MATHEMATICA
Policy Research

Research BRIEF

The Potential of Wastewater Testing for Rapid Assessment of Opioid Abuse

August 2016

The Potential of Wastewater Testing for Rapid Assessment of Opioid Abuse

RESEARCHERS

Mathematica Policy Research, Princeton, NJ, USA

Aparna Keshaviah
Ross Gitlin
Lindsay Cattell
William Reeves
Jennifer de Vallance
Craig Thornton

TABLE OF CONTENTS

Abstract

Municipal wastewater testing provides an opportunity to rapidly assess trends in opioid use and, accordingly, to evaluate initiatives to curb abuse. Despite detection limits and some complexities in deriving per capita use estimates, wastewater testing offers more comprehensive, objective, timely, and cost-effective measures of drug use than are available from self-reported surveys, overdose statistics, and drug-related crime data. Fully harnessing the potential of sewage epidemiological research will require the coordinated input of researchers, technicians, and policymakers to develop best practices for implementation. In conjunction with traditional data sources, wastewater testing provides an efficient means to identify areas with the greatest need for intervention, and programs with the greatest promise to reduce illicit drug use.

BACKGROUND

The epidemic level of opioid drug use across the United States has spurred a renewed focus on ways to prevent and reduce drug diversion, abuse, addiction, and overdose. However, an inability to obtain accurate, consistent, and timely measures of opioid abuse via existing channels hinders efforts to curb abuse. The National Governors Association is working with health care professionals, policymakers, and law enforcement to identify successful strategies to address this national epidemic (National Governors Association 2016), and recently President Obama signed the bipartisan Comprehensive Addiction and Recovery Act of 2016, which created a number of new opioid-related grant programs and initiatives. As part of a balanced approach, any growth in policies and programs must be mirrored by growth in the assessment of those efforts. However, existing data sources that inform program assessments suffer from high costs, low coverage, and long informational lags.

Wastewater testing can provide a widespread and objective picture of opioid use that is cost-effective and complements conventional monitoring methods.

The developing field of sewage epidemiology can provide a valuable new tool to address this area of growing public health concern. Municipal wastewater testing provides a potential means to rapidly detect drug use in a geographic region and, accordingly, the opportunity to hasten implementation and evaluations of public health and safety programs. The methodology exploits infrastructure and analytic methods created in the 1970s as part of the Clean Water Act to collect, treat, and test wastewater—a combination of household sewage, industrial runoff and, in some areas, storm water. Wastewater testing can provide a widespread and objective picture of opioid use that is cost-effective and complements conventional monitoring methods. While it is currently underused in the United States, European countries like Italy and Switzerland have successfully used wastewater testing to serve a variety of purposes, including identifying susceptible areas and populations for policy development, assessing the effectiveness of new drug treatment and prevention programs, and providing an early warning system for new drugs of abuse (Castiglioni et al. 2014; Been et al. 2015; McCall et al. 2016).

To realize the full potential of wastewater testing, we propose to create a coordinating center that would, as a first step, bring together researchers, technicians, and policymakers to develop best practices for wastewater testing implementation. Because few labs around the United States test wastewater for illicit substances, the input of such experts will help to standardize sampling and analytic methods for new illicit drugs. Subsequently, the coordinating center could support place-specific evaluations of initiatives to address opioid abuse, and also help communities identify geographic regions or populations with the greatest need for intervention. Data from wastewater testing could be synthesized with information from traditional data sources (such as self-reported surveys; hospitals, pharmacies, and drug treatment centers; and drug trafficking and criminal databases), or used alone in pilot studies to examine trends in abuse on a smaller scale among communities that might not be able to afford or wait for data from traditional sources. The application of advanced analytics and data mapping techniques to the rich spatial data produced by sewage epidemiological research can help policymakers promptly identify and respond to population needs, and could ultimately allow for the development of a national tracking system.

Application of advanced analytics and data mapping techniques to the rich spatial data produced by sewage epidemiological research can help policymakers promptly identify and respond to population needs, and could ultimately allow for the development of a national tracking system.

LIMITATIONS OF TRADITIONAL MONITORING METHODS

The most common approaches to measuring drug use in a population consist of self-reported surveys (including community-based, public school, and national telephone surveys); consequence data (such as drug treatment admissions, emergency room visits, fatal overdoses, toxicology lab results, and medical examiner reports); and drug-related crime and drug trafficking patterns (Banta-Green and Field 2011; Subedi and Kannan 2014). Each of these methods suffers from biases, coverage gaps, and time delays that can distort the data and limit their utility for evaluating a new policy or program.

Data from self-reported surveys are vulnerable to a number of biases, including nonresponse bias (because of social stigma), selection bias (due to the difficulty in surveying marginalized populations with high drug use), and reporting or recall bias (stemming from inaccuracies in remembering prescription medications or associating their names with the terms captured by the survey). Surveys also come with a high price tag and substantial lag before usable information is available, due to the time and effort involved in their design, testing, administration, and analysis. Furthermore, changes in questionnaires over time—including the anticipated methodological changes to the National Survey on Drug Use and Health, and the replacement of the Drug Abuse Warning Network with the National Hospital Care Survey—result in discontinuity that can hamper analyses of longitudinal trends.

Consequence data also suffer from serious drawbacks, including the fact that they measure drug effects and not actual usage. By their very nature, the data are available at a stage when it might be too late to intervene for some users, while for others who do not experience fatal or extreme adverse drug reactions, no data are captured. Furthermore, some physicians or medical examiners might not recognize health-related complications due to drug use as being drug-related, and thus medical records and death certificates might be incomplete. Finally, a percentage of illicit drug users might not be treated within the health care system at all.

Crime statistics and drug seizures also yield an incomplete and unreliable picture of drug use in a region. Changes in crime statistics can be difficult to interpret because they could reflect changes in enforcement activity in addition to changes in drug availability. Moreover, because laws differ from one state to the next, along with the resources available to enforce those laws, crime statistics and drug seizures in different regions might not be comparable.

... wastewater analyses focus on quantifying levels of drug metabolites to detect the concentrations of drugs actually ingested, rather than those flushed down the toilet.

TESTING WASTEWATER FOR ILLICIT SUBSTANCES

The techniques used for wastewater sample collection, storage, transport, and analysis have advanced over the past decade, and the Sewage Analysis CORE Group—a Europe-wide network of experts—has established standard protocols. When possible, wastewater analyses focus on quantifying levels of drug metabolites (compounds excreted in urine after the body breaks down a drug during metabolic processing) so as to detect the concentrations of drugs actually ingested, rather than those flushed down

An Overview of Wastewater Monitoring

The foundational idea of using wastewater testing to estimate illicit drug use originated at the U.S. Environmental Protection Agency (EPA) in 2001 (Daughton 2001), and Italian researchers first developed and implemented the analytic methodology in 2005 (Zuccato et al. 2005). In the early 2000s the Office of National Drug Control Policy conducted a proof of concept demonstration in seven regions across the United States, and found that drug use levels were significantly higher than those found in self-report surveys. The office acknowledged the value of wastewater testing for policy and program development in areas of demand reduction as well as supply reduction and interdiction.

Since then, the field of sewage epidemiology has grown rapidly, and researchers in Europe and the United States have examined its capacity with respect to a variety of illicit drugs. A study in Oregon that included 65 percent of the state's population across 96 cities found that the geographic distribution of methamphetamine and cocaine use as detected in a single day's sample was consistent with expected urban–rural patterns based on conventional data sources (Banta-Green and Field 2009). In a recent study in Lausanne, Switzerland, researchers found that methadone loads agreed with estimates derived from opioid substitution therapy registries, and heroin loads were on the same order of magnitude as estimates derived from syringe distribution data and general population surveys (Been et al. 2015). And in an ongoing study funded in part by the National Institutes of Health, researchers are examining the impact of marijuana legalization in Washington State on the prevalence of use. By combining data from wastewater testing with sales reports from the liquor control board, they will also be able to assess whether legal marijuana is replacing black- and medicinal-market sources (Johnson 2015).

the toilet. The methodology is particularly useful for detecting drugs that have unique metabolites (enabling an exact match between the metabolite detected and the parent compound) as well as those with high stability in wastewater systems (because sewer design and operation can alter drug concentrations). A recent review of the stability of illicit drugs in wastewater systems found that oxycodone, methamphetamine, cannabis, MDMA (ecstasy/Molly), LSD, ketamine, and MDPV had high stability under controlled conditions; cocaine and fentanyl had medium stability; heroin had low stability; and methadone had variable stability, depending on the particulate matter content that was suspended in the wastewater (McCall et al. 2016).

If desired, the drug concentrations in wastewater samples can be converted into estimates of drug use within the community by taking into account several factors, including the wastewater sample volume, measured drug concentration in the sample, molecular weight of the metabolite and parent compound, drug-specific stability in wastewater, drug-specific pharmacokinetic excretion rate, and the size of the population served by the facility. Although each of these factors can be measured with error or uncertainty, a number of recent validation studies have nevertheless shown that wastewater testing can be a reliable and valid method for estimating drug use (Banta-Green and Field 2011; Subedi and Kannan 2014; Been et al. 2015; Kinyua et al. 2015). Researchers are also developing robust methods to factor the many sources of random noise (due to flow, population, analytic error, and sampling error) into the calculation of confidence intervals around drug use estimations. Such confidence intervals can be used to statistically compare drug use from one region to another, or across time points.

Current challenges

Important Challenges

- Some drugs are chemically identical and can be more difficult to pinpoint.
- Substances with low stability may yield concentrations below the limit of detection.
- Populations served by household septic systems will require a different form of assessment.

Some important challenges exist to using wastewater monitoring to estimate opioid abuse. Some drugs (such as heroin) have nonspecific metabolites that are chemically identical to other drugs (such as morphine), as seen in Table 1, and thus can be more difficult to pinpoint. However, with a complementary data source, such as data from the Prescription Drug Monitoring Program, morphine loads in wastewater samples could be parsed into levels due to legitimate versus illicit drug use if the number of prescriptions filled for morphine or for codeine (which also metabolizes into morphine) is known (and with some steady-state assumptions about population movements). Even without such secondary data sources, wastewater loads of morphine and other nonspecific metabolites can provide an upper bound on drug use within a community (for example, if all morphine detected were assumed to result from heroin use alone), and can be used to examine changes in use over time. Another challenge with using wastewater testing is that substances with low stability in wastewater can be difficult to quantify accurately because they often yield concentrations below the limit of detection (or between the limits of detection and quantification) of conventional lab assays. However, analytic methods exist to reliably account for such unobserved (left or interval-censored) values in the calculations. Wastewater testing may also be of limited use for detecting synthetic fentanyl, because the drug's high potency results in very small amounts being ingested, and therefore excreted (and detectable). Lastly, even a comprehensive wastewater monitoring system cannot access populations served by household septic systems, and thus will likely preclude the study of some high-risk populations. Spatial analyses could potentially be used to impute these missing data through averaging or smoothing across geographic units, and advanced predictive modeling could be used to obtain estimates for such populations based on measurable populations with similar demographic characteristics.

Table 1:
Major metabolites of prescription and illicit opioids

Drug	Half-life (hours)	Major metabolites
Morphine	1.5–6.5	**Hydromorphone (< 2.5%)**
Hydrocodone	3.5–9.0	**Hydromorphone, dihydrocodeine**
Codeine	1–4	**Morphine, hydrocodone (< 11%)**
Oxycodone	4–12	**Oxymorphone**, noroxycodone
Oxymorphone	3–6	6-hydroxy-oxymorphone
Tramadol	6–7	*O*-desmethyltramadol, nortramadol
Heroin	< 0.5	**Morphine**, 6-monoacetylmorphine (6-MAM), 3-MAM
Fentanyl	3–16	Norfentanyl, despropionylfentanyl

Sources: HealthPartners Institute for Medical Education (2016); Mayo Medical Laboratories (2014); and Mayo Clinic Proceedings (Smith 2009).

* **Bolded** metabolites are identical to pharmaceutically available drugs.

SEWAGE EPIDEMIOLOGY TO GAUGE TRENDS, PROGRAMS, AND NEW DRUGS OF ABUSE

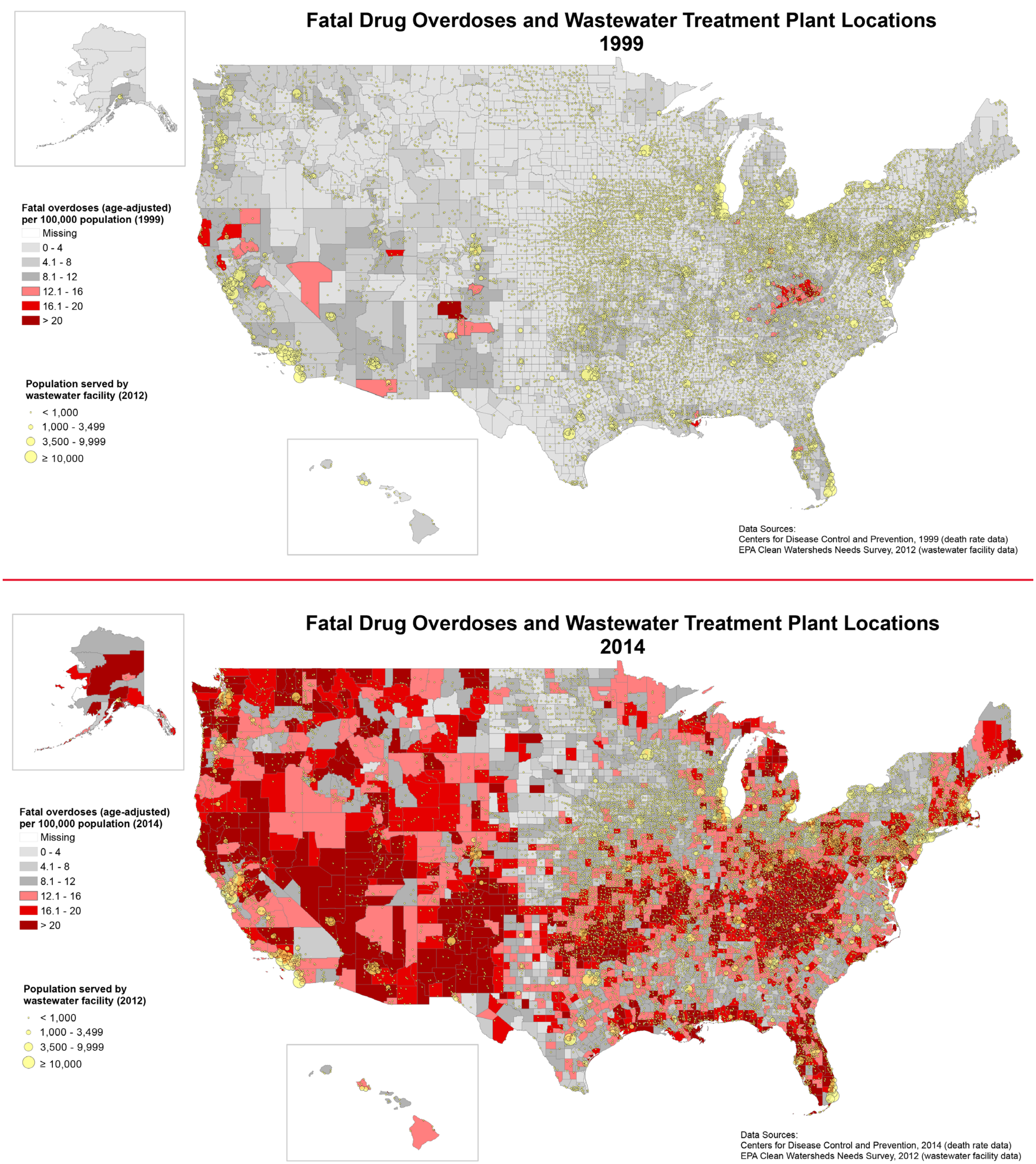
The steep rise in deaths due to drug overdose in nearly every county in the United States over the past 15 years (Figure 1) demonstrates the need for a more comprehensive approach to assessing drug use, intercession needs, and program effectiveness. The widespread geographic coverage and rapid turnaround possible with wastewater testing holds high potential to contribute to a comprehensive monitoring system that provides lawmakers and researchers access to local, regional, and/or national estimates of drug use trends. Data from wastewater testing is rich in spatial information, and can therefore be used to map hotspots of activity, assess trends over time, and even pinpoint drivers of opioid use by correlating locations of increased drug use with locations of infrastructural features, activities or events, and demographic characteristics. The application of advanced analytics and data visualization techniques could further yield insights into which regions might benefit from increased policing, or where pilot programs, such as the planned expansion of the Heroin Response Strategy under the High Intensity Drug Trafficking Areas program, would prove most fruitful.

... wastewater monitoring is readily scaleable.

A particular advantage of wastewater monitoring is that it is readily scalable. Because wastewater plants routinely collect samples of their inflow for quality control and regulatory purposes, the sampling and storage infrastructure needed for sewage epidemiological research is already in place around the country. Today, almost 15,000 centralized wastewater treatment facilities serve 226 million (71 percent) Americans and the vast majority (81 percent) of U.S. households (Center for Sustainable Systems 2015). The specificity of information available with this methodology is high, with almost 40 percent of wastewater facilities serving fewer than 1,000 people, and two-thirds serving fewer than 3,500 people (USEPA 2012). For those plants serving 3,500 people or more, granularity in the data could be increased by placing portable sampling stations upstream from where sewer pipes in different subcatchment areas merge. Although portable sampling stations can be labor-intensive to use, they have been successfully deployed in the United States and Europe to study small, targeted populations such as prisons, schools, and city districts (Castiglioni et al. 2014). The fact that data from wastewater testing cannot identify individual users should mitigate potential privacy concerns. Indeed, drug concentration data are obtainable only in aggregate, which is why human research ethics committees have deemed sewage epidemiological research to be of low risk, and often waive the need for ethical review altogether (Prichard et al. 2014). Nevertheless, researchers must exercise care when discussing results from studies of areas with dense populations of a specific ethnicity, or of specific schools and workplaces, so as not to stigmatize communities (Hall et al. 2012).

The development of a coordinated regional or national system in the United States would facilitate the conduct of longitudinal studies of drug use across the country, which could be used to map opioid use on a fine scale. Large-scale, coordinated studies using wastewater methods have already been successfully conducted in Europe—one study using wastewater sampling in 44 cities across 18 countries in the European Union and Norway found distinct geographical and temporal patterns of drug use

Figure 1:
Wastewater treatment plant locations in relation to fatal overdose hotspots



Large-scale, coordinated studies using wastewater methods have already been successfully conducted in Europe.

from east to west and north to south (European Monitoring Centre for Drugs and Drug Addiction 2014). Establishing a comprehensive monitoring system in the United States will require coordinated efforts and input from sampling methodologists, policy evaluation experts, sewage epidemiology researchers, health care organizations, and lawmakers. To inform the feasibility of using sewage epidemiology for widespread monitoring of opioid use, a dedicated conference followed by a regional pilot program is recommended. A coordinating center would be useful to synthesize input from researchers, develop the logistical and methodological details of a coordinated monitoring system, and engage testing laboratories. At present, very few labs in the United States test wastewater for illicit substances, and existing production labs might not have standardized processes in place for testing new illicit drugs. A harmonization of research efforts through a coordinating center could additionally create the demand needed to incentivize more labs to test for illicit substances.

Another benefit of sewage epidemiology is its promise for evaluating the effectiveness of interventions aimed at curbing opioid abuse (McCall et al. 2016). For example, the impact of potential changes to the patient satisfaction surveys tied to Medicare reimbursement, or of possible new laws to require high-risk patients to fill their prescriptions only at certain pharmacies, as recommended by the National Governors Association (NGA 2016), could be estimated by comparing pre- versus post-intervention wastewater loads of opioids within communities affected by the program. For programs already underway, such as the Drug Enforcement Administration's take-back program (which allows pharmacies, hospitals, clinics, long-term care facilities, and other such facilities to serve as authorized drop-off sites for unused prescription drugs), researchers can use wastewater testing within a quasi-experimental program evaluation framework to efficiently estimate and compare opioid use between communities covered by take-back programs and matched communities without such programs in place. Likewise, the impacts of state-specific policies could be examined by comparing opioid use in communities that are proximal, but on opposite sides of state lines.

Finally, wastewater monitoring can be useful as an early warning system for new psychoactive substances (McCall et al. 2016), similar to what the member states of the European Union use through the European Monitoring Centre for Drugs and Drug Addictions. A case in point is the emerging use of antidiarrheal medications such as loperamide (Immodium) to achieve a high or ease withdrawal symptoms (Eggleston et al. 2016). Little to no national data exist on the abuse of loperamide, and routine drug screens in emergency departments cannot detect the substance. But loperamide has been detected using liquid chromatography, an approved analytic testing method for pharmaceutical pollutants within the Clean Water Act, and thus could be measured through wastewater testing.

CONCLUSIONS

In the era of big data, information is available through many unseen channels and can be harnessed in novel ways to answer urgent questions. That wastewater has literally been mined for gold illustrates the multilayered bits of information buried in this resource (Westerhoff et al. 2015). Despite some calibration complexities in measurement and back-calculations to derive per capita estimates, measuring opioid use through municipal wastewater testing holds four key advantages over traditional methods: it (1) produces a comprehensive and impartial picture of opioid use across an entire community; (2) provides timely information, even when used over a large geographic region; (3) can be fairly readily deployed because it leverages existing infrastructure; and (4) yields estimates of drug use that are comparable across the country because of the consistency in infrastructure and methodology used. U.S. policy experts and researchers in Europe have already laid much of the groundwork needed to develop a comprehensive wastewater monitoring system by identifying best practices and standardizing methodology. A coordinated effort to establish a similar regional or national monitoring system in the United States would provide lawmakers and drug prevention, treatment, and enforcement organizations with rapid feedback on the efficacy of their initiatives to reduce opioid abuse. In combination with advanced analytics and data visualization tools, sewage epidemiological research provides the potential to more efficiently distribute resources by identifying areas with the greatest need, and by enabling the sorting of programs based on their effectiveness. Ultimately, such methods can empower local, state, and federal officials to begin predicting, rather than reacting to, the movements of drug abuse and addiction as it morphs across the country.

Advantages of This Approach

- Methodology produces comprehensive, impartial measures of opioid use.
- Timely information allows for rapid feedback for program evaluations.
- Deployment leverages existing infrastructure.
- Consistency of technique allows for comparisons across the country.

REFERENCES

Banta-Green, C., and J. Field. "City-Wide Drug Testing Using Municipal Wastewater: A New Tool for Drug Epidemiology." *The Royal Statistical Society*, June 2011.

Been, F., L. Benaglia, S. Lucia, J.P. Gervasoni, P. Esseiva, and O. Delémont. "Data Triangulation in the Context of Opioids Monitoring Via Wastewater Analyses." *Drug and Alcohol Dependence*, vol. 151, 2015, pp. 203–210.

Castiglioni, S., K.V. Thomas, B. Kasprzyk-Hordern, L. Vandam, and P. Griffiths. "Testing Wastewater to Detect Illicit Drugs: State of the Art, Potential and Research Needs. *Science of the Total Environment*, vol. 487, 2014, pp. 613–620.

Center for Sustainable Systems, University of Michigan. "U.S. Wastewater Treatment Factsheet." Pub. no. CSS04-14. Ann Arbor, MI: Center for Sustainable Systems, 2015.

Daughton, C.G. "Illicit Drugs in Municipal Sewage: Proposed New Non-Intrusive Tool to Heighten Public Awareness of Societal Use of Illicit/Abused Drugs and Their Potential for Ecological Consequences. In *Pharmaceuticals and Personal Care Products in the Environment: Scientific and Regulatory Issues*, edited by C.G. Daughton and T. Jones-Lepp. Symposium series 791, pp. 348–364. Washington, DC: American Chemical Society, 2001.

Eggleston, W., K.H. Clark, and J.M. Marraffa. "Loperamide Abuse Associated with Cardiac Dysrhythmia and Death." *Annals of Emergency Medicine*, 2016 (in press).

European Monitoring Centre for Drugs and Drug Addiction. "Perspectives on Drugs: Wastewater Analysis and Drugs: A European Multi-City Study." Lisbon: European Monitoring Centre for Drugs and Drug Addiction, 2014. Available at http://www.emcdda.europa.eu/attachements.cfm/att_228234_EN_POD2014_Wastewater%20analysis%20and%20drugs.pdf. Accessed May 11, 2016.

Hall, W., J. Prichard, P. Kirkbride, R. Bruno, P.K. Thai, C. Gartner, F.Y. Lai, C. Ort, and J.F. Mueller. "An Analysis of Ethical Issues in Using Wastewater Analysis to Monitor Illicit Drug Use." *Addiction*, vol. 107, no. 10, 2012, pp. 1767–1773.

HealthPartners Institute for Medical Education. "Interpretation of Opiate Urine Drug Screens." 2012. Bloomington: Health Partners Institute, 2014. Available at https://www.healthpartners.com/ucm/groups/public/@hp/@public/@ime/@content/documents/documents/cntrb_031044.pdf. Accessed May 11, 2016.

Johnson, Gene. "Feds Paying for Sewer Analysis of Pot Usage in Washington." *Seattle Times*, June 22, 2015. Available at http://www.seattletimes.com/seattle-news/marijuana/feds-paying-for-sewer-analysis-of-pot-usage-in-washington/. Accessed June 8, 2016.

Kinyua, J., A. Covaci, W. Maho, A.K. McCall, H. Neels, and A.L.N. van Nuijs. "Sewage-Based Epidemiology in Monitoring the Use of New Psychoactive Substances: Validation and Application of an Analytical Method Using LC-MS/MS." *Drug Testing and Analysis*, vol. 7, 2015, pp. 812–818.

Mayo Medical Laboratories. "Test ID: FENTU. Fentanyl with Metabolite Confirmation, Urine." Rochester: Mayo Clinic, 2014. Available at http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/89655. Accessed May 12, 2016.

McCall, A.K., R. Bade, J. Kinyua, F.Y. Lai, P.K. Thai, A. Covaci, L. Bijlsma, A.L.N. van Nuijs, and C. Ort. "Critical Review on the Stability of Illicit Drugs in Sewers and Wastewater Samples." *Water Research*, vol. 88, 2016, pp. 933–947.

National Governors Association. "Governors Priorities for Addressing the Nation's Opioid Crisis." Washington, D.C.: NGA, 2016. Available at http://www.nga.org/files/live/sites/NGA/files/pdf/2016/1602PrioritiesOpioidCrisis.pdf. Accessed March 22, 2016.

Prichard, J., W. Hall, P. de Voogt, and E. Zuccato. "Sewage Epidemiology and Illicit Drug Research: The Development of Ethical Research Guidelines." *Science of the Total Environment*, vol. 472, 2014, pp. 550–555.

Smith, Howard S. "Opioid Metabolism." *Mayo Clinic Proceedings*, vol. 84, no. 7, 2009, pp. 613–624.

Subedi, B., and K. Kannan. "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." *Environmental Science & Technology*, vol. 48, no. 12, 2014, pp. 6661–6670.

United States Environmental Protection Agency. "EPA Clean Watersheds Needs Survey, 2012." Washington, DC: EPA, 2012. Available at https://ofmpub.epa.gov/apex/cwns2012/f?p=134:3. Accessed May 10, 2016.

Westerhoff, P., S. Lee, Y. Yang, G.W. Gordon, K. Hristovski, R.U. Halden, and P. Herckes. "Characterization, Recovery Opportunities, and Valuation of Metals in Municipal Sludges from U.S. Wastewater Treatment Plants Nationwide." *Environmental Science & Technology*, vol. 49, no. 16, 2015, pp. 9479–9488.

Zuccato, E., C. Chiabrando, S. Castiglioni, D. Calamari, R. Bagnati, S. Schiarea, and R. Fanelli. "Cocaine in Surface Waters: A New Evidence-Based Tool to Monitor Community Drug Abuse." *Environmental Health*, vol. 4, no. 14, 2005.