2): 133-137

Markers and # sites monitored (*metabolites are identified in italics*)

- One (1) prison site
- Methamphetamine, Cocaine, benzoylecgonine

Key findings

- Methamphetamine was observed in each sample of prison wastewater.
- Cocaine and benzoylecgonine were below limits of quantification.

Study 4 - United States of America

Reference

Burgard, D. A., R. Fuller, B. Becker, R. Ferrell and M. J. Dinglasan-Panlilio (2013). "Potential trends in Attention Deficit Hyperactivity Disorder (ADHD) drug use on a college campus: wastewater analysis of amphetamine and ritalinic acid." *Sci Total Environ* 450-451: 242-249

Markers and # sites monitored (*metabolites are identified in italics*)

- One (1) school institution
- Amphetamine-type compounds Adderall (mixed amphetamine salts) and Ritalin (methylphenidate)

Key findings

- Identify a trend between amphetamine use and academically stressful periods.

Study 5 - United States of America

Reference

Chiaia, A. C., C. Banta-Green and J. Field (2008). "Eliminating solid phase extraction with large-volume injection LC/MS/MS: analysis of illicit and legal drugs and human urine indicators in U.S. wastewaters." *Environ Sci Technol* 42(23): 8841-8848

Markers and # sites monitored (*metabolites are identified in italics*)

- Seven (7) municipalities

- MDMA, MDA, amphetamine, methamphetamine, cocaine, benzoylecgonine, oxycodone, hydrocodone, methadone, PCP, LSD, flunitrazepam, caffeine, cotinine, ephedrine, creatine

Key findings

- Methamphetamine concentrations and loads were the highest.
- Cocaine concentrations were similar to European locations.
- Creatinine was proposed as an indicator of population size.

Study 6 - United States of America

Reference

Croft, T. L., R. A. Huffines, M. Pathak and B. Subedi (2020). "Prevalence of illicit and prescribed neuropsychiatric drugs in three communities in Kentucky using wastewater-based epidemiology and Monte Carlo simulation for the estimation of associated uncertainties." *J Hazard Mater* 384: 121306

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Cocaine, amphetamine, methamphetamine, heroin, morphine, methadone, MDMA, MDEA, MDA, THC, methylphenidate, codeine, fentanyl, oxycodone, hydrocodone, hydromorphone, buprenorphine, quetiapine, aripiprazole, lorazepam, alprazolam, diazepam, oxazepam, temazepam, carbamazepine, sertraline, fluoxetine, venlafaxine, citalopram

Key findings

- Monte Carlo simulation used to account multiple uncertainties and propagation of errors.
- Higher prevalence of cocaine in the central business district while consumption rates of amphetamine and methamphetamine were higher in a rural community.
- Estimates of consumption higher than amounts prescribed for buprenorphine, oxycodone, and alprazolam.

Study 7 - United States of America

Reference

Duvallet, C., B. D. Hayes, T. B. Erickson, P. R. Chai and M. Matus (2020). "Mapping Community Opioid Exposure Through Wastewater-Based Epidemiology as a Means to Engage Pharmacies in Harm Reduction Efforts." *Prev Chronic Dis* 17: E91

Markers and # sites monitored (*metabolites are identified in italics*)

- Ten (10) residential manholes
- Opioids metabolites (not listed)

Key findings

- Results were mapped and provided actionable information to stakeholders involved in opioid response efforts (public health officials, pharmacies, etc.).

Study 8 - United States of America

Reference

Foppe, K. S., D. R. Hammond-Weinberger and B. Subedi (2018). "Estimation of the consumption of illicit drugs during special events in two communities in Western Kentucky, USA using sewage epidemiology." *Sci Total Environ* 633: 249-256.

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTTPs
- Sampling during a normal week and special events (e.g. holidays)
- Cocaine (benzoylecgonine, norcocaine, cocaethylene), Amphetamine, Heroin (6-MAM), Morphine, methadone (EDDP), MDMA, MDEA, MDA, THC (THCA, OH-THC)

Key findings

- Consumptions were different between
- two similar-sized communities.
- Cocaine was similar to the conventional estimates, but amphetamine and methamphetamine consumed were 2-fold higher than the conventional estimate.
- Several comparisons made between communities and with literature.

Study 9 - United States of America

Reference

Gerrity, D., R. A. Trenholm and S. A. Snyder (2011). "Temporal variability of pharmaceuticals and illicit drugs in wastewater and the effects of a major sporting event." *Water Res* 45(17): 5399-5411

Markers and # sites monitored (*metabolites are identified in italics*)

- One (1) WWTP
- Sampling during normal days and during the Super Bowl
- Methamphetamine, amphetamine; Cocaine, ecgonine, ecgonine methyl ester, benzoylecgonine, norcocaine; MDMA, MDA, heroin, 6-MAM, morphine, THC, THC-COOH (also includes some pharmaceutical and potential endocrine disruptors)

Key findings

- No indication of significant effect of the Super Bowl on the loadings or loading rates of many of the compounds.
- Suggested that cocaine use was elevated during Super Bowl but methamphetamine use was slightly lower.
- Reported that a more comprehensive database of "normal" temporal variability is required to assess effect of events.
- Provided information on removals during treatment in addition to WBE.

Study 10 - United States of America

Reference

Gushgari, A. J., E. M. Driver, J. C. Steele and R. U. Halden (2018). "Tracking narcotics consumption at a Southwestern U.S. university campus by wastewater-based epidemiology." *J Hazard Mater J* 359: 437-444.

Markers and # sites monitored (*metabolites are identified in italics*)

- One (1) university campus
- Morphine, codeine, oxycodone, heroin, fentanyl, methadone, buprenorphine, amphetamine, methylphenidate, alprazolam, Cocaine, MDMA

Key findings

- Reported the ranked average consumption heroin > cocaine > amphetamine > methylphenidate > methadone > oxycodone > alprazolam > MDMA > codeine > morphine

Study 11 - United States of America

Reference

Gushgari, A. J., A. K. Venkatesan, J. Chen, J. C. Steele and R. U. Halden (2019). "Long-term tracking of opioid consumption in two United States cities using wastewater-based epidemiology approach." *Water Res* 161: 171-180

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Monthly sampling between 2015 and 2017
- Morphine, codeine, oxycodone, heroin, fentanyl, and select opioid metabolites

Key findings

- First study to utilize wastewater analysis data to estimate the number of expected overdoses and to monitor fentanyl over the course of a log period (1 year).

Study 12 - United States of America

Reference

Montgomery, A. B., C. E. O'Rourke and B. Subedi (2021). "Basketball and drugs: Wastewater-based epidemiological estimation of discharged drugs during basketball games in Kentucky." *Sci Total Environ* 752: 141712

Markers and # sites monitored (*metabolites are identified in italics*)

- Sampling during a college and a high school basketball game outside the stadium.
- Cocaine, benzoylecgonine, norcocaine, cocaethylene, amphetamine, methamphetamine, methylphenidate, morphine, methadone, EDDP, fentanyl, oxycodone, hydrocodone, hydromorphone, buprenorphine, MDMA, MDEA, MDA, THC, THC-COOH, THC-OH, aripiprazole, quetiapine, alprazolam, diazepam, oxazepam, temazepam, carbamazepine, gabapentin, sertraline, fluoxetine, venlafaxine, citalopram, methcathinone, 4-methyl amphetamine, mCPP, 4-methyl penterdrone, 4-ANPP

Key findings

- Amphetamine was higher in the high school game, while cocaine was higher in college game.
- The ratio of cocaine to its metabolite suggested a discharge of cocaine during the game.
- Two synthetic cathinones (methcathinone and 4-methyl penterdrone) and three other NPSs (4-ANPP, mCPP, and 4-methylamphetamine) were quantified, with methcathinone as the most abundant.

Study 13 - United States of America

Reference

Rushing, R. and D. A. Burgard (2019). Utilizing Wastewater-Based Epidemiology To Determine Temporal Trends in Illicit Stimulant Use in Seattle, Washington. *Acs Sym Ser*, American Chemical Society. 1319: 155-166

Markers and # sites monitored (*metabolites are identified in italics*)

- One (1) WWTP
- MDMA, amphetamine, methamphetamine, cocaine, benzoylecgonine

Key findings

- Estimates of daily drug consumption indicated increased loads of illicit stimulants, specifically MDMA, on the days surrounding Seattle Pride

Study 14 - United States of America

Reference

Skees, A. J., K. S. Foppe, B. Loganathan and B. Subedi (2018). "Contamination profiles, mass loadings, and sewage epidemiology of neuropsychiatric and illicit drugs in wastewater and river waters from a community in the Midwestern United States." *Sci Total Environ* 631-632: 1457-1464

Markers and # sites monitored (*metabolites are identified in italics*)

- One (1) WWTP
- Cocaine, benzoylecgonine, norcocaine, cocaethylene, amphetamine, methamphetamine, morphine, methadone, EDDP, MDMA, MDEA, MDA, THC, THCA, THC-OH, aripiprazole, quetiapine, lorazepam, alprazolam, diazepam, oxazepam, temazepam, carbamazepine, sertraline, fluoxetine, venlafaxine, citalopram, methylphenidate, codeine, fentanyl, oxycodone, hydrocodone, hydromorphone, buprenorphine

Key findings

- The consumption of methamphetamine and amphetamine was the highest ever reported in the USA.
- Codeine and hydrocodone were the most consumed prescription opioids
- Also discussed were the residual concentrations in treated wastewater

Study 15 - United States of America

Reference

Subedi, B. and K. Kannan (2014). "Mass loading and removal of select illicit drugs in two wastewater treatment plants in New York State and estimation of illicit drug usage in communities through wastewater analysis." *Environ Sci Technol* 48(12): 6661-6670

Markers and # sites monitored (*metabolites are identified in italics*)

- Two (2) WWTPs
- Cocaine, benzoylecgonine, norcocaine, cocaethylene, morphine, morphine-3- β -D-glucuronide, morphine-6- β -D-glucuronide, methadone, EDDP, amphetamine, methamphetamine, MDMA, MDEA, paraxanthine

Key findings

- The mass load of methadone and MDA were shown to respectively be 3.2 and 51 times higher for the larger population studied.
- Report information about adsorption to particulate material in the wastewater.
- Also discussed the removal of these compounds during treatment.

Uruguay (1 study)

Study 1 - Uruguay

Reference

José Castro, M., I. Pretrini and E. Umpièrerez (2019). Informe Final: "Screening de New psychoactive substances, THC and cocaine in urine samples obtained at a musical party in the metropolitan area", Pando Institute of Technology: 28

Markers and # sites monitored (*metabolites are identified in italics*)

- One (1) rave party event, 28 samples collected – each representing about five people
- Fentanyl, JWH-018 Synthetic Cannabinoids (JWH-015, JWH-018, JWH-019, JWH-073, JWH-200, AM-2201) and their metabolites, JWH-250 Synthetic Cannabinoids (JWH-250, JWH-018, JWH-073, JWH-200, JWH-203, RCS-8, AM-2201) and their metabolites, Synthetic Cannabinoids UR-144/XLR-11 (UR-144, XLR-11, A-834735) and their metabolites, Cathinones (mephedrone, methedrone, methylone, buphedrone, 4-fluoromethcathinone, 3-fluoromethcathinone, methcathinone), THC (THC-COOH), cocaine and its metabolites, 6-MAM, LSD and its metabolites

Key findings

- Approach was to determine the presence of substances in urine samples from partygoers.
- Report the consumption of synthetic cannabinoids (JWH-248, JWH-208), which are rarely reported worldwide.
- The second-generation synthetic cannabinoids UR-144/XLR-11 were detected for the first time, but no third-generation drugs were found.
- 1,4-Butanediol, GHB, GBL, and sedatives/hypnotics such as Barbitol, which could be associated with cases of sexual submission, were detected.
- Hallucinogens such as Psilocin, Alpha-methyltryptamine, and LSD were reported at increased levels relative to prior studies.
- Indicate that WBE data can be a source of information for health personnel to support intervention in cases of intoxicated patients.

AEME: Anhydroecgonine methyl ester

EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (metabolite of methadone)

LSD: Lysergic acid diethylamide

MDA: 3,4-methylenedioxyamphetamine

MDEA: 3,4-methylenedioxyethylamphetamine

MDMA: 3,4-methylenedioxymethamphetamine

OH-COT: Trans-3'-hydroxycotinine (metabolite of nicotine)

PCP: Phencyclidine

THC: Tetrahydrocannabinol

THCA: acidic form of THC

THC-COOH: 11-nor-9-carboxy- Δ^9 - tetrahydrocannabinol (metabolite of cannabis)

OH-THC: 11-hydroxy- Δ^9 -tetrahydrocannabinol (metabolites of cannabis)

6-MAM: 6-Acetylmorphine (metabolite of heroin)

APPENDIX 1.

SEARCH PHRASES ON GOOGLE SCHOLAR

The following search phrases were used to conduct the literature review. Google Scholar was used, considering that it follows an inclusive and automated approach, indexing more broadly the scholarly documents available on the academic web. The relevant papers are summarized in Table 3 and papers on closely related topics, although not based on WBE studies, are listed here.

Antigua “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [8 results, 0 relevant, 1 related topic]

Pitarch Motellón, J. (2020). Espectrometría de masas de dilución isotópica y deconvolución de perfiles isotópicos aplicada a problemas complejos: Determinación de esteroides en muestras clínicas y drogas en aguas residuales (Doctoral dissertation, Universitat Jaume I, in Spanish). – Interesting analytical method

Barbuda “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [3 results, 0 relevant]

Argentina “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [80 results, 0 relevant]

Barbados “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [9 results, 1 relevant]

Belize “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [7 results, 0 relevant]

Bolivia “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [38 results, 0 relevant]

Brazil “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [268, 10 relevant, 1 related topic]

Tundisi, J. G., Garcia, J. A., Matsumura-Tundisi, T., Tundisi, J. E. M., Patrizzi, L. J., and Ghiglieno, F. (2020). Monitoring wastewater for assessing community health in cities: Perspectives and a proposal. *Brazil. J. Biol.*, 80: 946-947. – Interesting to show the other possible applications of WBE

Feitosa, R. S., Sodr , F. F., and Maldaner, A. O. (2013). Drugs of abuse in waters and wastewaters: occurrence, analytical determination and forensic applications. *Quimica Nova*, 36: 291-305. – In Portuguese.

Silva, K. M. D. (2018). Coca na, metab litos e adulterantes no esgoto: estrat gias para estimar o poliuso de drogas e o perfil de usu rios. – Thesis

Alc ntara, G. B. (2020). Estimativa do consumo e predic o da concentra o ambiental de diazepam via epidemiologia do esgoto. – Thesis

Canada “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [646 results, 3 relevant]

Chile “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [56 results, 0 relevant]

Colombia “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [142 results, 3 relevant]

Costa Rica “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [59 results, 1 relevant, 1 related topic]

Causanilles Llanes, A. (2018). Wastewater-based epidemiology, an analytical chemical approach for the investigation of human consumption of lifestyle chemicals. – Thesis – Interesting for a broad list of chemicals

Cuba “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [34 results, 0 relevant]

Dominica “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [5 results, 0 relevant]

Dominican Republic “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [9 results, 0 relevant]

Ecuador “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [33 results, 0 relevant]

El Salvador “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [9 results, 0 relevant]

Grenada “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [5 results, 0 relevant]

Guatemala “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [16 results, 0 relevant]

Guyana “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [8 results, 0 relevant]

Haiti “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [15 results, 0 relevant]

Honduras “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [7 results, 0 relevant]

Jamaica “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [33 results, 0 relevant]

Mexico “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [142 results, 1 relevant]

Nicaragua “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [10 results, 0 relevant]

Panama “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [15 results, 0 relevant]

Paraguay “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [28 results, 0 relevant]

Peru “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [45 results, 0 relevant]

Saint Kitts and Nevis “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [1 result, 0 relevant]

Saint Lucia “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [3 results, 0 relevant]

Saint Vincent and the Grenadines “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [2 results, 0 relevant]

Suriname “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [39 results, 0 relevant]

The Bahamas “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [4 results, 0 relevant]

Trinidad and Tobago “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [5 results, 0 relevant]

United States “wastewater-based epidemiology” OR “sewage epidemiology” AND drugs -SARS -COVID -Europe -China -Australia -Italy -Spain [76 results, several relevant]

Relevant references but not WBE for drugs: 10.1016/j.mehy.2015.06.020 (lifestyle); 10.1021/bk-2019-1319.ch010 (diet); 10.1016/j.coesh.2019.05.001 (nutritional status), 10.1016/j.coesh.2019.05.001 (analytical method); 10.1016/j.scitotenv.2019.06.419 (metal exposure); 10.1016/j.scitotenv.2018.11.350 and 10.1016/j.scitotenv.2020.138492 (alcohol and nicotine); 10.1016/j.scitotenv.2020.138406 (seasonal population size); 10.2166/ws.2022.395 (estimating flowrate); 10.1021/es802309v (method); ; several not tracked for COVID-19

Uruguay “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [31 results, 1 relevant]

Lizasoain, A., Mir, D., Salvo, M., Bortagaray, et al. (2021). First evidence of enterovirus A71 and echovirus 30 in Uruguay and genetic relationship with strains circulating in the South American region. PloS one, 16(8), e0255846. – Interesting for information on viruses.

Venezuela “wastewater-based epidemiology” OR “sewage epidemiology” -SARS [32 results, 0 relevant, 1 related topic]

Devault, D. A., Karolak, S. (2020). Wastewater-based epidemiology approach to assess population exposure to pesticides: A review of a pesticide pharmacokinetic dataset. Environ. Sci. Poll. Res, 27(5), 4695-4702.



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