A comparison of trends in wastewater-based data and traditional epidemiological indicators of stimulant consumption in three locations.

Neil Goulding[1], Matthew Hickman[1], Malcolm Reid[2], Ellen J. Amundsen[3], Jose Antonio Baz-Lomba[2], Jake W O'Brien[4], Ben J Tscharke[4], Pim de Voogt[5, 5a], Erik Emke[5], Wil Kuijpers[6], Wayne Hall[7], Hayley E Jones[1].

Population Health Sciences, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS82PS, UK[1], Norwegian Institute for Water Research, Gaustadalleen 21, NO-0349 Oslo, Norway[2], Department of Alcohol, Tobacco and Drugs, Norwegian Institute of Public Health, Oslo, Norway[3], The University of Queensland, Queensland Alliance for Environmental Health Sciences (QAEHS), 20 Cornwall Street, Woolloongabba, QLD, 4102, Australia [4], KWR Watercycle Research Institute, P.O. Box 1072, 3430 BB Nieuwegein, The Netherlands[5], Institute for Biodiversity and Ecosystem Dynamics, University of Amsterdam, The Netherlands[5a], Stichting Informatievoorziening Zorg (IVZ), Randhoeve 231, 3995 GA Houten, The Netherlands[6], The University of Queensland, Centre for Youth Substance Abuse Research, Herston, QLD, 4029, Australia[7]

Correspondence to: Neil Goulding, Population Health Sciences, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS82PS, UK. E-mail: N.Goulding@bristol.ac.uk

Running Head: Wastewater trends in stimulant consumption

Word Count: 4108

Declaration of Interests: None

Abstract

Aims To compare long-term trends in wastewater data with other indicators of stimulant use in three locations and to test the reliability of estimates based on one week of sampling.

Design Comparison of trends in quantities ('loads') of stimulants or their metabolites in wastewater with trends in other indicators of stimulant use (e.g. treatment, police, population survey data).

Setting and Participants Populations in Oslo (Norway), South-East Queensland (Australia) and Eindhoven (The Netherlands).

Measurements Wastewater data were modelled for MDMA (3,4-Methylenedioxy methamphetamine), benzoylecgonine (a metabolite of cocaine), amphetamine and methamphetamine in Oslo; benzoylecgonine in Eindhoven; and methamphetamine in South-East Queensland. Choice of stimulants modelled in each region was primarily determined by availability of useable data.

Findings In Oslo, wastewater data, driving under the influence of drugs statistics and seizure data all suggested increasing MDMA use between 2009 and 2017. In South-East Queensland, there was an estimated 31.1% (95%CI 29.4-32.9%) annual increase in daily loads of methamphetamine in wastewater between 2009 and 2016, compared with a 14.1% (95%CI 10.9-17.3%) annual increase in seizures. Some of the increase in wastewater can be explained by increased purity. In Eindhoven, there was no evidence of a change in cocaine consumption from wastewater, but a reduction was observed in numbers in treatment for cocaine use from 2012 to 2017. In approximately half the cases examined in Oslo, credible intervals around estimates of annual average loads from a regression model versus estimates based on a single week of sampling did not overlap.

Conclusions Long-term trends in loads of stimulants in wastewater appear to be broadly consistent with trends in other indicators of stimulant use in three locations. Wastewater data should be interpreted alongside epidemiological indicators and purity data. One week of wastewater sampling may not be sufficient for valid inference about drug consumption.

Keywords:

Sewage epidemiology, Long-term trends, Bayesian analysis, Methamphetamine, MDMA, Queensland, Oslo.

Introduction

Analysis of wastewater samples is a novel technique for observing patterns of community drug use (1). The method, known as 'wastewater-based epidemiology' or WBE, was first used in 2005 to investigate illicit drug use (2) and has become an increasingly popular approach for making inferences about drug consumption in the population.

The approach involves collection of samples of raw sewage from the inlet of a wastewater treatment plant (WWTP), with the flow rate recorded for each sample. The samples are analysed for concentrations of specific drug target residues, which can be measured with great accuracy and precision (3, 4). These concentrations and flow rates are used to estimate daily loads (e.g. in g/day), which are estimates of the total amount of drug target residue arriving at the treatment plant. These are divided by estimates of the size of the population connected to the WWTP to produce estimated population-normalised daily loads (5, 6), i.e. the amount of drug target residue arriving at the treatment plant each day, per 1000 people served by the treatment plant.

An ongoing European multi-city study (7) analyses one week of daily wastewater samples each year from many cities across Europe. These data are published by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as a complementary national indicator of drug consumption (8). Very few locations with large populations have collected wastewater data over longer time frames. There has therefore been very limited exploration of how much variation can be expected in wastewater samples over a longer time period (9) and therefore of how representative any single week might be of one year.

No single measure can provide a full picture of regional drug use and current trends (10, 11). A multi-indicator approach is required, incorporating commensurate data such as population surveys and police data (12-20). Several of the previous comparisons of wastewater data with other indicators of drug consumption have been limited by the single week of sampling issue. In this paper, we examine data from three case study locations in which more frequent and long-term wastewater data are available.

The specific aims of this study were:

1. To compare long-term trends in loads of stimulant drug target residues in wastewater data with trends in more traditional indicators of stimulant use, in three locations.
2. To explore whether one week of daily wastewater samples, typically undertaken in current surveillance exercises (7), can estimate daily average annual loads with sufficient accuracy.

Methods

Design

We identified three sites with populations greater than 200,000 people where regular wastewater data and commensurate epidemiological data were available over several years, from which we could compare trends in stimulant use: Oslo (Norway), South-East Queensland (Australia) and Eindhoven (The Netherlands). We focused on four stimulant drug target residues: benzoylecgonine (a metabolite of cocaine (21)), amphetamine, methamphetamine and MDMA. The choice of locations, and of which of the four stimulants to model in each location, was primarily determined by availability of useable data.

We acquired other regional indicators of stimulant consumption that matched the catchment of the WWTPs as closely as possible. Where this was not viable, we obtained national data.

Measures

Oslo

We amalgamated eight Oslo wastewater datasets, some of which have been analysed previously, e.g. (22-24). This includes the 1-week snapshots published by the EMCDDA each year from 2011-2017 (8), referred to herein as 'EMCDDA data'. These datasets had not previously been merged and analysed together, allowing long-term trends to be assessed. The combined data covers the period 2009 to 2017 and relates to a WWTP serving approximately two-thirds of the population of Oslo, primarily the western side (roughly 550,000 people). We present the results for MDMA in this article to provide a contrast to the other case studies. The results for methamphetamine, amphetamine and benzoylecgonine are given in the Supporting Information. 246 samples were analysed for MDMA in total, with a median of 24 samples per year (ranging from 7 samples per year in 2011 and 2013, to a maximum of 58 samples in 2016).

For each stimulant, we also examined annual numbers of people Driving Under the Influence of drugs (DUI) recorded by the police in Oslo (25) and annual numbers of police seizures (26) in Oslo, Asker and Bærum, over the same timeframe. Over similar timeframes, we examined annual national indicators of stimulant use in Norway. This included numbers of positive results from autopsy ((27), personal communications from Gerrit Middelkoop, Oslo University Hospital), numbers of people in treatment (28), prevalence estimates from general population surveys (GPS) and numbers of positive drug tests in prison (Oslo University Hospital).

South East (SE) Queensland

In recent years indicators have consistently evidenced an increase in methamphetamine use in Australia (29-32), whereas indicators of use for other stimulants have been relatively flat (33, 34). In SE Queensland, we therefore examined data relating to methamphetamine use only.

The wastewater data span the period 2009 to 2017 and relate to a WWTP serving approximately 230,000 inhabitants. 598 daily samples were analysed, with a median of 49 samples per year (ranging from 12 in 2009 to 188 in 2012). Some of the earlier parts of the dataset have been reported on previously, e.g. (17, 34-37).

We also examined the annual number of methamphetamine seizures in SE Queensland from 2010-2015 (17) and annual numbers of methamphetamine-related hospital admissions, emergency department presentations and psychiatric admissions in the state (Queensland) from 2010-2015/16 (29). Furthermore, we examined national annual numbers of methamphetamine-related deaths from 2009-2015 (32). We also obtained regional purity data from seizures of methamphetamine in SE Queensland, provided by the Queensland Health Forensic Chemistry Laboratory and Bruno *et al.* (2018, (17)).

Eindhoven

Although ‘long-term’ wastewater data in Eindhoven have been collected for each drug target residue of interest, direct disposals of unconsumed amphetamine and MDMA contaminated a considerable number of the daily samples (6), potentially indicating nearby production. Since it is unknown the quantity of each drug disposed of in this way, these could not be considered a reliable indicator of consumption (38, 39). Levels of methamphetamine in wastewater were at an extremely low level throughout the timespan of the data and there were no other indicators of methamphetamine consumption to compare with. Consequently, we modelled only the benzoylecgonine data. The wastewater data cover the period 2012 to 2017 and are from a WWTP serving an estimated population of 450,300 people in Eindhoven and several surrounding towns and villages. The wastewater data comprise of 187 daily samples in total. However, for the years 2012-2015 the data are much more limited than for the other two locations, consisting only of seven days of EMCDDA data (15 days in 2012). In addition to the EMCDDA data from 2016 and 2017, there were consecutive daily samples for approximately 3 months from May-July 2016 and seven weeks in July-August 2017.

We examined monthly cocaine treatment demand data for the Eindhoven region from 2012 to 2017. More specifically, the data consisted of the total number of people who attended treatment in each month with cocaine as their primary or secondary problem. This data set corresponds to a very similar geographical area to the WWTP catchment area, making comparisons with wastewater data more relevant. We also obtained cocaine-related national annual numbers of recorded DUI offences and deaths from 2013-2016 (40).

Statistical analysis

Modelling the wastewater data

We adopted a Bayesian statistical approach, which is well suited to modelling multiple sources of uncertainty and potentially complex hierarchical data structures. We accounted for three sources of sampling uncertainty in estimated population-normalised loads: analytical uncertainty in the concentration measurements, uncertainty in the daily flow estimates and uncertainty in the estimated population size served by the WWTP (41). These were determined by the authorship team to be the important sources of sampling variability when considering long-term trends. We extended the approach previously described (41) to a hierarchical log-linear regression modelling approach, in which we further accounted for three sources of temporal variation:

(1) Systematic differences in daily population-normalised loads by day of the week.

(2) Differences in monthly average population-normalised loads. We fitted three alternative models to these monthly averages on the log scale:

   (i) *Annual effects model*. Step change by calendar year

   (ii) *Annual and quarterly effects model*. Step change by year and by quarter of the year

   (iii) *Linear trend model*. Linear regression on month since first sample

(3) An additional amount of random daily variation around the fitted trend line within each month (assumed constant).

A log-linear modelling approach was used due to positive skewness in the data and to prevent negative fitted values. The basic functional form of the model was decided *a priori*, based on previous evidence and consideration of the characteristics of the data. For example, systematic differences in loads by day of the week are well established in the literature ((9),(23),(37)). Pragmatic decisions had to be made about modelling of systematic changes over time (models (i) to (iii) above) due to limited data availability: for example, there were insufficient data to include 'month' effects or year-by-quarter interaction terms in model (ii). Model (iii) was fitted specifically to facilitate comparison of long term trends with other indicators, through estimated gradients.

Models were fitted in WinBUGS (42), using all of the available wastewater data. The deviance information criterion (DIC) (43) was used to compare the fit after penalising for complexity of models (i) to (iii). This is a Bayesian generalisation of the Akaike information criterion, with models with lower DIC values preferred. In the Results section, for each stimulant and location we display annual estimates based on model (iii) and the best fitting of models (i) and (ii).

More information about the regression models and the assumptions made about uncertainties in the concentration, flow and population size parameters in each location is provided in the Supporting Information (S1).

Analysis of other regional and national indicators of stimulant use

Data such as annual or monthly numbers of seizures, hospital admissions, positive autopsy results, numbers in treatment and recorded offences for DUI were analysed using Poisson regression models, with time (year or month) as a covariate. A logistic regression model with year as a covariate was fitted to annual prevalence data from population surveys. These simple models were fitted as rough approximations only, to facilitate comparison of overall trends with the wastewater data. These analyses were performed in R.

Comparison of trends

We estimated annual percentage changes in population-normalised loads of stimulants in wastewater (based on model (iii) above) and in other indicators of stimulant consumption based on the regression models with time as a covariate. We compare these percentages with caution, since we would not anticipate changes in total population consumption to manifest in the same way across indicators. For example, a doubling in total consumption would not necessarily lead to a doubling of number of individuals in treatment.

Purity-adjustment in South East Queensland

Seizure data indicate that methamphetamine purity in SE Queensland varied considerably across the wastewater sampling period (17): increasing substantially from approximately 12.7% (95% confidence interval, CI, 9.6 to 15.9%) purity in 2009 to 68.8% (95% CI 67.2 to 70.3%) in 2015, then decreasing slightly to 60.8% (95% CI 57.7 to 64.0%) in 2017. To explore the potential impact of this, we produced purity-adjusted annual population-normalised loads of methamphetamine, by dividing annual estimates from the best fitting of our wastewater models by estimated percentage purity. Our simulations-based modelling approach provides estimates with 95% credible interval (Cr-Is) that account for uncertainty in estimates of percentage purity, in addition to the sources of uncertainty described above.

Comparison of annual daily averages from EMCDDA data and non-EMCDDA data

In Oslo and Eindhoven (which both contribute data to the annual EMCDDA estimation exercise), we compared results from EMCDDA and non-EMCDDA data for years in which there were 21 or more wastewater samples in addition to the EMCDDA data. We compared the following two estimates of average daily population-normalised loads in each year:

(i) based on analysis of the one week of EMCDDA data per year in isolation, accounting for uncertainty in concentration, flow and population parameters (41).

(ii) based on the best fitting of the three regression models above, applied to all available wastewater data *except* for the EMCDDA data. EMCDDA data were removed here to avoid biasing the comparison in favour of agreement.

We note that comparisons could only be made in Eindhoven for benzoylecgonine in 2016 and 2017, where data were available only for March to August in each year. We also compared the EMCDDA-based estimates with estimates based on any other seven-day consecutive period of sampling in the same year.

Results

1. MDMA use in Oslo

Recorded numbers of DUI MDMA offences and police seizures in Oslo increased annually on average over the timeframe of the data (Table 1; Figure 1). At the national level, there was also an increase in estimated prevalence of use and in annual numbers of positive results from autopsy and prison data (Table 1; Figure 1).

Daily population-normalised loads of MDMA in wastewater (Figure 2A) show a very large amount of variability, even among samples taken close together in time. This is particularly evident in 2014, where estimates range from 1.7 to 170.7 mg/day per 1000 people. Also plotted are the estimated daily average population-normalised loads for each year, based on model (i) and model (iii). From model (iii), average daily population-normalised loads are estimated to have increased over time (Table 1), but model (i) has a slightly better fit to the data (Table 2): this estimates a general increasing trend, but with some evidence of a peak in 2015 and extremely low values in 2011.

Part of the observed variability in wastewater loads is likely due to variation by day of the week: as shown in Figure 2B, there is evidence of loads being higher on average on weekends versus week days.

Use of other stimulants in Oslo

Long-term trends in methamphetamine measured in wastewater generally agreed with trends in other indicators of methamphetamine use in Oslo and Norway, all of which decreased over the timeframe of the wastewater data. There were no clear long-term trends in wastewater (or other indicators) for amphetamine or cocaine use. Full results for these other stimulants are provided in Supporting Information S2.

2. Methamphetamine use in SE Queensland

All indicators of methamphetamine use at regional, state and national level suggested increasing use over the timeframe of the data (Table 3; Figure 3).

The crude (unadjusted for purity) wastewater data (Figure 4A) are also consistent with a large increase in methamphetamine use from 2009 to 2016. There was also evidence of systematic variation by day of the week (Figure 4B). Model (iii) estimates an average annual increase in daily population-normalised loads between 2009 and 2017 (Table 3). However, this linear trend model does not fit the data well (Table 2), due to strong evidence of a *reduction* in loads between 2016 and 2017. The more flexible model (ii) fits the data better (Table 2) and estimates a 32.3% (95% Cr-I 22.3 to 41.1%) reduction in average daily loads between these two years. Since data from the other indicators examined are not yet available for 2017, it is not yet possible to ascertain whether the recent reduction according to the wastewater data is reflected in other indicators.

Estimates of the purity of methamphetamine in SE Queensland between 2009 and 2017 are shown in the Supporting Information (S1.3). After adjusting for changes in purity, the estimated trend looks quite different (Figure 4A – red). Purity-adjusted estimates varied less across years (estimated 2.4 fold variation across annual estimates, versus 9.0 fold prior to adjusting for purity). As indicated on the plot, the total amount of (impure) methamphetamine consumed by the population may have actually reduced in 2012 and 2013 relative to 2010, subsequently rising again, with a large peak in consumption in 2016.

3. Cocaine use in Eindhoven

There was an overall reduction in the number of people attending treatment in Eindhoven with cocaine as their primary or secondary problem between 2012 and 2017 (Table 4; Figure 5A– although we note the large amount of overdispersion around the fitted trend line). In contrast, nationally there was an increase in numbers of recorded DUI offences per year and recorded cocaine-related deaths (Table 4; Figure 5B).

The daily averaged population-normalised loads of benzoylecgonine plotted in Figure 6A show a very large amount of variability, even among samples taken close together in time, and no clear temporal trend. Model (iii) provided little evidence of change over time (Table 4), but model (i) fitted the data much better (Table 2) and gave strong evidence of a reduction in daily loads on average between 2016 and 2017. There is evidence of a delayed weekend effect (Figure 6B): the WWTP has advised us that this is likely due to the retention time in the system prior to reaching the treatment plant.

Estimating annual loads from one week of sampling

Estimates of annual average daily wastewater loads based on EMCDDA and non-EMCDDA data are displayed for Oslo in Figure 7. The two sets of credible intervals (red versus green) did not overlap in approximately 50% of the cases. Furthermore, the credible intervals from the EMCDDA data (red) did not overlap with other weekly averages from the same year (blue) in approximately 40% of the cases. For Eindhoven in 2016 and 2017 the EMCDDA versus non- EMCDDA based credible intervals overlapped (see Figure S3.1 in Appendix S3 of the Supporting Information).

Discussion

Main Findings

In Oslo, long-term trends in wastewater data were broadly consistent with evidence from more traditional epidemiological indicators: in particular, suggesting an increase in MDMA use between 2009 and 2017. Loads of methamphetamine in wastewater increased drastically in SE Queensland between 2009 and 2016, consistent with large increases observed in numbers of methamphetamine-related deaths, hospital admissions and seizures. Observed increases in methamphetamine loads in wastewater appear to be partly driven by changes in purity, which may also be an important driver of increases in methamphetamine-related harms (hospital admissions and deaths). In Eindhoven, where the wastewater data are much more sparse in time, wastewater data did not evidence a clear trend in cocaine consumption, whereas there was a large reduction in treatment demand for cocaine problems during the same time period.

Across all three locations that we studied, there was a large amount of variability in daily population-normalised loads of stimulants in wastewater. Although some of this variability can be explained by weekend effects (particularly for MDMA), there was clear residual variation beyond this. One or two weeks of wastewater sampling can raise hypotheses about differences in drug use by geographical area. However, based on our comparisons of estimates based on just seven days (‘EMCDDA data’) and estimates based on longer term sampling in Oslo and Eindhoven, we cannot be confident that inferences based on just one week are robust.

Strengths and Limitations

We compared long-term trends in wastewater data with other indicators of stimulant use in three locations over a timeframe of up to nine years, much longer than previous studies. We developed and applied a Bayesian hierarchical regression model that allows for uncertainty in concentration, flow and population parameters and also multiple sources of temporal variation in loads. We fitted log-linear or linear trend models as approximations for all indicators, to facilitate comparison of long term trends across data sets. We compared fit with some slightly more flexible models for the wastewater data, but not for the other indicators, such that estimated coefficients (Tables 1, 3, 4) should be interpreted with caution. The linearity assumption was clearly violated in some specific instances (e.g. Supplementary materials Figure S2.3: seizures and prison data).

We note that it was difficult to identify suitable locations for this study, since there are few wastewater data sets with more than 1-2 weeks of samples per year over a number of years. Further, wastewater data generally relate to a local level (city, or some fraction of a city served by a particular treatment plant), for which other indicators of stimulant use are not necessarily available. We therefore had to use national data to compare trends of some indicators with wastewater data; these comparisons should be treated with caution as it is difficult to assess how representative these selected cities are for the country as a whole. In addition, other indicators are often available only as annual counts and are not always stimulant-specific. We also acknowledge that epidemiological data also can give uncertain, incomplete and biased perspectives on drug use trends in the population – but we lacked sufficient information to identify and adjust for inconsistencies in the evidence. For example, information was not available on levels of police activity, changes in which could affect trends in DUI and/or seizure data. We could not adjust wastewater loads for purity in Oslo or Eindhoven as regional purity data were not available.

Estimated population-normalised loads of drug target residues in wastewater will be biased if inaccurate population size estimates are used in the standardisation. We used population size estimates provided by the WWTPs, usually based on census data. The level of uncertainty that we allowed for in these estimates (see Supporting Information S1) may not be sufficient to allow for the bias. More accurate estimates of the size of the population served by a WWTP could be obtained through mobile phone, ammonia or biomarker data (35, 44-46). Future research should continue to investigate cost-effective approaches to accurately estimate '*de facto*' population size, to minimise the use of inaccurate census-based estimates in wastewater calculations.

Comparison with Other Evidence

Other studies that have used a multi-indicator approach (12-20) have also found a general agreement between trends in drug target residues in wastewater and trends in other indicators of drug consumption. Our study was conducted over a much longer time frame and accounts for multiple sources of uncertainty, such as the concentration measurements, the daily flow estimates and the estimated population sizes, through our Bayesian hierarchical regression model.

Our finding that one week of wastewater sampling may not be sufficient is in agreement with the study of Ort *et al* (9), which presented an analysis of 1369 consecutive days of sampling in a German village with approximately 7160 inhabitants. They reported an approximate 60% relative error in estimates of annual means based on any one week of samples (9). To date, no formula has been derived to determine the minimum number of samples required for robust inference across all scenarios.

Bruno *et al* (17) noted that changes in purity of methamphetamine may be a key driver of observed increases in loads in wastewater in SE Queensland, which we extended to provide purity-adjusted estimates over a longer time-period. We included new data which shows that both purity and wastewater loads of methamphetamine in SE Queensland have very recently reduced. It will be interesting to see whether such a reduction is later reflected in other indicators of use and harm and, if so, how much of a time lag there is before such a reduction can be detected from other time series data. We note that analysis of Finnish data has previously suggested that wastewater analysis could provide an 'early warning' of changes in drug consumption, before such changes are evident from other indicators (18).

Implications

Changes in street purity could be a key driver of observed changes of drug target residues in wastewater and indeed of changes in other indicators of use. Where possible, trends in purity data should be assessed and, if appropriate, adjusted for.

Further research is required to determine the minimum sampling period for wastewater data to be meaningful as an annual indicator of drug consumption. The issue is complicated by the fact that this will vary by the prevalence and frequency of drug use in the population studied and the ratio of episodic to dependent use (47), in addition to the drug target residue (due to varying excretion profiles), and the size of the population served by the WWTP (9).

With regular, long-term sampling, wastewater data could reliably estimate the direction of trends in stimulant use. However, while the current focus is on much sparser sampling, it is unlikely that wastewater data will be robust enough to be the sole information on consumption trends. Further, local information (e.g. on purity and patterns of use) is required to interpret the evidence. Our case study in Eindhoven illustrated the difficulty in assessing long-term trends with sparse wastewater data and few other regional indicators of stimulant consumption. For robust comparisons of wastewater data with other indicators, sampling should be targeted at locations known to have commensurate epidemiological data on drug use and where other indicators of stimulant use can be mapped approximately to the catchment of the WWTP.

Funding

This work was supported by the Wastewater Analysis of Traces of illicit drug-related Chemicals for law enforcement and public Health (WATCH) project, which was funded by the European Commission (Contract HOME/2015/ISFP/PR/DRUG/0062). MH and NG acknowledge support from the NIHR Health Protection Research Unit in Evaluation of Interventions at University of Bristol. HEJ was supported by a Medical Research Council (MRC) career development award in biostatistics (MR/M014533/1).

Acknowledgements

We would like to thank Daan van der Gouwe and Raymond Niesink (Trimbos Institute, Utrecht, NL) and Jeroen Wisselink (IVZ, Houten, NL) for helpful discussions, and Peter Greeven (Novadic-Kentron, Eindhoven, NL) for provision of regional treatment demand data in Eindhoven. We would also like to thank Gerrit

Middelkoop (Oslo University Hospital) for provision of national stimulant-related autopsy data in Norway and Christoph Ort (Eawag, Switzerland) for helpful discussions in relevant sources of uncertainty in wastewater analysis when modelling long-term trends.

References

1. Castiglioni S, Thomas KV, Kasprzyk-Hordern B, Vandam L, Griffiths P. Testing wastewater to detect illicit drugs: state of the art, potential and research needs. Sci Total Environ. 2014;487:613-20.
2. Zuccato E, Chiabrando C, Castiglioni S, Calamari D, Bagnati R, Schiarea S, et al. Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Environ Health. 2005;4:14.
3. Baker DR, Kasprzyk-Hordern B. Multi-residue analysis of drugs of abuse in wastewater and surface water by solid-phase extraction and liquid chromatography-positive electrospray ionisation tandem mass spectrometry. J Chromatogr A. 2011;1218(12):1620-31.
4. Castiglioni S, Bijlsma L, Covaci A, Emke E, Hernandez F, Reid M, et al. Evaluation of Uncertainties Associated with the Determination of Community Drug Use through the Measurement of Sewage Drug Biomarkers. Environ Sci Technol. 2013;47(3):1452-60.
5. Thomas KV, Bijlsma L, Castiglioni S, Covaci A, Emke E, Grabic R, et al. Comparing illicit drug use in 19 European cities through sewage analysis. Sci Total Environ. 2012;432:432-9.
6. Ort C, van Nuijs AL, Berset JD, Bijlsma L, Castiglioni S, Covaci A, et al. Spatial differences and temporal changes in illicit drug use in Europe quantified by wastewater analysis. Addiction. 2014;109(8):1338-52.
7. SCORE (2018). Wastewater monitoring data 2011-2017 Sewage analysis CORe group Europe, COST Action ES1307, http://score-cost.eu/monitoring2017/ . Accessed: 2018-10-02.
8. European Monitoring Centre for Drugs and Drug Addiction. Wastewater analysis and drugs — a European multi-city study (available at) http://www.emcdda.europa.eu/topics/pods/waste-water-analysis.
9. Ort C, Eppler JM, Scheidegger A, Rieckermann J, Kinzig M, Sorgel F. Challenges of surveying wastewater drug loads of small populations and generalizable aspects on optimizing monitoring design. Addiction. 2014;109(3):472-81.
10. Frost N, Griffiths P, Fanelli R. Peering into dirty waters: the potential and implications of a new approach to monitoring drug consumption. Addiction. 2008;103(8):1239-41.
11. Jones HE, Goulding N, Hickman M. Commentary on Lai et al. (2018): Potential and limitations of wastewater-based epidemiology in monitoring substance use. Addiction. 2018;113(6):1137-8.
12. Bade R, Tscharke BJ, Longo M, Cooke R, White JM, Gerber C. Investigating the correlation between wastewater analysis and roadside drug testing in South Australia. Drug Alcohol Depen. 2018;187:123-6.
13. Baz-Lomba JA, Salvatore S, Gracia-Lor E, Bade R, Castiglioni S, Castrignano E, et al. Comparison of pharmaceutical, illicit drug, alcohol, nicotine and caffeine levels in wastewater with sale, seizure and consumption data for 8 European cities. Bmc Public Health. 2016;16(1):1035.
14. Been F, Benaglia L, Lucia S, Gervasoni JP, Esseiva P, Delemont O. Data triangulation in the context of opioids monitoring via wastewater analyses. Drug Alcohol Depend. 2015;151:203-10.
15. Been F, Bijlsma L, Benaglia L, Berset JD, Botero-Coy AM, Castiglioni S, et al. Assessing geographical differences in illicit drug consumption--A comparison of results from epidemiological and wastewater data in Germany and Switzerland. Drug Alcohol Depend. 2016;161:189-99.

16. Bramness JG, Reid MJ, Solvik KF, Vindenes V. Recent trends in the availability and use of amphetamine and methamphetamine in Norway. Forensic Sci Int. 2015;246:92-7.
17. Bruno R, Edirisinghe M, Hall W, Mueller JF, Lai FY, O'Brien JW, et al. Association between purity of drug seizures and illicit drug loads measured in wastewater in a South East Queensland catchment over a six year period. Sci Total Environ. 2018;635:779-83.
18. Kankaanpaa A, Ariniemi K, Heinonen M, Kuoppasalmi K, Gunnar T. Current trends in Finnish drug abuse: Wastewater based epidemiology combined with other national indicators. Sci Total Environ. 2016;568:864-74.
19. Reid MJ, Langford KH, Grung M, Gjerde H, Amundsen EJ, Morland J, et al. Estimation of cocaine consumption in the community: a critical comparison of the results from three complimentary techniques. BMJ Open 2012;2:e001637.
20. van Wel JH, Kinyua J, van Nuijs AL, Salvatore S, Bramness JG, Covaci A, et al. A comparison between wastewater-based drug data and an illicit drug use survey in a selected community. Int J Drug Policy. 2016;34:20-6.
21. van Nuijs AL, Pecceu B, Theunis L, Dubois N, Charlier C, Jorens PG, et al. Can cocaine use be evaluated through analysis of wastewater? A nation-wide approach conducted in Belgium. Addiction. 2009;104(5):734-41.
22. Baz-Lomba JA, Harman C, Reid M, Thomas KV. Passive sampling of wastewater as a tool for the long-term monitoring of community exposure: Illicit and prescription drug trends as a proof of concept. Water Res. 2017;121:221-30.
23. Reid MJ, Langford KH, Morland J, Thomas KV. Quantitative assessment of time dependent drug-use trends by the analysis of drugs and related metabolites in raw sewage. Drug Alcohol Depen. 2011;119(3):179-86.
24. Thomas KV, Amador A, Baz-Lomba JA, Reid M. Use of Mobile Device Data To Better Estimate Dynamic Population Size for Wastewater-Based Epidemiology. Environ Sci Technol. 2017;51(19):11363-70.
25. Rusmiddelstatistikk Funn i blodprøver hos bilførere mistenkt for påvirket kjøring 2016 [Drug statistics findings in blood tests at drivers suspected of affected driving 2016] Oslo universitetssykehus, fag Afr; 2017. https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2016/rusmiddelstatistikk-pdf.pdf.
26. Narkotika- og dopingstatistikk [Drug and doping statistics]. Kripos; 2009-2016.
27. Middelkoop G, Heide G, Edvardsen HME. Obduksjonsstatistikk. Funn i blodprøver fra obduksjoner analysert i 2016 [Autopsy statistics. Findings in blood tests from autopsies analysed in 2016]. Utgitt av Oslo universitetssykehus, fag Afr; November 2017.
28. Skretting A, Vedøy TF, Lund K, Bye EK. Rusmidler i Norge 2016 [Drugs in Norway 2016]. Norwegian patient register.
29. Queensland Methamphetamine Paper, Queensland Health Jan 2017, https://www.health.qld.gov.au/__data/assets/pdf_file/0021/641316/methpaper.pdf
30. Action on Ice. The Queensland Government’s plan to address use and harms caused by crystal methamphetamine. In: Government Q, editor. Feb 2018.
31. The Social Costs of Methamphetamine in Australia 2013/14 National Drug Research Institute, Curtin University; July 2016.
32. Darke S, Kaye S, Duflou J. Rates, characteristics and circumstances of methamphetamine-related death in Australia: a national 7-year study. Addiction. 2017;112(12):2191-201.
33. Illicit Drug Data Report 2017–18. Australian Criminal Intelligence Commission. https://www.acic.gov.au/sites/default/files/illicit_drug_data_report_2017-18.pdf?v=1564727746.
34. Lai FY, O'Brien JW, Thai PK, Hall W, Chan G, Bruno R, et al. Cocaine, MDMA and methamphetamine residues in wastewater: Consumption trends (2009-2015) in South East Queensland, Australia. Sci Total Environ. 2016;568:803-9.

35. Lai FY, Anuj S, Bruno R, Carter S, Gartner C, Hall W, et al. Systematic and Day-to-Day Effects of Chemical-Derived Population Estimates on Wastewater-Based Drug Epidemiology. Environ Sci Technol. 2015;49(2):999-1008.
36. Lai FY, Bruno R, Hall W, Gartner C, Ort C, Kirkbride P, et al. Profiles of illicit drug use during annual key holiday and control periods in Australia: wastewater analysis in an urban, a semi-rural and a vacation area. Addiction. 2013;108(3):556-65.
37. Lai FY, Ort C, Gartner C, Carter S, Prichard J, Kirkbride P, et al. Refining the estimation of illicit drug consumptions from wastewater analysis: Co-analysis of prescription pharmaceuticals and uncertainty assessment. Water Res. 2011;45(15):4437-48.
38. Emke E, Evans S, Kasprzyk-Hordern B, de Voogt P. Enantiomer profiling of high loads of amphetamine and MDMA in communal sewage: a Dutch perspective. Sci Total Environ. 2014;487:666-72.
39. Emke E, Vughs D, Kolkman A, de Voogt P. Wastewater-based epidemiology generated forensic information: Amphetamine synthesis waste and its impact on a small sewage treatment plant. Forensic Sci Int. 2018;286:e1-e7.
40. Van Laar MW VGB, Cruts AAN et al. Nationale Drug Monitor: jaarbericht 2017. Trimbos-instituut/WODC: Utrecht/Den Haag; 2017.
41. Jones HE, Hickman M, Kasprzyk-Hordern B, Welton NJ, Baker DR, Ades AE. Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part B: Placing back-calculations in a formal statistical framework. Sci Total Environ. 2014;487:642-50.
42. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. Stat Comput. 2000;10(4):325-37.
43. Spiegelhalter DJ, Best NG, Carlin BR, van der Linde A. Bayesian measures of model complexity and fit. J Roy Stat Soc B. 2002;64:583-616.
44. Baz Lomba JA, Di Ruscio F, Amador A, Reid M, Thomas KV. Assessing alternative population size proxies in a wastewater catchment area using mobile device data. Environ Sci Technol. 2019.
45. Been F, Rossi L, Ort C, Rudaz S, Delemont O, Esseiva P. Population Normalization with Ammonium in Wastewater-Based Epidemiology: Application to Illicit Drug Monitoring. Environ Sci Technol. 2014;48(14):8162-9.
46. O'Brien JW, Thai PK, Eaglesham G, Ort C, Scheidegger A, Carter S, et al. A Model to Estimate the Population Contributing to the Wastewater Using Samples Collected on Census Day. Environ Sci Technol. 2014;48(1):517-25.
47. Humphries MA, Bruno R, Lai FY, Thai PK, Holland BR, O'Brien JW, et al. Evaluation of Monitoring Schemes for Wastewater-Based Epidemiology to Identify Drug Use Trends Using Cocaine, Methamphetamine, MDMA and Methadone. Environ Sci Technol. 2016;50(9):4760-8.

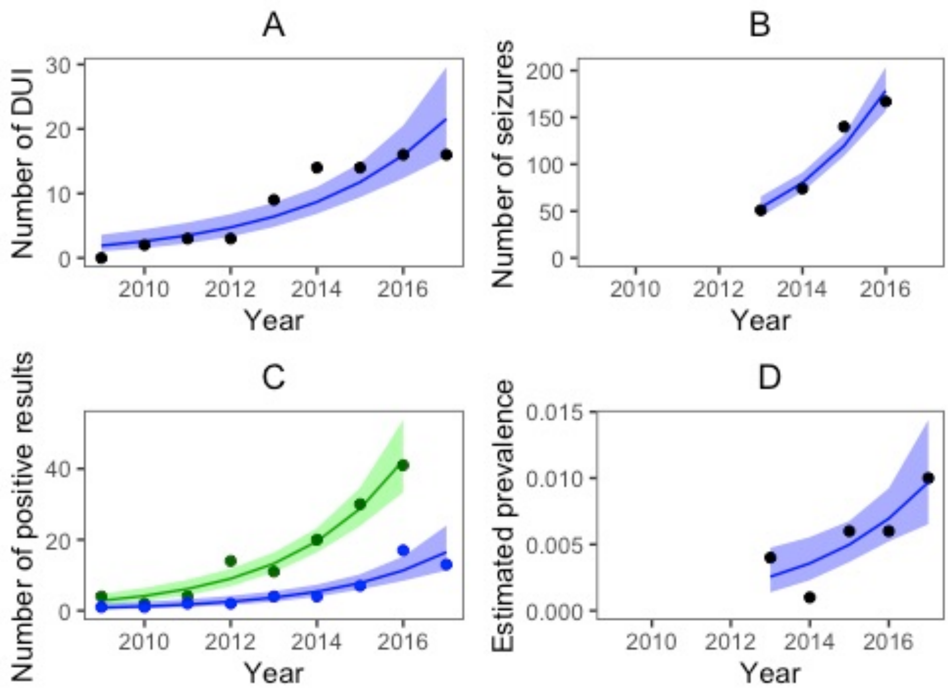

Figure 1. A-B: regional (Oslo) data, C-D: national (Norway) data. Number of recorded driving under the influence offences (A), seizures* (B), positive results from autopsy (C-blue) and prison (C-green) data for MDMA from 2009 to 2017: observed data and Poisson log-linear trends with 95% confidence intervals (CIs). D: Estimated prevalence of MDMA use in Norway amongst 15 to 64 year olds* based on GPS data and logistic regression with 95% CIs (blue). [* Data were available for 2013 to 2016/17 only].

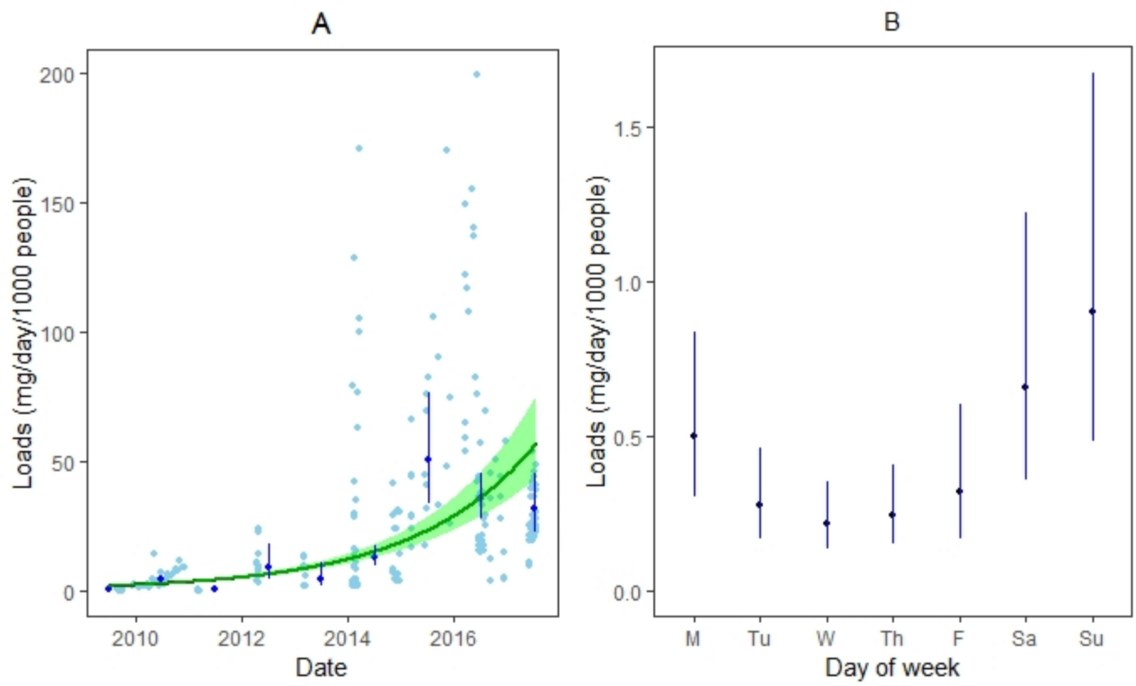

Figure 2. A: Estimated daily population-normalised loads of MDMA in wastewater in Oslo 2009 to 2017 (light blue), with estimated averages for each year from the annual effects model (dark blue) and a trendline for the log-linear model (green), with 95% Cr-Is. B: Estimated daily population-normalised loads of MDMA in wastewater by day of the week with 95% Cr-Is, calibrated to 2009.

Indicator	MDMA
Wastewater (R)	55.1% (47.8, 62.8%)
Number of recorded DUI (R)	35.4% (22.2,50.0%)
Number of police seizures (R)	49.2% (36.4, 63.3%)
Number of positive autopsy results (N)	45.4% (26.9, 66.6%)
Number of positive results in prison (N)	47.2% (34.0, 61.8%)
Prevalence (N)	39.5% (13.1, 72.0%)

Table 1. Estimated average annual percentage change (with 95% confidence intervals) in regional (R) and national (N) indicators of MDMA use in Oslo/Norway.

	Oslo (MDMA)			SE Queensland (methamphetamine)			Eindhoven (benzoylecgonine)		
	$\bar{D}$	pD	DIC	$\bar{D}$	pD	DIC	$\bar{D}$	pD	DIC
Model (i):	**394.9**	**148.0**	**542.9**	-184.4	137.7	-46.7	**-68.1**	**78.7**	**10.6**

annual effects									
Model (ii): annual and quarterly effects	394.6	155.4	550.0	**-178.2**	**99.8**	**-78.4**	-68.2	80.9	12.7
Model (iii): linear trend	394.3	154.6	548.9	-187.0	228.7	41.7	-69.1	111.7	42.6

Table 2. Deviance Information Criterion (DIC) comparison between wastewater regression models fitted to each location (and drug target residue). pD is a measure of complexity of the model, $\overline{D}$ is the posterior mean of the deviance and DIC = pD + $\overline{D}$. The best fitting model after penalising for complexity (model with the lowest DIC) for each location is indicated by bold font.

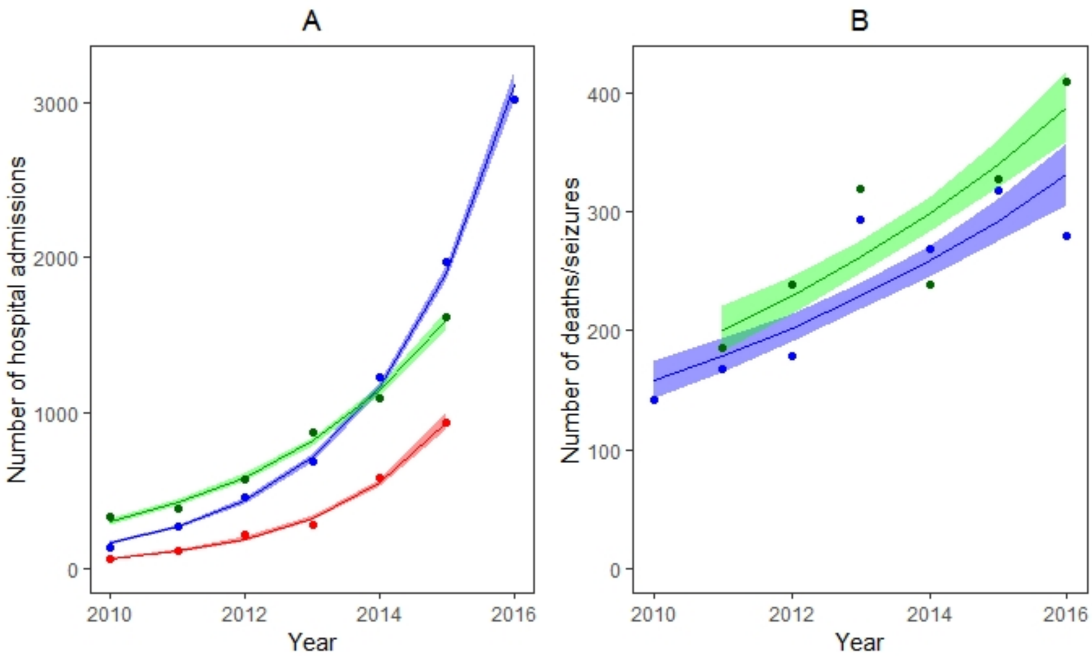

Figure 3. A: Numbers of methamphetamine-related hospital admissions (blue), emergency department presentations (green) and psychiatric admissions (red) in Queensland from 2010 to 2016, with fitted Poisson log-linear trends and 95% CIs. We note that there is some overlap between hospital admissions and emergency department presentations (29). B: Number of seizures (green) in SE Queensland 2010 to 2015 and number of methamphetamine-related deaths (blue) in Australia 2009 to 2015, with fitted Poisson log-linear trends and 95% CIs.

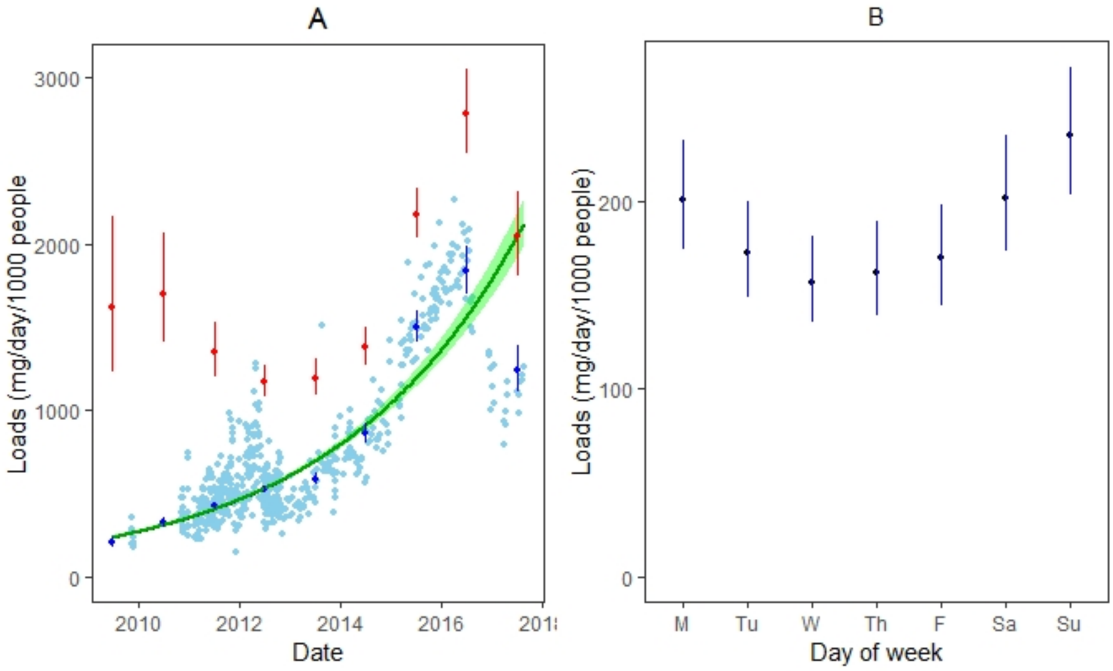

Figure 4. A: Estimated daily population-normalised loads of methamphetamine in wastewater in the SE Queensland region 2009-2017 (light blue), with estimated averages for each year from the annual and quarterly effects model (dark blue) and a trendline for the log-linear model (green), with 95% Cr-Is. Purity-adjusted estimated yearly averages are displayed in red with 95% Cr-Is. B: Estimated daily population-normalised loads of methamphetamine in wastewater by day of the week, with 95% Cr-Is, calibrated to the 1st quarter of 2009.

Indicator	Methamphetamine
Wastewater (R)	31.1% (29.4, 32.9%)
Number of police seizures (R)	14.1% (10.9, 17.3%)
Number of hospital admissions (S)	63.3% (61.0, 65.7%)
Number of emergency department presentations (S)	39.6% (37.1, 42.1%)
Number of psychiatric admissions (S)	71.3% (66.0, 76.7%)
Numbers of methamphetamine-related deaths (N)	13.1% (10.4, 15.9%)

Table 3. Estimated average annual percentage change (with 95% confidence intervals) in regional (R), state (S) and national (N) indicators of methamphetamine use in SE Queensland/Queensland/Australia.

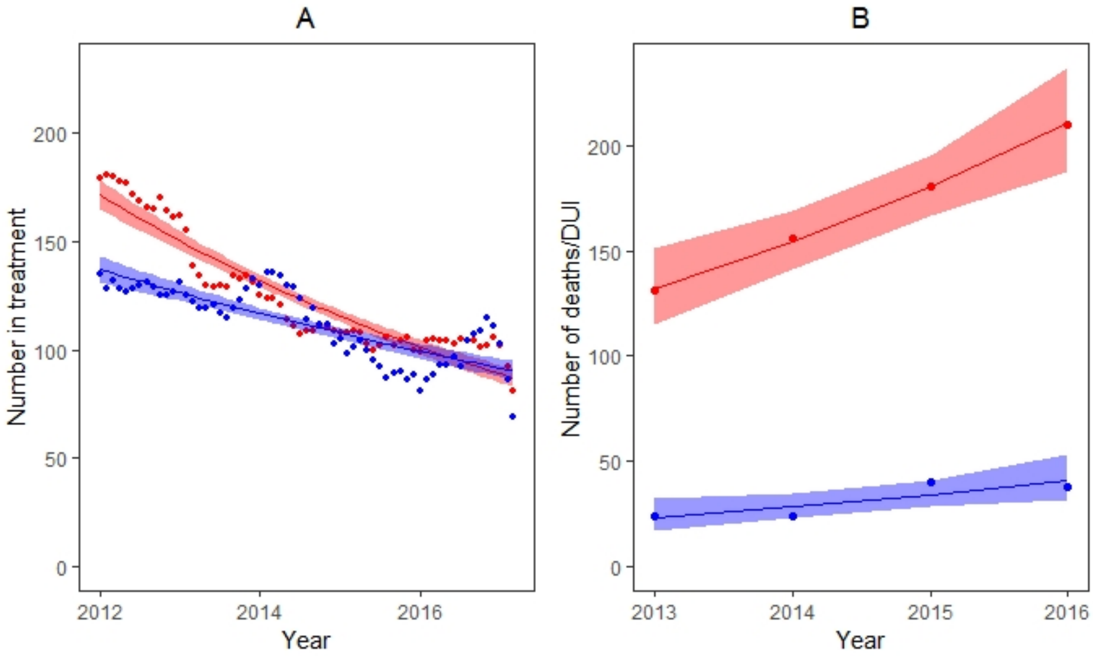

Figure 5. A: Total number of people attending treatment in each month with cocaine as their primary problem (blue) or secondary problem (red) in the Eindhoven region 2012-2017: observed data and fitted Poisson log-linear trend, with 95% CIs. B: Annual numbers of DUI (red) and deaths (blue) due to cocaine in The Netherlands 2013-2016.

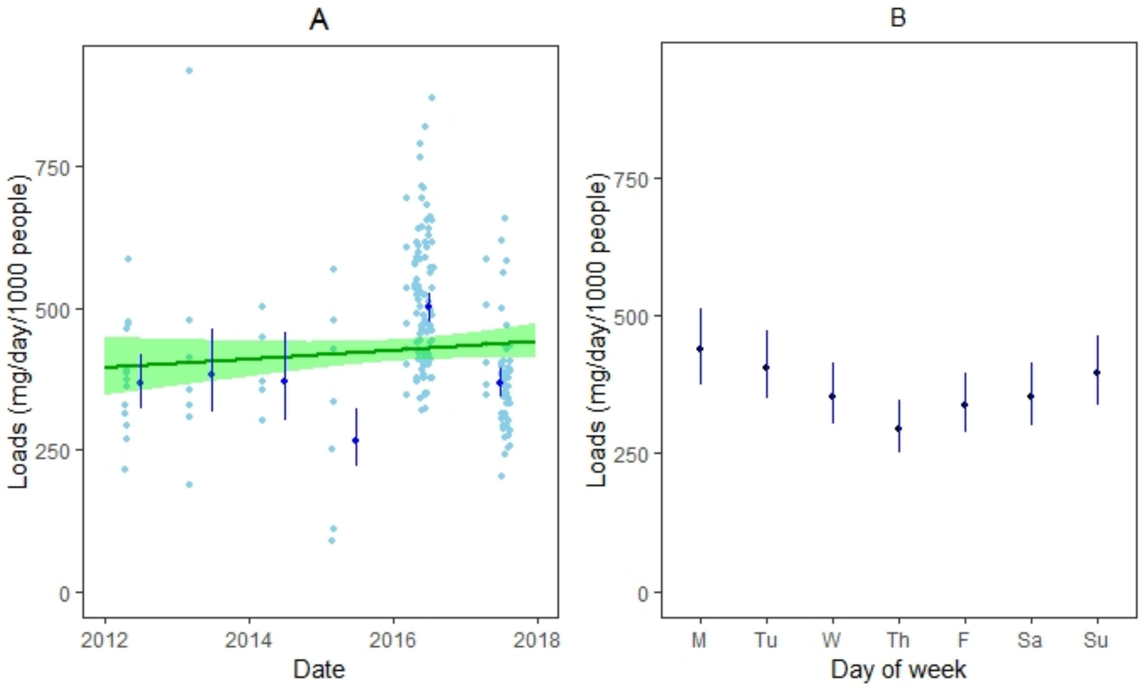

Figure 6. A: Estimated daily population-normalised loads of benzoylecgonine in wastewater in Eindhoven 2012-2017 (light blue), with estimated averages from the annual effects model (dark blue) and a trendline for the log-linear model (green), with 95% Cr-Is. B: Estimated daily population-normalised loads of benzoylecgonine in wastewater by day of the week, with 95% Cr-Is, calibrated to 2012.

Indicator	Cocaine
Wastewater (R)	1.9% (-1.0, 4.9%)
Treatment demand – primary (R)	-7.8% (-8.6, -6.9%)
Treatment demand – secondary (R)	-12.3% (-13.1, -11.6%)
Numbers of recorded DUI (N)	16.8% (9.2, 25.1%)
Number of recorded cocaine-related deaths (N)	20.4% (2.8, 41.1%)

Table 4. Estimated average annual percentage change (with 95% confidence intervals) in regional (R) and national (N) indicators of cocaine use in Eindhoven/Netherlands.

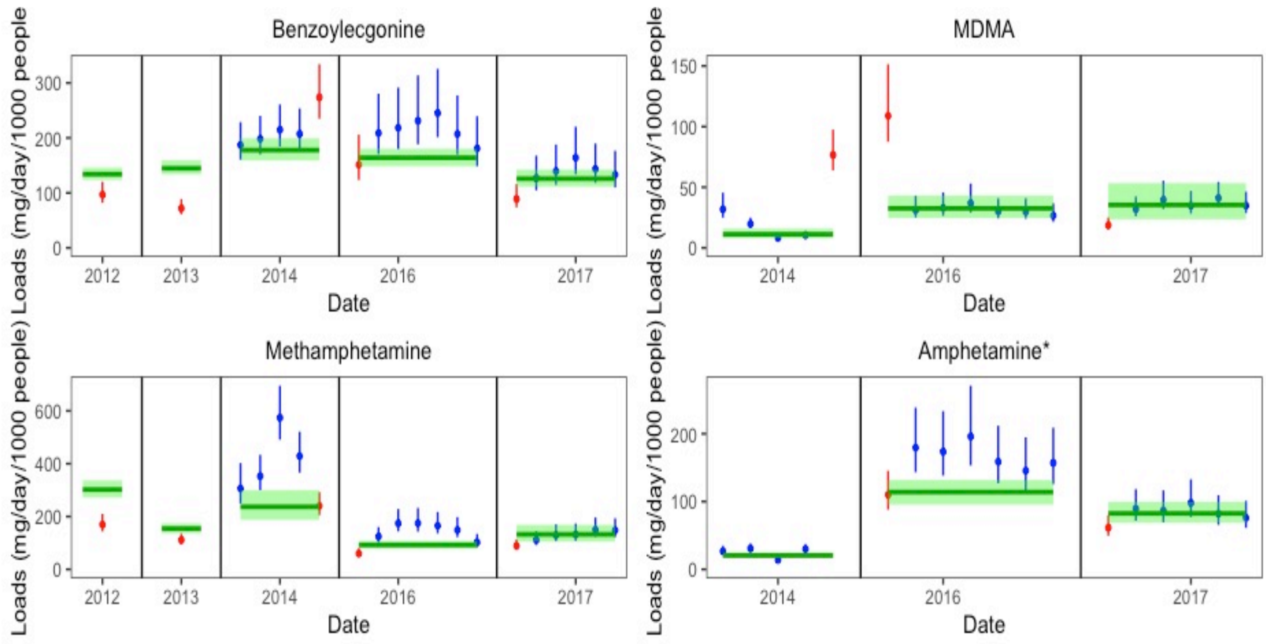

Figure 7. Estimates of average daily wastewater loads per year in Oslo from EMCDDA data (red) versus non-EMCDDA (green) and all other weekly averages from the same year (blue) with 95% Cr-Is, for benzoylecgonine, MDMA, methamphetamine and amphetamine. *There were no EMCDDA data (red) for amphetamine in 2014, but there were other seven-day consecutive periods of sampling in 2014 (blue).