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Wastewater-based estimates of cannabis and drug use in Canada: Analytical methods and supplementary information

by **Andrew Brennan, Jack Gambino, Geneviève Vézina, Laurie Reedman** and **Caroline Pelletier**

This document describes the statistical methods supporting the detailed results provided in Wastewater-based Estimates of Cannabis and Drug Use in Canada: Pilot test Detailed Results. The analyses are based on the metabolite load per capita (MLC), which is the mass of drug passing through the sampled wastewater treatment plants during the sample week, scaled by an estimate of the population contributing to the sampled wastewater. MLC was estimated for each drug metabolite every month in every city.

MLC is a positive quantity that, in most cases, had a right-skewed distribution across months, as expected for positive quantities with moderate or high variability. Therefore, the statistical methods chosen for this analysis account for such data, whether through log-transformations to make the monthly MLC closer to a normal distribution or through non-parametric tests that do not rely on a particular underlying distribution.

The p-values for these methods indicate the strength of the evidence against the null hypothesis that all the months or all the cities have the same average MLC. Lower p-values indicate that the evidence is stronger. When a binary decision was required, p-values below 0.05 were considered evidence of statistically significant differences.

Comparing metabolite load per capita across cities and months

The MLC was analyzed for evidence of a monthly pattern that was consistent across the cities and for differences between cities that repeated regularly over the 12 months. This was achieved using a 2-factor Analysis of Variance (ANOVA), with factors for city and month. The ANOVA was based on log-transformed MLC to make the data more symmetric and closer to a normal distribution.

Table 1
ANOVA p-values for month and city factors (Type 3 sum of squares)

Drug metabolite	Month p-value	City p-value
THC-COOH	<0.0001	<0.0001
Benzoylecgonine	0.004	0.33
Methamphetamine	0.15	<0.0001
Morphine	0.66	<0.0001
Codeine	0.000	<0.0001

A significant month factor indicates the months differed more than expected by random fluctuations alone, which is evidence of a temporal pattern that was not constant across the months. However, this temporal pattern cannot yet be considered seasonality since seasonality implies the temporal pattern repeats at the same time each year and cannot be determined based on a single year of data.

A significant city factor is evidence that the cities do not all have the same average MLC for that drug metabolite. If the city p-value was under 0.05, the ANOVA was followed up with tests between each pair of cities to determine which cities were different from one another. The pairwise testing was done using the Wilcoxon signed-rank test because it is non-parametric and robust to outliers and therefore suitable for the right-skewed MLC data. This test is based on how many of the months the MLC in one city is higher than the MLC in the other, with an adjustment to weight each month by the rank of the magnitude of the difference. Therefore, a difference between cities will only be identified if it repeats regularly across the 12 months.

Table 2
THC-COOH Wilcoxon signed-rank p-values

	Halifax	Montreal	Toronto	Edmonton	Vancouver
Halifax		0.27	0.04	0.01	0.02
Montreal	0.27		0.003	0.001	0.003
Toronto	0.04	0.003		0.28	0.90
Edmonton	0.01	0.001	0.28		0.76
Vancouver	0.02	0.003	0.90	0.76	

Table 3
Methamphetamine Wilcoxon signed-rank p-values

	Halifax	Montreal	Toronto	Edmonton	Vancouver
Halifax		0.001	0.006	0.002	0.001
Montreal	0.001		0.43	0.03	0.005
Toronto	0.006	0.43		0.004	0.004
Edmonton	0.002	0.03	0.004		1.00
Vancouver	0.001	0.005	0.004	1.00	

Table 4
Morphine Wilcoxon signed-rank p-values

	Halifax	Montreal	Toronto	Edmonton	Vancouver
Halifax		0.001	0.01	0.70	0.08
Montreal	0.001		0.52	0.001	0.001
Toronto	0.01	0.52		0.001	0.004
Edmonton	0.70	0.001	0.001		0.28
Vancouver	0.08	0.001	0.004	0.28	

Table 5
Codeine Wilcoxon signed-rank p-values

	Halifax	Montreal	Toronto	Edmonton	Vancouver
Halifax		0.001	0.02	0.02	0.27
Montreal	0.001		0.001	0.001	0.001
Toronto	0.02	0.001		0.002	0.21
Edmonton	0.02	0.001	0.002		0.001
Vancouver	0.27	0.001	0.21	0.001	

These tests are based on differences in MLC between months and cities, not drug consumption. Extending these results to infer differences in drug consumption requires one additional step because MLC is affected not only by drug consumption but also by the potency of the target drug, the excretion rate, and metabolite degradation in the sewers. These parameters could theoretically differ between cities. For example, if cannabis edibles were more common in one city than another then the city excretion rates would differ since edibles have a different excretion rate than smoked cannabis; or if the sewer systems had different residence times and microbial environments then they could have different degradation. However, the impact of these differences on the results is expected to be very small compared to the large differences in MLC observed between cities. Therefore, most of the differences in MLC are expected to arise from differences in drug consumption. More information on the importance and uncertainty of these parameters in the context of cannabis consumption estimation can be found in Statistics Canada Publication 13-605-X201900100006, 2019.

For the city bar graphs in the main text (Charts 2, 4, 6, 7, and 8), the bar height is the across-month average MLC and the error bars represent the standard error of the mean, which is the expected variation of the mean estimate based on the variability in the data.

Estimating drug consumption

For a given amount of drug consumed, there are several parameters that dictate how much metabolite will be measured in the wastewater: the excretion rate of the metabolite, the degradation of the metabolite, and the potency of the drug in the case of cannabis. These parameters have been estimated in the literature with varying degrees of uncertainty. Therefore, wastewater-based estimates of drug consumption will incur the uncertainty of the MLC estimates as well as the uncertainty of the parameter values (Statistics Canada Publication 13-605-X201900100006, 2019).

The estimate of mean MLC, combining all sites and averaging across months, carries some uncertainty due to the monthly variation and the fact that only 12 of the 52 weeks were sampled during the year. This uncertainty was characterized using parametric bootstrap T intervals (Hesterberg, 2015), which were chosen because of their ability to estimate uncertainty in the setting of skewed data and few measurements (12 months). This procedure fit the 12 monthly MLC estimates, combined across all sites, with a log-normal distribution. The parametric log-normal distribution takes the place of the empirical bootstrap distribution and serves to stabilize the bootstrap T confidence intervals in the context of few measurements that are non-negative and right-skewed. This procedure allows asymmetric confidence intervals that are appropriate for the right-skewed MLC measurements.

The uncertainty for each parameter was characterized by a probability distribution based on the available literature. The exact distributions that were used and the literature from which they were derived are detailed in the next section.

A collection of drug consumption estimates was then calculated for 10,000 different scenarios, where each scenario involved a set of parameters and a mean MLC value, each drawn independently from its own probability distribution. The resulting collection of drug consumption estimates captures the range of results that can be expected given the likely values of the unknown parameters and estimated MLC. The 2.5 and 97.5 percentiles of the 10,000 drug consumption estimates form the limits of the reported 95% confidence intervals. This approach is based on the Monte Carlo method outlined in Jones et al. (2014).

Characterizations of parameter uncertainties

For each drug, each parameter was characterized by a probability distribution based on the available literature. Both the probability distribution and literature from which it was based are described below.

The parameters required for the estimation of drug consumption are the in-sample metabolite stability, the in-sewer metabolite stability, and the excretion rate of the metabolite. In the case of cannabis, these parameters result in an estimate of THC consumption. To extend this estimate to the mass of dried cannabis plant, the THC potency of the plant must be included as an additional parameter.

The in-sample metabolite stability accounts for loss of the drug metabolite after the wastewater samples were collected but before they were analyzed. This was a period of typically 1-2 months where the samples were frozen at -20°C or colder. The value refers to the proportion of metabolite remaining at the time of analysis.

The in-sewer metabolite stability accounts for loss of the drug metabolite from the time it was excreted to the time the sample was frozen. This includes a few hours in the sewer system, where the temperatures are around 10°C to 20°C. It also includes the time when the samples are accumulating: for example, the wastewater collected at 1:00am must wait 23 hours, held at around 4°C, before the daily composite sample is finished and ready to be frozen. As with in-sample degradation, the value refers to the proportion of metabolite remaining at the time the sample was frozen.

The excretion rate of the metabolite is the number of molecules of metabolite excreted into the wastewater versus the number of molecules of the parent drug consumed. For cannabis, the excretion rate is expressed as THC-COOH excreted versus THC consumed. The excretion rate is parameterized as a molar ratio and later corrected by the molar mass ratio to account for the different masses of the metabolite and parent drug molecule.

The literature typically specifies a mean and variance for the parameters but not a distribution. Therefore, distributions were chosen to incorporate known constraints: beta distributions for data bounded by 0 and 1, log-normal distributions for non-negative data, and normal distributions when no other information is known or the variance is very small compared to the mean. The distribution parameters were chosen so that the resulting probability distribution had the desired mean and variance.

Sometimes, the same parameter was estimated by several studies with different experimental conditions and the conditions of the pilot study were not known. To combine these studies into a single estimate, the unweighted mean and standard deviation across the study estimates were used to characterize the parameter. This approach recognizes that the parameter value could depend on the experimental conditions of the study, such as the water temperature and pH for degradation, or drug consumption method and dose size for excretion rates. Since the conditions of the pilot study are unknown, they are not assumed to be the average of the existing studies, as would happen with a fixed-effects meta-analysis, but instead to fall within the wider range spanned by the existing studies. Under this framework, having many more studies would not necessarily reduce the parameter uncertainty since the standard deviation across studies with different conditions would not be expected to change. Instead, the uncertainty comes from unknown conditions in the pilot study. This method is analogous to a random-effects meta-analysis but it is more conservative since it supposes studies provide perfect information where in reality there is also variation due to small sample sizes, which serves to widen the distribution across studies.

Cannabis parameters

THC-COOH in-sample metabolite stability was estimated from Heuett, Ramirez, Fernandez, and Gardinali (2015), in which the long-term stability of drug metabolites was tested in frozen samples. THC-COOH had approximately 91%±8% stability after 27 days, which is the most relevant condition. Since THC-COOH is only created in a body, a stability over 100% is not possible so this distribution was characterized as a beta distribution, bounded by 0% and 100%.

The in-sewer metabolite stability was estimated from McCall et al. (2016), who collected stability information for drug metabolites in various sewer conditions. They determined that THC-COOH has under 20% degradation in unfiltered wastewater at 20°C, which are similar conditions to the pilot study. Therefore, the in-sewer stability was estimated to be 90%±5%. As with the in-sample degradation, a beta distribution was used to enforce stability under 100%.

The excretion rate for THC-COOH is challenging to estimate for two reasons. The first reason involves fecal excretion of THC-COOH, which is a major route of excretion for cannabis metabolites. The amount of THC-COOH excreted in feces has never been measured after smoking cannabis, the most common method of consumption in Canada (Statistics Canada, National Cannabis Survey, 2019). Furthermore, there is uncertainty whether fecally-excreted THC-COOH ends up dissolved in the wastewater and measured in the samples, although most researchers believe this should be the case (Khan & Nicell, 2012; Been, Schneider, Zobel, Delémont, and Esseiva, 2016). These limitations in the published research make it very difficult to know the total amount of THC-COOH that ends up dissolved in the wastewater after smoking cannabis. The second challenge with the cannabis excretion rate is that it depends on the consumption method (e.g. smoking, vaping, edibles), but it is difficult to know the fraction of cannabis consumed by each method and the excretion rate for each. Because of these challenges, a THC-COOH excretion rate based on pharmacokinetic data would be highly uncertain, ranging from 0.5% in the case that measured THC-COOH comes only from urine (Gracia-Lor, Zuccato, and Castiglioni, 2016) to 5.5% based on models that add fecal excretion (Khan & Nicell, 2012) and possibly higher when accounting for other consumption methods.

Instead, the THC-COOH excretion rate was estimated based on THC-COOH wastewater measurements. Burgard et al. (2019) tested wastewater in a city in the state of Washington, USA, and compared it to local cannabis sales. They found THC-COOH in the wastewater represented 4.6% of the THC sold within a 3-month period. They argued that this is an upper bound for an excretion rate since it does not account for illegally-acquired cannabis. However, they also argued that the urine-only excretion rate of 0.5% (Gracia-Lor et al., 2016) is implausibly low because that would require legal sales, including the medical sales, to account for only 10% of consumption, 2 years after recreational cannabis stores opened. They recommended an excretion rate closer to the 2.5% used by Postigo, de Alda, and Barceló (2011). This method accounts for the fecally-excreted THC-COOH that ends up dissolved in the wastewater and the mixture of consumption methods in the sampled city.

Based on the results of Burgard et al. (2019), the excretion rate was chosen to havea log-normal distribution, to ensure positive excretion rates, with 90% confidence limits of 1% to 4.6%. The 10% of the distribution extending beyond these limits allows the average excretion rate to differ in Canada, where the mixture of consumption methods might be different than the state of Washington. While this method is more informative than pharmacokinetic data at this time, the excretion rate remains highly uncertain and limits the overall precision of cannabis consumption estimates.

The molar mass ratio for THC to THC-COOH is 0.91.

Table 6
Summary of cannabis parameters

Parameter	Distribution	Distribution parameters	Implied mean (μ) and std (σ)
In-sample metabolite stability	Beta(a,b)	a=10.74	μ=0.91
		b=1.06	σ=0.08
In-sewer metabolite stability	Beta(a,b)	a=31.5	μ=0.9
		b=3.5	σ=0.05
Excretion rate (ER) of the metabolite	Lognormal	log(ER)~Normal(-3.84,0.465^2)	μ=0.024
			σ=0.0118
THC potency of the plant	Normal	μ=0.13	μ=0.13
		σ=0.015	σ=0.015

The best evidence for the potency of cannabis comes from ElSohly et al. (2016), who found that seized cannabis in the United States had a THC potency of 12% in 2014, steadily increasing from 4% in 1995. Their estimate of 2014 potency was modified upward to account for the general rising trend to an estimate of 13%±1.5%.

Cocaine parameters

Heuett et al. (2015) estimated the stability of benzoylecgonine in a frozen sample to be 125%±15% after 27 days. This value reflects the fact that cocaine can transform into benzoylecgonine within the sewer system, not just within the body, and so the measured concentration of benzoylecgonine can be higher than the amount that was excreted.

The in-sewer stability for benzoylecgonine was similarly high, estimated to be 111%±5% based on the 7 studies of benzoylecgonine in-sewer stability reported in van Nuijs et al. (2012). The studies were combined into a single estimate using their unweighted mean and the standard deviation across studies since they differed in their testing conditions and the conditions of the pilot treatment plants were unknown.

The benzoylecgonine excretion rate was taken from Jones et al. (2014), who did a meta-analysis of the studies collected by Khan and Nicell (2011). They used a compound excretion rate with one value for smoking, another value for nasal insufflation, and a mixing proportion indicating the fraction of cocaine consumed by each method. The molar mass ratio for cocaine to benzoylecgonine is 1.05.

Table 7
Summary of cocaine parameters

Parameter	Distribution	Distribution parameters	Implied mean (μ) and std (σ)
In-sample metabolite stability	Normal	μ=1.25	μ=1.25
		σ=0.15	σ=0.15
In-sewer metabolite stability	Normal	μ=1.11	μ=1.11
		σ=0.05	σ=0.05
Excretion rate of the metabolite	Mixture of Beta(a,b)	Proportion of cocaine smoked: Beta(a,b) with a=61.6 b=887	Proportion of cocaine smoked: μ=0.065 σ=0.008
		Smoking excretion rate: Beta(a,b) with a=85.2 b=894	Smoking excretion rate: μ=0.087 σ=0.009
		Nasal insufflation excretion rate: Beta(a,b) with a=170.4 b=369	Nasal insufflation excretion rate: μ=0.316 σ=0.020

Methamphetamine parameters

Heuett et al. (2015) estimated the in-sample stabilityof frozen methamphetamine to be 94%±9% after 27 days.

Methamphetamine is considered very stable in the sewers. Estimating it in the same way as benzoylecgonine, the 4 studies reported in van Nuijs et al. (2012) were combined into a single estimate of 102%±4%.

The methamphetamine excretion rate seems to depend little on the consumption method but more strongly on the dose, and the typical dose is not known in a Canadian context. Therefore, the 14 individual studies collected by Gracia-Lor et al. (2016) were combined into a single estimate by taking the unweighted mean and standard deviation across the studies, allowing the pilot conditions to fall anywhere within the range of doses and consumption methods in the collected studies. This resulted in an estimate of 40.7%±7%. Note that only the studies of S(+) methamphetamine were included, as recommended by Gracia-Lor et al. (2016).

Table 8
Summary of methamphetamine parameters

Parameter	Distribution	Distribution parameters	Implied mean (μ) and std (σ)
In-sample metabolite stability	Normal	μ=0.94	μ=0.94
		σ=0.09	σ=0.09
In-sewer metabolite stability	Normal	μ=1.02	μ=1.02
		σ=0.04	σ=0.04
Excretion rate of the metabolite	Normal	μ=0.407	μ=0.407
		σ=0.07	σ=0.07

Data Treatment

In addition to the methamphetamine spike in June mentioned in the main text, the MLC data contained two stark outliers, both in the first month when the analysis method was still under development. In Edmonton, the MLC for benzoylecgonine was 9 times higher than the average of the other months and 4.5 times higher than the next-highest month. In Vancouver, morphine was 10 times higher than the average of the other months and 6 times higher than the next-highest month. These two measurements were removed from the analysis and imputed.

In addition, sample shipping issues in November rendered the Toronto and Edmonton samples unusable, so those values were imputed for all the drug metabolites. The imputations were based on an ANOVA of log-transformed MLC data with factors for the month and city. The ANOVA only considered the time spanning two months before the missing data (where available) until two months after the missing data to allow for possible short-term trends within cities. The imputed values were not used for statistical testing purposes.

The methamphetamine measurements in June were very high for four of the five cities, as mentioned in the main text. Therefore, instead of imputing them, the entire month was removed from the analysis. When June is included in the analysis, the p-values of the city comparisons do not change substantially except that Vancouver becomes less statistically distinguishable from Toronto and Montreal ($p=0.07$ and $p=0.06$ respectively). The overall consumption estimate changes to 1.1 tonnes in the pilot area, with a 95% confidence interval spanning from 0.31 to 3.8 tonnes.

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