WASTEWATER-BASED EPIDEMIOLOGY

Harnessing wastewater-based surveillance in the fight against illicit drugs

A Water Research Commission-funded project used wastewater-based epidemiology to assess illicit drug usage in two communities. Article by Sue Matthews.

Wastewater-based epidemiology (WBE) has been in the news a lot recently, because its potential as a Covid-19 monitoring tool and early warning system is being tested in studieds around the world. South Africa's own National Covid-19 Water and Sanitation Surveillance Programme, coordinated by the Water Research Commission (WRC), entered the pilot-scale monitoring phase in November, following the successful completion of the proof-of-concept phase.

The WBE approach was originally proposed 20 years ago, as a means of monitoring not infectious disease, but community-level usage of illicit drugs. In 2001, Christian Daughton, the then head of the United States Environmental Protection Agency's environmental chemistry branch, based in Las Vegas, outlined his idea in the final chapter of a book he co-edited, titled ***Pharmaceuticals and Personal Care Products in the Environment***. He suggested that monitoring illicit drugs in the influents of sewage treatment facilities – known in South Africa as wastewater treatment works (WWTW) – would allow the scale of the drug problem to be assessed in a non-intrusive way, assuring the confidentiality of individuals, while also providing data on the exposure risk to aquatic biota.

The first known application of the approach was by a group of researchers in Italy, led by Ettore Zuccato. In 2005 they published a paper detailing the presence of cocaine and its main urinary

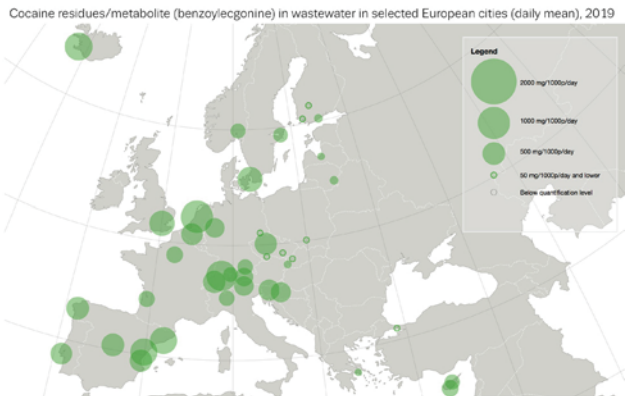
metabolite, benzoylecgonine, in water samples collected from the River Po and a number of WWTW in medium-sized Italian cities. Five years later, European experts on illicit drug analysis established a network called SCORE – an acronym for Sewage Analysis CORe group Europe – to standardise methodologies and coordinate joint studies. In 2011, the first annual Europe-wide monitoring campaign was conducted, together with an intercalibration exercise that allowed the uncertainties of the approach to be characterised. With the support of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), participation grew rapidly from the initial 19 cities in 11 countries to 42 cities in 21 countries in 2013. By 2019, when the campaign was conducted during a single week in March, 24-hour composite samples were collected in more than 70 cities in 25 countries, providing a snapshot of the 'drug problem' in Europe.

The first use of the WBE approach on the African continent was by Edward Archer and Gideon Wolfaardt from Stellenbosch University's microbiology department, in collaboration with researchers from the Department of Chemistry at the University of Bath in the United Kingdom (UK). The research formed part of a broader WRC-funded project on micropollutants and endocrine-disrupting contaminants (EDCs) in wastewater treatment systems (**WRC Project No. K5/2733**), but this component of the research was co-funded by the UK's Engineering and Physical Sciences Research Council (EPSRC). The research report for the WRC project was completed in October last year, although the findings of the WBE study on illicit drugs had already been published in ***Science of the Total Environment*** (Archer et al. 2018).

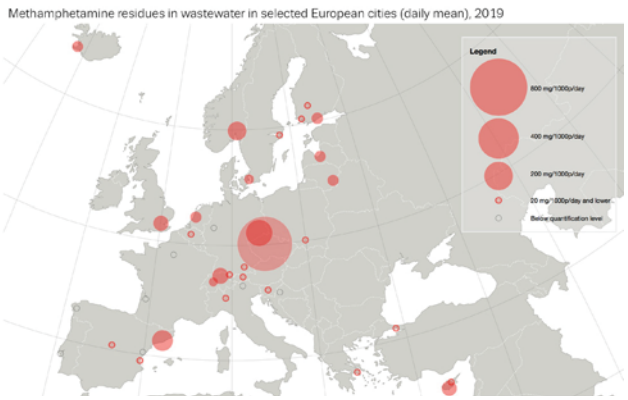
During 2017, sampling was done at seven consecutive days at two WWTW – one in Gauteng and the other in Cape Town. Samples were taken from the influent raw sewage, the final effluent, the return activated sludge, as well as from river water collected upstream and downstream of the WWTW. These samples were screened for various illicit drugs and their metabolites, as well as prescription drugs that are frequently abused. For example, ketamine is a class III schedule drug used as an anaesthetic in hospitals and other medical facilities, but it is also used as a recreational drug because of its hallucinogenic, tranquillising and dissociative effects. Medications for attention-deficit hyperactivity disorder (ADHD), such as Adderall and Ritalin, are similarly abused because their active ingredients – the stimulants amphetamine and methylphenidate, respectively – create feelings of euphoria when a number of the pills are crushed and then either snorted or injected with water.

Rather than considering only the concentration of compounds in the samples, the mass loads (grams per day) were calculated for each to compensate for the variation in daily influent and effluent flow rates, and this was then used to determine the removal of the compounds during wastewater treatment. Population-normalised drug loads (mg per day per 1 000

The research team found that most of the 38 compounds analysed – including medications and human biomarkers like caffeine, nicotine and alcohol as well as illicit drugs – were removed with high efficiency at both treatment plants.



The 2019 SCORE monitoring campaign confirmed that cocaine remains the most widely and heavily abused illicit drug in Europe.



The use of methamphetamine – known in South Africa as 'tik' – was historically restricted to Czechia and Slovakia, but has been steadily increasing in other countries in recent years.

inhabitants), taking into account the population served by each WWTW, were also calculated to estimate drug use patterns in the different communities.

In addition, in order to distinguish between consumption of drugs and their direct disposal into the wastewater system, the researchers quantified urinary metabolites as drug target residues (DTR) and also performed enantiomeric profiling of chiral drugs of abuse. Chiral compounds occur in two mirror-image forms, called enantiomers, which cannot be superimposed on one another, like our left and right hands – indeed, the term chiral is derived from the Greek word for hand. The biological activity of a drug is often related to its 'handedness', with one form sometimes being beneficial and the other inactive or even toxic. The two enantiomers are differentiated by the prefix R or S, and a homogeneous mixture of the two in equal proportions is said to be racemic. However, since the enantiomeric ratio changes after human metabolism, this can be used to determine whether drugs detected in wastewater originated from consumption, rather than direct disposal.

For example, methamphetamine – known in South Africa as 'tik', but as crystal meth, ice or speed in many other parts of the world – was found to be the most prevalent illicit drug at both WWTW. Its mass loads were dominated by S-(+)-methamphetamine, which is known to be the primary enantiomer of illicit use. When the population-normalised loads were compared, it was clear that the scale of methamphetamine use in the community around the WWTW sampled in Cape Town was much higher than that around the Gauteng one. The maximum result of approximately 1 185 mg/day/1 000 inhabitants was the daily mean recorded for the Sunday of the sampling week – as was the case for many of the other drugs included in the study, the results reflect heavier drug use within the community at weekends.

Surprisingly, though, at the Gauteng WWTW the average concentration of S-(+)-methamphetamine at the river sampling station 3.5 km downstream of the final effluent discharge point was 18 times higher than in the upstream river water. Since the enantiomer is removed by the WWTW with relatively high efficiency, it is clearly entering the river from an additional source downstream of the WWTW.

In Europe, methamphetamine use has historically been restricted to Czechia and Slovakia, but there has been an increasing trend in other countries in recent years, and the 2019 SCORE results showed that the drug was also present in wastewater in cities in Cyprus, the east of Germany, Spain and several northern European countries. The highest result was 770 mg/day/1 000 inhabitants for the weekend mean in Prague, which is far exceeded by the 2017 figure for Cape Town. Prague was not part of the SCORE study in 2017, and at that stage the highest results were from Chemnitz and Erfurt in Germany, with weekend means in the 215–230 mg/day/1 000 inhabitants range.

In the case of cocaine, its use was also more prevalent in the community served by the WWTW in Cape Town in 2017, compared to the Gauteng one. Population-normalised mass loads of the metabolite benzoylecgonine ranged from a low of 257 mg/day/1 000 inhabitants on the Thursday to a peak of almost 590 mg/day/1 000 inhabitants on the Sunday. The metabolite cocaethylene, which is formed when cocaine is taken with alcohol, was also detected, and showed a similar spike on weekends.

"The research team found that most of the 38 compounds analysed – including medications and human biomarkers like caffeine, nicotine and alcohol as well as illicit drugs – were removed with high efficiency at both treatment plants."

Cocaine use is considerably higher in Europe, particularly in cities in Belgium and the Netherlands, where the mean population-normalised mass loads of benzoylecgonine for the week exceeded 950 mg/day/1 000 inhabitants in Antwerp and Amsterdam in 2019. Similar maxima were recorded in 2017, although then it was Barcelona and Zurich that had the highest results, and the SCORE data for Europe as a whole have shown an increasing trend for benzoylecgonine since 2016. A 2018 EMCDDA study noted that this could potentially be attributed to more people consuming cocaine, the same people consuming

more cocaine, increased purity of the drug, or a combination of all three.

The drug known as Ecstasy or Molly is more correctly called MDMA, short for 3,4-methylenedioxy-methamphetamine. There appeared to be negligible use of this drug in the community served by the Gauteng WWTW in 2017, while at the Cape Town WWTW the population-normalised mass loads ranged from 9–62 mg/day/1 000 inhabitants, with these results reflecting the Thursday and Sunday daily means, respectively. In Europe, MDMA use is widely believed to have peaked in the early to mid-2000s, but the SCORE data showed that for 11 out of the 12 cities with data for both 2011 and 2019, MDMA loads were higher in 2019 than in 2011. The highest overall mean for the week was recorded for Antwerp in Belgium and three cities in the Netherlands, all exceeding 100 mg/day/1 000 inhabitants but reaching 287 mg/day/1 000 inhabitants in Amsterdam.

The metabolite of heroin, 6-monoacetylmorphine (6-MAM), was detected in raw effluent of the WWTW in Cape Town, confirming that the drug is used within the surrounding community. However, 6-MAM is known to be unstable in wastewater, so it cannot be used for quantitative estimates, and is omitted from the SCORE data for Europe.

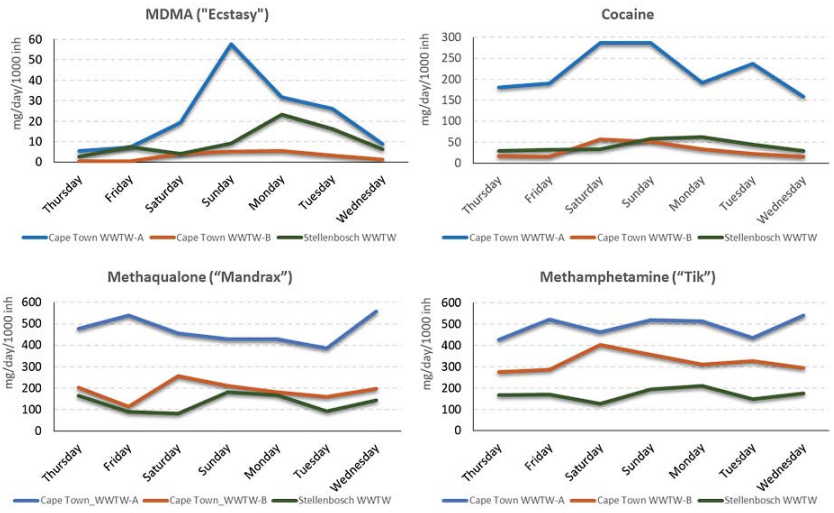
The results of the WRC-funded research provide insight into drug use within the communities served by the particular WWTW included in the study – other WWTW in Cape Town and Gauteng may yield quite different results, depending on the demographics, socio-economic pressures and lifestyles of the surrounding communities. But what are the implications for aquatic biota?

The research team found that most of the 38 compounds analysed – including medications and human biomarkers like caffeine, nicotine and alcohol as well as illicit drugs – were removed with high efficiency at both treatment plants. The exceptions were the opioid pain-reliever tramadol and the antidepressant venlafaxine and their metabolites. A follow-up study at two other WWTW in Cape Town, also conducted as part of the WRC project, likewise found that illicit drugs were well removed, apart from methaqualone – better known as mandrax. The drug had not been included in the 2017 study; in fact, this was the world's first-ever report to show the presence and fate of the drug in a wastewater monitoring study. Methaqualone is not widely used in other parts of the world, with the possible exception of the Indian subcontinent.

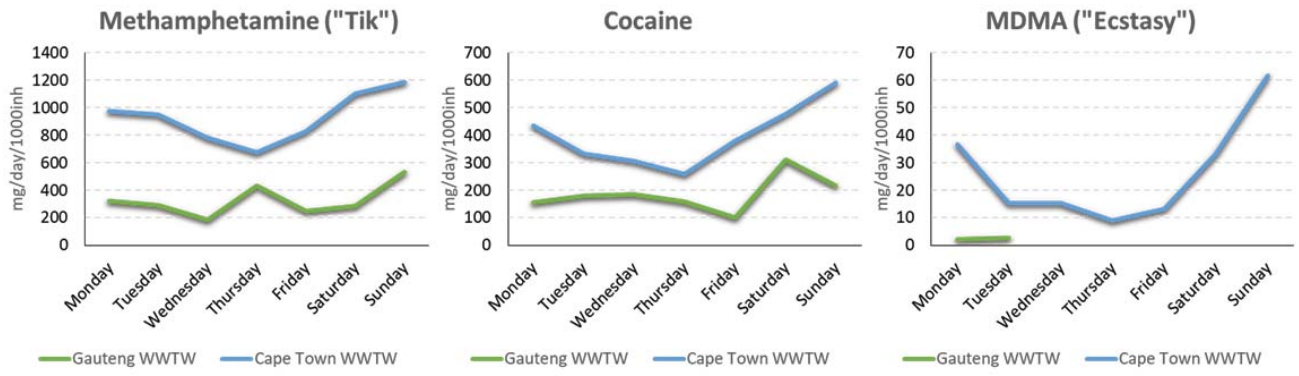
In addition to methaqualone, the antibiotic sulfamethoxazole, the NSAID diclofenac, the ARVs emtricitabine and efavirenz, and the anti-convulsant 10,11-dihydro-hydroxycarbamazepine were found in the follow-up study to have moderate to low removal, while carbamazepine had negative removal, being found in higher concentrations in the final effluent than in the influent wastewater. The project team therefore recommended that methaqualone and the medications identified in the two studies should be prioritised for further research on their potential ecological risk, their interaction with various biochemical pathways (potential sub-lethal toxicity responses), as well as the persistence of their breakdown products and bio-accumulation in freshwater biota.

Also of concern, of course, is the fact that illicit drugs were found in river water samples upstream of WWTW, often at concentrations similar to or even higher than those in the final effluent discharged from the WWTW back into the river. This is indicative of sewage reaching the river via leaking sewers or direct disposal by households not connected to the wastewater network, particularly where rivers pass through informal settlements.

An environmental risk assessment conducted by the project team, using Predicted No Effect Concentration (PNEC) acute toxicity data from the literature for algae, cladocerans or fish, showed that the concentrations of illicit drugs both in the final effluent and the river waters posed a low risk, with the exception of morphine in river water in the vicinity of the WWTW in Cape Town. Nevertheless, such PNEC-derived risk values do not



The researchers who conducted the WRC project have been participating in the SCORE monitoring week for the past three years. In 2019, this involved round-the-clock sampling at two WWTW in Cape Town and one in Stellenbosch. The samples were analysed for methaqualone (mandrax) too, although this drug is not included in SCORE because usage is very limited outside southern Africa, East Africa and the Indian subcontinent, where it originated.



Results of a week-long monitoring exercise at two wastewater treatment works, conducted in 2017 as part of the WRC project, showed higher drug use in the community surrounding the Cape Town one.

consider the long-term health effects of continual exposure to the drugs – either individually or in combination, exerting cumulative impacts – over many generations of aquatic biota.

The researchers note that the broader application of the WBE approach in South Africa can serve as a support system to compare drug use and abuse trends between communities and over periods of time. Currently, collation of such information is largely limited to substance-abuse treatment centres and law-enforcement reports, which may lead to inaccurate estimations of illicit drug use.

The WBE approach can provide near real-time monitoring of a social ill that is closely tied to criminal activity and has a ripple effect on other problems in communities, including high unemployment, gender-based violence, petty theft and gang warfare. And since wastewater samples can be used to monitor a wide variety of other biological and chemical substances, the WRC sees it as a cost-effective approach that should ideally be scaled-up to a nation-wide monitoring programme.

SCORE data and images from SCORE (2020). Wastewater monitoring data 2011-2019. Sewage analysis CORe group Europe, http://score-cost.eu/monitoring2019

To download the WRC report, ***Substances of emerging concern in South African aquatic ecosystems. Volume 1: Fate, environmental health risk characterisation and substance use epidemiology in surrounding communities*** (**Report No. 2733/1/20**), visit: www.wrc.org.za.