# Interpreting Methamphetamine Levels in a High-Use Community

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**Abbreviations:** Methamphetamine (MA), wastewater treatment plant (WWTP),

**ABSTRACT**

Illicit drug use is a largely hidden phenomenon and population measures are notoriously problematic. Reliable and valid data for local, regional and national public health and other interventions are needed. To address this information we examined temporal trends within and across weeks in methamphetamine (MA) in a single location in order to inform a sampling plan for understanding long-term trends in MA use based on sampling raw influent to waste water treatment plants. The measured concentrations in wastewater are used to estimate the total mass of MA consumed MA rather than the number of doses due to the uncertainty surrounding methamphetamine purity, mass of MA per dose, and the number of doses used per day. Results from a region with high levels of MA use indicate that MA levels do not differ significantly between weekdays and weekends ($p=0.1$), consistent with a predominately regular, daily use pattern use. The potential contribution of legal sales of d- and l-MA to the mass of MA consumed within the community was estimated to range from 3-8%. Limitations and uncertainties associated with estimating the mass of MA consumption include small contributions of prescription and over-the-counter drugs that are metabolized to MA as well as measurement and sampling variability.

## INTRODUCTION

The use of illicit drugs is a largely hidden phenomenon and determining valid, accurate population estimates of usage are extremely challenging (National Institute of Drug Abuse 2006). Reliable and valid data for local, regional and national planning are needed. Methamphetamine is an example of a drug which is increasingly abused worldwide (United Nations Office on Drugs and Crime 2009), but for which specific, local geographic and temporal patterns of use are poorly documented.

Use of illicitly manufactured methamphetamine has had a substantial impact on public health throughout much of East and South-East Asia (United Nations Office on Drugs and Crime 2009), Australia (Cate et al. 2009), and some regions of North America (Maxwell and Rutkowski 2008). While methamphetamine abuse dominates much of Asia, amphetamine abuse is more common in Europe and the Near and Middle East and is also available by prescription in the US. Methamphetamine is present in Europe, though generally at lower levels than amphetamine and cocaine (European Monitoring Centre for Drugs and Drug Addiction 2009). Trends in methamphetamine use, manufacturing, and distribution are very fluid, with frequent changes and much geographic variability in use, manufacturing and sources (Cunningham et al. 2010; United Nations Office on Drugs and Crime 2009). The geographic variability for methamphetamine is more pronounced than for most other drugs of abuse in the United States, Mexico and Canada (Caulkins 2003; Maxwell and Rutkowski 2008).

Patterns of MA consumption appear to vary dramatically across and within US communities. In the Western United States and parts of the Midwest there appear to be substantial populations of regular MA users as well as those who use only intermittently

while in areas of the Eastern and Midwestern United States, for instance New York City and Chicago, the total proportion of the population that uses MA appears to be much lower and most use appears to be intermittent (National Institute on Drug Abuse 2010). The State of Oregon, in the Western region of the United States, is an area with relatively high rates of MA use in which many users are believed to be regular users MA (National Drug Intelligence Center 2009; Sudakin and Power 2009).

Unlike many other illicit drugs such as cocaine and heroin, MA use is often as common, if not more common, in less metropolitan areas (Office of Applied Studies 2007). These less populated locales are areas for which accurate drug usage data can be difficult to obtain. Testing of raw influent wastewater from wastewater treatment plants (WWTPs) can provide a relatively low cost, widely applicable methodology for drug surveillance (Frost et al. 2008). Data based upon samples collected from municipal WWTPs in the State of Oregon in 2008 indicated the presence of MA in every one of 96 municipalities tested, of which 35% were small rural towns, 27% large rural city/towns, and 38% urban (Banta-Green et al. 2009). This contrasted with cocaine, which was identified in 90% of municipalities, and 3,4-methylene-dioxy methamphetamine (MDMA or ecstasy) in 63%. Methamphetamine is detected in raw wastewater from other countries as well; however, those in Europe have generally reported much lower concentrations and loads (mass/person/day) than found in the United States as well as detection in a smaller proportion of municipalities (Boles and Wells 2010; Postigo et al. 2008a; van Nuijs et al. 2009a).

Patterns of MA use are poorly described. Estimates indicate that the average days of use in a month may be higher for MA than for cocaine (Cate et al. 2009; Simon et al.

2002). Wastewater sampling for systematic drug abuse epidemiology and surveillance purposes is unlikely to be obtained on a daily basis due to cost and logistical reasons. Therefore, there is a need to discern the temporal pattern of MA loads so that a valid, efficient, and cost-effective plan for sampling WWTPs can be developed for use in monitoring the long-term temporal trends in MA consumption at the community scale. Few estimates of the amount of MA consumed based on measured levels in influent raw wastewater samples are reported (Chiaia et al. 2008; Huerta-Fontela et al. 2008b; Zuccato et al. 2008) Accurate estimates of MA loads are needed in order to make summary judgments about both the absolute and the comparable level of excretion (and consumption) over time and between places.

While it is expected that most MA detectable in wastewater in Oregon is from illicit sources, MA also has legal sales of the d- (as Desoxyn) and l-forms (e.g., Vicks inhaler) as well as drugs that are metabolized to form d- and l-MA (e.g., Selegiline, Famprofazone, and Benzphetamine). Ascribing MA (or any other illicit drugs with a range of possible origins) to illicit use at the whole municipality level faces the same challenges as those attempting to determine the source of MA detected in an individual. To the best of our knowledge, potential contributions of legal uses of MA or drugs that are metabolized to MA have not been examined critically. For such analyses, data from communities where MA is readily detected due to high use levels is ideal.

The aims of this study are to 1] describe the temporal patterns of MA use across days of the week for a single location with endemic MA use in order to inform a sampling plan for discerning long-term trends in MA use, 2] estimate the mass of MA consumed within the community as back-calculated from measured loads in the

community's influent wastewater, and 3] estimate the contribution of legal sources of MA to wastewater loads.

## 1 MATERIALS AND METHODS

**2.1 Sample Collection**. A total of fifty-four 24hr flow-normalized composites of raw wastewater influent were collected during three periods. Period 1 was 17 days in July and August 2007; Period 2 was 18 days in September and October 2007; and Period 3 was 22 days in March and April 2008. The WWTP sampled is located in the Pacific Northwest and serves a population of 55,000 and treats around 90% domestic and 10% industrial waste. The location was selected because the sewer system and daily composite sampling approach are well characterized and the staff has consistently been cooperative with the investigators for several years. It is for these reasons that the location was included in earlier studies (Banta-Green et al. 2009; Chiaia et al. 2008). Flow-normalized composites were collected on ~ 20 min intervals over 24 hr periods and the composites were housed in a 4 $^{o}$C compartment during collection. Composite samples were transferred into individual 150 mL high density polyethylene bottles (VWR International, West Chester, PA) and transported back to the laboratory at Oregon State University where they were frozen immediately and stored at -20 $^{\circ}$C until analysis. The samples were analyzed within two weeks of collection. Preliminary test indicated no loss of MA upon centrifugation, storage in polyethylene bottles, and storage over the two week period.

**2.2 Large-Volume, Direct Injection Liquid Chromatography/Tandem Mass Spectrometry.** The standards, reagents and analytical method has been previously

93 described (Chiaia et al. 2008). Briefly, 7 mL of raw influent was centrifuged for 30 min.
94 After centrifugation, supernatant was transferred to a 6 mL autosampler vial and spiked
95 with (±) methamphetamine-$d_5$ as the internal standard. Large-volume (1,800 μL), direct
96 injection and separation was performed on a modified Agilent 1100 system (Santa Clara,
97 CA) (Chiaia et al. 2008) that was fitted with a C18 security guard column (Phenomenex,
98 Torrance, CA) and a 150 × 4.6 mm × 5 $\mu$m particle size Atlantis T3 C18 column (Waters
99 Corp., Milford, MA). Detection and quantification of analytes was performed on a
100 Waters Quattro Micro tandem mass spectrometer (Milford, MA) operated in positive
101 mode with an electrospray ionization interface (ESI). The accuracy of the method was
102 demonstrated with statistically equivalent (95% CI) concentrations determined by
103 standard addition and solvent-based calibration curves. The lower limit of quantification
104 for MA was 10 ng/L. The method precision for MA was 4% for within-day and 8%
105 between days.

106 **2.3 Statistical Analysis.** Data were analyzed with the 'mixed procedure' in SAS
107 (version 9.2) using a first-order autoregressive model for the correlation between
108 observations and fixed effects period, weekend (binary variable: Sat-Sun/Mon-Fri), and
109 period by weekend interaction (to allow day of the week effects to vary between periods).

110 **2.4 Index Loads (mg/person/day).** Index loads were calculated by multiplying
111 the measured concentration (ng/L) by the measured average flow (L) provided by WWTP
112 personnel (based upon daily flow meter readings) and divided by the estimated total
113 population served by the WWTP in the sampling periods (54,890 in 2007 and 54,880 in
114 2008) (Proehl 2009). The index loads of MA are reported as mass (mg) per population
115 per day (mg/person/day). To estimate the uncertainty in the computed loads (error bars

shown in Figure 1), the error about the concentration (measured concentration x the between-day precision of 15%) was then multiplied by the flow for each day and divided by population.

## 2 RESULTS AND DISCUSSION

**2.1 Statistical Analysis and Temporal Trends in Load**s. Methamphetamine (MA) was quantified in each sample collected with concentrations ranging from 120 to 780 ng/L. Total index loads ranging from 0.13 ± 0.02 to 0.38 ± 0.06 mg/person/day (Figure 1). Methamphetamine levels do not differ significantly between weekdays and weekends ($p=0.1$), consistent with a predominately regular, daily use pattern use within the community.

The observed concentrations of MA for raw influent are similar to those observed in a previous studies with samples from the western US (Banta-Green et al. 2009; Chiaia et al. 2008) but much greater than those reported by others for locations in the US (e.g. Kentucky with concentrations ranging from not detected to 100 ng/L) (Loganathan et al. 2009). Methamphetamine concentrations in other countries are < 20 ng/L (Bijlsma et al. 2009; Castiglioni et al. 2006; Postigo et al. 2008b; van Nuijs et al. 2009b) except for two reports for Spain in which values ranged from 2-277 ng/L (Huerta-Fontela et al. 2008b) and in Switzerland where MA in wastewater ranged from below the LOQ up to 27 ng/L (Berset et al. 2010).

Because concentrations are influenced by the flow of wastewater (dilution) and the population utilizing the WWTP systems, loads are computed to facilitate comparability within location, as in this study, and between locations. The computed

index loads for MA are consistent with those published in an Oregon-wide study (Banta-Green et al. 2009) and appear to be greater than the MA loads reported by others (Huerta-Fontela et al. 2008b; Zuccato et al. 2008).

The statistical analysis (n=54) does not give evidence of interaction between each of the three sampling periods and weekend dates for MA (p=0.2), that is the lack of a change in loads on weekends did not differ by sampling period (Figure 1). In this study we found that MA levels do not differ significantly between weekdays and weekends. The implication for sampling of this finding is that in an endemic area sampling could reasonably be done on any day(s) of the week.

There was a significant period effect for MA (p=0.001) in period 3 which was significantly different than period 1 (p=0.0003) and period 2 (p=0.0018) and there was no significant difference between periods 1 and 2 (p=0.2). Limited data on temporal trends in MA from Spain, a country with low MA use levels, indicated concentrations above detection on weekends but below detection on weekdays (Huerta-Fontela et al. 2008b).

**2.2 Estimating Mass of Methamphetamine Consumed.** Back calculating the number of illicit drug doses and users is an exercise that has been performed primarily for other substances of abuse including cocaine (Banta-Green et al. 2009; Huerta-Fontela et al. 2008a; Zuccato et al. 2008) and heroin (Zuccato et al. 2008). Although percentages of MA excreted for back calculations are presented (Boles and Wells ; Zuccato et al. 2008), to the best of our knowledge, few calculations have been performed using measured MA levels in wastewater due to the low and intermittent detection of MA (Postigo et al. 2010).

Although amphetamine is major a metabolite of MA and occurs at quantifiable levels in wastewater (Banta-Green et al. 2009; Chiaia et al. 2008), amphetamine is sold legally in the US and thus its occurrence cannot be attributed solely to MA use. In addition, while standards are available for hydroxy-methamphetamine, no stable-isotope labeled standards are available for hydroxy-methamphetamine.

Pharmacokinetic studies on d- and l-MA reveal that 37 to 54% is excreted within 24 hrs as MA (Cook et al. 1993; Cook et al. 1992; Cruickshank and Dyer 2009; Kim et al. 2004; Li et al. 2010; Oyler et al. 2002). Detailed studies on the pharmacokinetics of MA indicate that the percentage of MA excreted by users may be treated as independent of dose and the route of administration. For example, the percent of MA excreted as MA in urine when MA is smoked (36.8±11.1%) (average ±95%CI) and via intravenous injection (45.0±24.4%) are not statistically different (Cook et al. 1993). Cook et al. (Cook et al. 1992) found no difference in the pharmacokinetics of a low and high doses of MA administered over a 15 day period (Logan 2002). Therefore, the pharmacokinetics (e.g., the percent mass of MA per dose excreted over time) can be assumed to be similar for all routes of uptake and for users of high and low doses.

However, we argue that estimating the *number* of illicit MA doses is problematic. First, purity (percent as the d- form) in the Seattle-King county area (located in Washington state, north of Oregon), which has similar patterns of MA use as well as sources, varied widely during the study period (0-99%) (National Institute on Drug Abuse 2008) while the national estimate of average purity for 2007 in the US was 41% during autumn of 2007. Furthermore, MA potency has changed over time and MA users compensate for decreasing potency and/or purity with increasing consumption (Lee et al.

184 2007). For example, potency declined with increasing regulation limiting sales of
185 ephedrine and pseudoephedrine precursors in the US, Canada, and Mexico (Cunningham
186 et al. 2009) and the switch to precursors that lead to racemic mixtures with decreased
187 potency. While potency may change, the pharmacokinetics of the d- and l-MA forms are
188 similar (Li et al. 2010; Mendelson et al. 2006); thus, the mass of MA excreted is not
189 influenced by potency. For these reasons, we have elected to present the total mass of
190 MA consumed based on measurements of MA concentrations, total flow of wastewater,
191 and a range of excretion rates obtained from the literature rather than a single value,
192 which is likely more representative of the variation that occurs among MA users.
193 For this study, the lower and upper bound of MA consumed were estimated
194 assuming 50% and 30% excretion of MA ingested on a g/g basis, respectively. For
195 sampling Period 1, the lower estimated mass of MA consumed ranged from 18±1 to 31±2
196 g while the upper estimates of MA mass consumed ranged from 31±2 to 52±4 g (Table
197 1). While the estimated lower and upper masses of MA consumed in sampling Period 1
198 and 2 were not statistically different at the 95% CI (Table 1), they were statistically
199 higher than those of Period 3 (Table 1).
200 **3.3 Legal Sales of d-and l-Methamphetamine**. Desoxyn is a prescription drug
201 that contains d-MA and its sales are tabulated by three digit zip code for each of the 50
202 states in the US. The total sales of d-MA for the 973 zip code for Oregon in the third
203 quarter of 2007 (July – September) was 11.6 g (Drug Enforcement Administration). In
204 2007, the population of the studied municipality studied was 11.1% of the total
205 population for the three digit zip code (Proehl 2009). Assuming that the mass of d-MA is
206 evenly consumed over the 90 day period, we estimate that a per capita consumption of

207 $2.2 \times 10^{-7}$ g/day/person. Given the range in excretion rates (30 to 50%) of MA, the mass
208 of MA consumed that potentially can be attributed to the prescription use of Desoxyn
209 ranges from 3-5 % in Periods 1 and 2 to 5-8% in Period 3 (Table 1).

210 Our laboratory, and those of others who measure MA in wastewater, do not
211 distinguish between the d- and l-forms of MA, thus total MA (d- plus l-forms)
212 concentrations are reported for wastewater. There is a single report demonstrating the
213 potential to separate the enantiomers of MA in wastewater (Kasprzyk-Hordern et al.);
214 however, MA levels in the samples obtained from location in the United Kingdom were
215 below quantification levels. Until chiral separations of MA enantiomers are performed,
216 other potential sources of d- and l-MA must be considered as well as other drugs that are
217 metabolized to the two forms of MA since they are not analytically distinguished during
218 the analysis of wastewater. Just as in forensic science, where other sources potentially
219 confound the attribution of MA detection to illicit MA consumption (Cody 1996; Logan
220 2002; Nishida et al. 2006) the same issues are important when considering consumption
221 at the whole municipality scale.

222 **3.4 Other Pharmaceuticals that Metabolize to form Methamphetamine.** A
223 source of l-MA is from the use of Vicks inhaler (Logan 2002). While it is difficult to
224 estimate the amount of Vick's inhaler used within the northwest municipality studied, the
225 over-the-counter product is sold throughout the nation. Assuming similar usage and
226 prevalence of the over-the-counter medication, if usage of the inhaler resulted in MA in
227 wastewater, then quantifiable levels of MA should be nationwide. However, MA
228 concentrations were below the limits of detection in wastewater collected from locations
229 in the northeastern US (unpublished data). The absence of detectable MA in northeastern

U.S. wastewater as well as many European cities indicates that the potential contributions of the l-MA in Vick's inhalers is low. The absence of MA in wastewater from locations in the northeastern US is consistent with the low prevalence of illicit MA use (National Institute on Drug Abuse 2008).

Other drugs that humans metabolize to form MA (d- and/or l forms) include Selegiline, Famprofazone, and Benzphetamine (Logan 2002). Selegiline is a prescription drug used for Parkinson's disease and is metabolized to MA (Nishida et al. 2006; Romberg et al. 1995). The prevalence of Parkinson's disease in the United States is approximately 1 in every 120-180 people (McInerney-Leo et al. 2004). Assuming this level of prevalence, a municipality with ~55,000 residents would result in 300-450 cases of Parkinson's disease. For Parkinson's disease, Selegiline doses range from 6 mg/day (transdermal) to 10 mg/day (oral) (2009) and 20% of the parent dose results in MA excretion (Hasegawa et al. 1999). Using the published range in doses and urinary excretion factor along with a conservative estimate that all Parkinson's disease patients take Selegeline, which results in an upper estimate of the mass consumed, Selegiline prescriptions potentially account for 3-6% of the observed MA mass in this study.

Famprofazone is an analgesic that is metabolized to d- and l-MA (5 to 14% of dose excreted as MA) (Cody 1996; Neugebauer et al. 1997; Tseng et al. 2007); however, it is not approved for use in the US and is considered an insignificant contributor to the MA in the study (Hope Personal communication July 23, 2010). Benzphetamine in the form of Didrex is prescribed for obesity (Cloyd 1997; Cody and Valtier 1998; Stafford and Radley 2003) Utilization of Benzphetamine in Oregon is considered low because its use is greater among those with health insurance and Oregon Medicaid (health insurance)

has not approved amphetamines for weight loss (Hope Personal communication July 23, 2010). However, changes in the prescribing practices for Selegiline and Famprofazone or the approval and introduction of Famprofazone would potentially impact the MA residues detected in wastewater.

## 3 CONCLUSIONS

Endemic use of MA within a community results in no statistical differences in loads (mg/person/day) between days. As a result, it appears reasonable that sampling to determine MA use in an endemic use area can be accomplished by sampling wastewater on any day or days of the week. It also appears that different intra-week patterns of use may correspond to the stage of community wide drug use, such that areas with few, occasional users are likely to see peak use on weekends, whereas areas with many, regular users will have generally constant loads of MA across days of the week. Therefore, wastewater testing may be of value in determining the stage of drug use for a community as well as the level of use. This is a premise that warrants further, specific investigation. The estimated mass of MA consumed can be determined from wastewater measurements of concentration and flow. Calculations to estimate the numbers of MA doses or users is not, yet, recommended due to the variable purity and unknown patterns of actual use. Although there are legal sales of pharmaceuticals containing the d- and l-forms of MA as well as pharmaceuticals that metabolize to form MA, these sources are considered relatively minor compared to the illicit use of MA.

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**Table 1.** Lower and upper estimated ranges (average ± 95% CI) of methamphetamine mass for a municipality of approximately 55,000 residents for the three sampling time periods in 2007-8.

| | Period 1<br>July 13-Aug 5, 2007 | Period 2<br>Sept. 21-Oct. 11, 2007 | Period 3<br>March 25 – April 15, 2008 |
|---|---|---|---|
| Range in mass of methamphetamine consumed (g) ± 95% CI | 31±2 to 52±4 | 28±3 to 46±5 | 18±1 to 31±2 |
| % attributable to legal sales of Desoxyn (l-form) | 3-5 | 3-5 | 5-8 |