Crystal Clear: Prevalence of fentanyl in methamphetamine and cocaine samples collected by community-based drug checking services

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Running title: Fentanyl in cocaine and methamphetamine

Highlights

- 12-15% of powder methamphetamine and powder cocaine samples sent to a drug checking service also contained fentanyl.

- Fentanyl prevalence in crystal methamphetamine and crack cocaine was less than 1%.

- Other adulterants, including heroin and xylazine, were found in unregulated stimulants.

- The presence of xylazine reduced sample donors' ability to detect fentanyl.

ABSTRACT

Background: Overdose deaths involving stimulants and opioids simultaneously have raised the specter of widespread contamination of the stimulant supply with fentanyl.

Methods: We quantified prevalence of fentanyl in street methamphetamine and cocaine, stratified by crystalline texture, analyzing samples sent voluntarily to a public mail-in drug checking service (May 2021-June 2023). Samples from 77 harm reduction programs and clinics originated in 25 US states. Sample donors reported expected drug and physical descriptions. Substances were identified by gas chromatography-mass spectrometry. Negative binomial models were used to calculate fentanyl prevalence, adjusting for potential confounders related to sample selection. We also examined if xylazine changed donors' accuracy of detecting fentanyl.

Results: We analyzed 718 lab-confirmed samples of methamphetamine (64%) and cocaine (36%). The adjusted prevalence of fentanyl was 12.5% (95% CI: 2.2%, 22.9%) in powder methamphetamine and 14.8% (2.3%, 27.2%) in powder cocaine. Crystalline forms of both methamphetamine (Chisq=57, p<0.001) and cocaine (Chisq=18, p<0.001) were less likely to contain fentanyl: less than 1% of crystal methamphetamine (2/276) and no crack cocaine (0/53). Heroin was present in 6.6% of powder cocaine samples. Xylazine reduced donors' ability to detect fentanyl, with correct classification dropping from 92% to 42%.

Conclusions: Fentanyl was detected primarily in powder forms of methamphetamine and cocaine. Recommended interventions include expanding community-based drug checking, naloxone and fentanyl test strip distribution for stimulant users, and supervised drug consumption sites. New strategies to dampen variability in street drug composition are needed to reduce inadvertent fentanyl exposure.

1.   INTRODUCTION

Deliberate consumption of stimulants and opioids, either in combination (e.g., speedballs, goofballs) or in sequence, is a well-documented and persistent phenomenon (Harding et al., 2022; Meacham et al., 2016; Ondocsin et al., 2023). In Vancouver, Canada, 75% of urine samples from a syringe service program that tested positive for fentanyl also tested positive for amphetamine or methamphetamine (Hayashi et al., 2018). Stimulants are commonly consumed in conjunction with opioids to counteract sedation or to enhance effects of one or the other drug (Glick et al., 2021; Rhed et al., 2022). Consuming stimulants such as cocaine or methamphetamine in combination with fentanyl is a risk factor for opioid overdose (Hedegaard, 2021). In 2019, one-third of US overdose deaths involved both opioids and stimulants (O'Donnell et al., 2020). However, it is unknown to what extent opioid-stimulant deaths are attributable to deliberate consumption of opioids in combination with stimulants, or to inadvertent exposure to fentanyl via adulterated stimulants, or both.

Law enforcement drug seizure data through 2016 revealed that up to 7.5% of cocaine samples and up to 6.1% of methamphetamine samples tested positive for fentanyl (though varying by location) (Park et al., 2021), raising the possibility that some overdose deaths involving stimulants and opioids are attributable to opioid exposure from a mixed drug supply. In Canada, a drug checking program using Fourier-transform infrared (FTIR) spectrometry reported that 5.9% of "speed" and crystal methamphetamine samples contained fentanyl in 2018 (Tupper et al., 2018). In 2019, a urine testing company reported 8.4% of methamphetamine-positive urine samples tested positive for fentanyl (Twillman et al., 2020). Outbreaks of overdoses from fentanyl-contaminated cocaine have been reported (Canning et al., 2021), and a study in San Francisco suggested ingestion of fentanyl may have been unintentional among many stimulant users who died of overdose (Coffin et al., 2022).

While prevalence of fentanyl in unregulated stimulants may be relatively low on an absolute level (e.g., less than 10% in previous studies), there are persistent concerns in the news media and scientific reports of widespread contamination of stimulants with fentanyl (Baumgaertner, 2021; Daniulaityte et al., 2023; Green et al., 2020; HealthDay, 2023; Lockwood et al., 2021; Norman et al., 2023; Shin et al., 2022; Weiland and Sanger-Katz, 2022). In response, many harm reduction groups initiated drug checking programs allowing individuals to determine the composition of their street drugs. One common drug checking technology, fentanyl test strips,(Green et al., 2020; Norman et al., 2023) can have high false positive rates in concentrated methamphetamine samples (Lockwood et al., 2021) and these test stripsare limited by their ability to detect only one substance. On the other hand, point-of-care (McCrae et al., 2019; Ti et al., 2020) and lab-based (Delaney et al., 2023; Whitehead et al., 2023) drug checking services provide detailed information about drug composition (Crepeault et al., 2023; Tupper et al., 2018; Wallace et al., 2021) and yield more reliable results. No published study we could identify has examined fentanyl prevalence within stimulants accounting for crystalline versus powder form of the stimulant, but given geographic variability in drug forms and differences in manufacturing processing, crystalline versus powder drugs may have different rates of adulteration. Based on literature (Meacham et al., 2020; Scarfone et al., 2022; Vidal Giné et al., 2016), field observations and lived experience of study team members and drug

checking service-users, we hypothesized that fentanyl would be more prevalent in powder methamphetamine and cocaine compared to crystal methamphetamine and crack cocaine. In conversations with drug user unions using the drug checking service, we noted fierce debate as to whether methamphetamine contains fentanyl. Specifically, we observed strongly held beliefs, specifically among people who use crystal methamphetamine, that fentanyl was not present in this supply. We were therefore motivated to conduct this analysis to provide scientific evidence to inform the debate.

To determine the prevalence of fentanyl in street-based stimulant samples and test our hypothesis, we examined data from a mail-in drug checking program, designed as a low-threshold public service using the Evidence Making Intervention framework (Rhodes and Lancaster, 2019). This framework shifts the locus of evidence production away from restrictive sampling and inclusion criteria, which sometimes prioritize generalizability at the expense of the ability of findings to reflect the lived experiences of people for whom interventions such as drug checking are designed. Instead, an Evidence Making Intervention framework prioritizes a more contextualized scientific process in which data and conclusions are generated through localized processes serving immediate and applied needs. In this case, data from a drug checking service were used to examine the prevalence of fentanyl in submitted samples. Therefore, the purpose of this analysis is not to generate estimates of fentanyl prevalence in the national drug supply, but in the drugs that are in circulation among users of drug checking services.

2. METHODS
2.1 Drug samples
Samples were sent to a public mail-in drug checking service with original collection dates between May 5, 2021 and June 15, 2023 (94% collected in 2022 or 2023). On the date of analysis (July 1, 2023) there were 1,898 lab-confirmed results available, of which 914 contained methamphetamine and/or cocaine in trace or primary abundance. They were provided by 77 harm reduction programs, drug user unions, health departments, and medical clinics, originating in 96 counties in 25 states: North Carolina (n=328 samples), Washington (n=213), New York (n=82), California (n=79), Tennessee (n=55), Michigan (n=45), Oregon (n=17), Ohio (n=13), Texas (n=12), Arizona (n=10), Maine (n=8), Pennsylvania (n=8), New Mexico (n=7), Virginia (n=5), Wisconsin (n=5), Florida (n=4), Indiana (n=4), South Carolina (n=4), Georgia (n=3), Montana (n=3), Nevada (n=3), Mississippi (n=2), West Virginia (n=2), Illinois (n=1), and Rhode Island (n=1). Samples were collected at each participating program using a standardized protocol (see Supplemental Material), with training provided via video. Samples were collected as crystal/powder (57%), swabs of empty bags or paraphernalia (18%), used cottons (10%), and fragments of pills (2.3%), with 12% collection method unknown or multiple methods. Sample donors provided information about expected drug, sensations, and physical description through circled choices on a standardized form, and were provided with a link to a website to obtain results (https://streetsafe.supply). In 58% of samples, information provided by the donor suggested the sample had been consumed prior to submission for testing.

2.2 Laboratory analysis

Acetonitrile-dissolved samples (see Supplemental Material) were mailed in compliance with federal regulations and analyzed with gas chromatography-mass spectrometry (GCMS) with an electron ionization source. Gas chromatography separation was performed using a Thermo TraceGOLD TG-5SilMS column (30 m x 0.25 mm × 0.25 μm). Qualitative results from a Thermo Scientific Q Exactive GC Orbitrap are presented; substances were classified as being either in "primary" or "trace" abundance, with the latter defined as less than 5% chromatogram peak height area relative to the most abundant substance. Xcalibur Qual Browser Version 4.5 (ThermoFisher, Breman, Germany) was used for substance identification using untargeted search, with fragmentation analysis searching three libraries of drug standards (see Supplemental Material). All detected substances were positively identified and confirmed with pure, commercially available reference standards.

2.3   Confounders

Since collection was voluntary, samples may have been submitted because they were perceived to be unusual, which could bias prevalence estimates of fentanyl to be higher than in typical supply. This was anticipated in prospective design of the drug checking service. Some samples were submitted as part of complementary ("confirmatory") testing for 16 FTIR-based point-of-care drug checking programs, including samples difficult to interpret on FTIR and random or sequential selections for quality assurance, which could lead to more samples with fentanyl being submitted than typical supply. Samples from swabs of used pipes, cookers, or foil may contain residue from multiple or polydrug use sessions, which could also bias prevalence estimates higher. Since the decision to send a sample for analysis could be predicated on if it was consumed and produced unexpected sensations, we evaluated if fentanyl positivity was different in samples that had not been consumed (e.g., no sensations or overdose reported). We also adjusted for the presence of xylazine (in trace or primary abundance) because sedation effects could be subjectively similar to fentanyl, increasing suspicion bias as a motivation for sending the sample and influencing donors' ability to identify fentanyl. Therefore, we first explored confounding through restriction, and included all five potential confounders in subsequent multivariable modeling. In the restriction analysis, we quantified the impact of these potential confounders on fentanyl-positivity by individually removing samples that were: 1) described as "weird" (n=85); 2) from FTIR-based programs (n=281); 3) collected by swab (n=130); 4) consumed prior to donation (n=404); 5) lab-positive for xylazine (n=38).

2.4   Statistical analysis

2.4.1   Descriptive

The main outcome was GCMS-confirmed fentanyl in primary abundance. The main exposure was primary abundance of lab-confirmed stimulant (methamphetamine or cocaine). Five samples containing both cocaine and methamphetamine were excluded. We stratified samples by crystalline texture (e.g., powder methamphetamine vs. crystal methamphetamine, and powder cocaine vs. crack cocaine). For categorical variables, differences between groups are reported using the Pearson Chi-square test for homogeneity. Independent samples t-tests were used to compare (arithmetic) average number of substances detected by GCMS, stratified by texture.

2.4.2 Multivariable models

Generalized estimating equations (GEE) were constructed using negative binomial (NB2) regression, with county-level geographic clustering to account for repeated measures, and independent correlation matrix to accommodate within-county time correlation. Multivariable models including all five confounders used Huber-White robust standard errors; we interpreted the exponentiated intercept in identity (Gaussian) link models as adjusted prevalence. Data processing, statistics, and modeling were conducted in Stata MP version 17 (College Station, Texas) with 'tabulate, chi2' and 'xtgee'.

2.4.3 Classification statistics

Expectations of fentanyl reported by donors were compared to laboratory results to quantify how accurately sample donors' predictions matched presence of fentanyl. Sensitivity, specificity, likelihood ratios (LR+, LR-), false positives, false negatives, area under the receiver operator characteristic (ROC) curve and 95% confidence intervals(DeLong et al., 1988) were generated using 'roctab' in Stata. Results were stratified by texture, type of stimulant, and presence of xylazine.

2.5   Study Conduct

2.5.1 Open science practices

Pre-registration (https://osf.io/qkf57). Dataset, codebook, data collection form, analytic code, and individual sample chromatograms: DOI 10.17605/OSF.IO/EV7NW.

2.5.2 Ethics

This investigation was reviewed by the UNC Office of Human Research Ethics and deemed exempt from human subjects research. The primary purpose of sample collection was a service providing information on drug composition to sample donors.

2.5.3 Participation of people with lived experience

People with lived experience were involved in the design and conduct of the service, study conceptualization, and interpretation of results.

3.   RESULTS

There were 1,898 GCMS-confirmed results available for analysis, including non-stimulant samples. Applying inclusion criterion for stimulants in primary abundance, and removing 5 samples which contained both cocaine and methamphetamine, resulted in an analytical sample of 718. Samples were 63.8% (n=458) methamphetamine and 36.2% (n=260) cocaine.

3.1   Substances Detected

Among 718 stimulant samples, 64 unique substances were detected in primary abundance using GCMS (78 including trace abundance). The number of unique substances ranged from 1 to 15 per sample, averaging 1.74 (95% CI: 1.64, 1.84) per sample. Powder methamphetamine had 2.01 (95% CI: 1.74, 2.28) substances detected, twice as many as crystal methamphetamine (1.07 95% CI: 1.03, 1.11; t=8.1, df 456, p<0.001)) (Table 1). Similarly,

powder cocaine had more unique substances than crack cocaine (powder: 2.39, 95% CI: 2.08, 2.71; crack: 1.07, 95% CI: 1.00, 1.23; t=4.1, df 258, p<0.001).

3.2 Fentanyl Positivity
3.2.1 Fentanyl in primary abundance
In total, 13.5% (97/718) of stimulant samples contained fentanyl in primary abundance. Fentanyl positivity was 8.9% (41/458) in methamphetamine samples and 21.5% (56/260) in cocaine samples sent to this drug checking service. Fentanyl-positive stimulants were submitted from 13 (out of 25) states: Arizona, California, Mississippi, Missouri, North Carolina, New York, Ohio, Oregon, Tennessee, Texas, Virginia, Washington, and Wisconsin. These states include locations with both low and high volumes of overall sample submissions. Notably, fentanyl and fentanyl analogues were not the only opioids detected alongside stimulants; 6.6% (12/182) of powder cocaine samples also contained heroin.

3.2.2 Multivariable modeling
Five potential sources of confounding were measured prospectively: samples perceived to be "weird" as reported by the donor, samples from FTIR programs, swab samples, samples consumed prior to analysis, and those containing xylazine. Stratified analyses suggested these factors should be taken into account when estimating overall fentanyl positivity (Table 2). In particular, "community" samples (not from point-of-care FTIR programs) and samples consumed prior to testing showed higher prevalence of fentanyl. Cocaine samples without xylazine had lower prevalence of fentanyl than corresponding samples of methamphetamine. All five *a priori* confounders were included in multivariable models, which also accounted for geographic clustering and within-county variation over time. The unadjusted estimate from negative binomial models with GEE was 13.4% (95% CI: 7.6%, 19.4%) for fentanyl positivity. After taking the five confounders into account, the overall adjusted prevalence of fentanyl in street stimulants submitted to this drug checking service was estimated to be 9.1% (95% CI: 3.2%, 15.0%). When stratified by stimulant type, adjusted prevalence was 6.2% (95% CI: 1.1%, 11.2%) in methamphetamine and 12.6% (95% CI: 2.4%, 22.8%) in cocaine.

3.3 Texture Analysis
3.3.1 Methamphetamine
Powder methamphetamine had a higher prevalence of fentanyl than crystal methamphetamine (Chisq=57, df 1, p<0.001): Of lab-confirmed methamphetamine samples that were crystal form, less than 1% (2/276) contained fentanyl in primary abundance. Out of 182 non-crystal methamphetamine (e.g., powder) samples, 39 contained fentanyl; the adjusted prevalence of fentanyl in powder methamphetamine was 12.5% (95% CI: 2.2%, 22.9%).

3.3.2 Cocaine
Powder cocaine had a higher prevalence of fentanyl than crack cocaine (Chisq=18, df 1, p<0.001). Out of 260 lab-confirmed cocaine samples, 53 were crack cocaine. None contained fentanyl. Of the remaining 207 powder cocaine samples, fentanyl was found in 56; the adjusted prevalence of fentanyl in powder cocaine was 14.8% (95% CI: 2.3%, 27.2%).

3.4   Anticipating Fentanyl

Fourteen percent of sample donors (99/718) reported on data collection cards that they thought their submitted sample contained fentanyl. Overall, 89% of stimulant samples were correctly classified in terms of fentanyl prevalence (Table 3 and Supplemental Material). Out of the 97 stimulant samples containing lab-confirmed fentanyl , donors correctly identified fentanyl in 60.8% (n=59) of samples (i.e., true positives); the sample donors did *not* identify fentanyl as being expected in 39.2% (n=38) of lab-confirmed samples with fentanyl (i.e., false negatives), however sensitivity was only 61%.

3.4.1   Powder Stimulants

For powder methamphetamine (n=182), 82% of samples were correctly classified for fentanyl. Sample donors correctly identified 74% (29/39) of samples that contained fentanyl, with false negatives at 26%, Table 3. Similarly, fentanyl was correctly classified in 54% (n=30) of powder cocaine samples, but with a higher false negative rate 46%, suggesting that fentanyl appears more often in powder cocaine unexpectedly.

3.4.2   Xylazine

Xylazine reduced donors' accuracy in predicting fentanyl in stimulants. There were 38 stimulant samples that contained xylazine in primary or trace abundance, of which 92% (35/38) also contained fentanyl. Cocaine samples were statistically significantly more likely to contain xylazine (28/260) compared to methamphetamine (10/458;Chisq=24, df 1, p<0.001). In the absence of xylazine, 92% of samples were correctly classified by donors with regard to fentanyl, but in the presence of xylazine, correct classification dropped to 42%, Table 3. Correspondingly, sensitivity dropped from 71% to 43%, and specificity from 94% to 33%; ROC curve area dropped from 0.82 to 0.38, well-below generally accepted accuracy. Xylazine-masking can be summarized by LR+ 0.64, indicating that in the presence of xylazine, sample donors were 1.5 times less likely to correctly detect fentanyl.

4.   DISCUSSION

We sought to determine the prevalence of fentanyl in street samples of methamphetamine and cocaine submitted to a drug checking service between 2021 and 2023, with the goal of estimating fentanyl prevalence in stimulants that are in circulation among users of drug checking services, and shedding light on possible etiologies of deaths associated with stimulants.

In adjusted models controlling for possible sample selection considerations, the overall prevalence of fentanyl in stimulant samples was 9.1%, but twice as high in cocaine (12.6%) compared to methamphetamine (6.2%). Unadjusted fentanyl prevalence in methamphetamine was 8.9%, consistent with estimates from a 2020 law enforcement methamphetamine seizure study, which reported 7% unadjusted fentanyl positivity prevalence (Jones et al., 2022). We posit that roughly 1-in-10 times that people consume illicit stimulants, the drug could be contaminated with fentanyl. This could account for a substantial share of deaths where fentanyl and stimulants are detected in tandem, but that the majority of opioid-stimulant deaths may have behavioral polysubstance use etiology. These findings challenge the narrative of universal fentanyl adulteration of unregulated stimulants, while also suggesting that stimulant users

should be aware of and guard against accidental fentanyl poisoning. Prevention recommendations include training in opioid overdose recognition and response, take-home naloxone for people who use stimulants, and access to point-of-care testing of illicitly manufactured stimulants using reliable methods (Green et al., 2020). Behavioral interventions and education could be considered to address dangerous polysubstance use conditions.

Supporting our hypothesis, crystalline forms of both stimulants showed little evidence of contamination with fentanyl (or other substances), likely explained by clandestine synthesis and purification methods. The differences in structure and physical properties between crystalline and powder substances contribute to why crystalline substances generally have a lower chance of contamination or adulteration compared to powder substances. Using a similar study design, a mail-in drug checking service in Spain found that adulteration of pressed tablet MDMA was two-fold higher than crystal MDMA (Vidal Giné et al., 2016). We posit that crystalline forms may serve as a physical quality assurance feature observable by the consumer that allows reliable, if not absolute, avoidance of fentanyl.

Fentanyl was not the only detected contaminant. In addition to clandestine synthesis by-products and leftover precursors, we also detected heroin, xylazine, levamisole, lidocaine, caffeine, and phenacetin. Powder methamphetamine and cocaine contained significantly higher numbers of adulterants (including fentanyl and heroin) than corresponding crystalline forms. We note that our underivatized GCMS protocol was tuned to detect psychoactive molecules, and excipients and bulking agents were not included in adulterant counts.

Fentanyl-positive stimulants were detected in 13 out of 25 states, including areas with both low and high submission counts to the drug checking service. While geopolitical state boundaries are provided for descriptive reporting, state was not used in modeling (we used county); not all stimulants in these states should be considered to contain fentanyl because of localized catchment areas in each program. Conversely, fentanyl-stimulant overdoses occur in every state, and our conclusions are not intended to suggest otherwise. Local context (changes in suppliers, particular batches, law enforcement interdiction, social networks, etc.) likely exerts stronger influence on individual exposure and overdose risk than aggregate geographic patterns (Carroll et al., 2020; Latkin et al., 2004; Ray et al., 2023). The observed lack of fentanyl in crack cocaine may be attributable to small sample size (n=53) and limited geographic reach (9 states), with most from Michigan, California and New York. Fentanyl- and fentanyl analogue-contaminated crack has been described across North America, albeit sporadically: British Columbia (Klar et al., 2016) and Connecticut (Canning et al., 2021) in 2019, North Carolina in 2021 ("Drug dealer who sold fentanyl-laced crack sentenced to more than 16 years after four people died in a single day," n.d.) and Ontario (Scarfone et al., 2022). Clearly, crack cocaine is not universally impervious to contamination with fentanyl and our conclusions should not be used to suggest that crack cocaine is "safe" from fentanyl.

The presence of xylazine (an increasingly common adulterant with sedating properties; (Kariisa et al., 2023)) appeared to reduce donors' ability to accurately identify fentanyl in stimulants. Correct classification of fentanyl dropped from 92% to 42% in the presence of xylazine.

Canadian scientists reported a similar phenomenon of less accurate fentanyl discernment by people who use drugs in the presence of potent benzodiazepines and synthetic cannabinoids (Scarfone et al., 2022). In the US most xylazine is detected in the presence of fentanyl (i.e., xylazine is rarely detected alone; (Delcher et al., 2023; Spencer et al., 2023)). Therefore, we speculate that most of the xylazine detected in the stimulants we tested is incidental and likely a carryover contaminant (or adulterant) that was introduced via fentanyl. However, we identified three samples (two cocaine, one methamphetamine) where xylazine was present and fentanyl was not, a phenomenon that has not been documented previously.

The theory of traditional harm reduction drug checking suggests that the primary benefit is to inform decisions before consumption (Bardwell et al., 2019; Measham, 2019). Yet, more than half the samples analyzed showed evidence of being consumed prior to testing, suggesting that donors may have sent samples because they produced unexpected effects. In fact, motivations for submitting samples to the programs varied widely, including to verify rumors of contamination or adulteration, to identify substances associated with an overdose, or to test the accuracy of local testing methods. We controlled for this in two ways. First, we separately evaluated samples described as "weird" by donors, which showed little difference from samples not so labeled. Second, we isolated samples with evidence of consumption and found that consumed methamphetamine samples were more likely to contain fentanyl than unconsumed ones, but less so for cocaine, suggesting that while selection bias may occur, it is not uniform and can be measured and adjusted for. These metrics rely on self-report; while we cannot preclude misclassification, the data were collected as part of a drug checking *service* (e.g., not a research study) where donors had incentive to report accurately.

As we have previously stated studies using harm reduction drug checking data have the limitation that sample collection is voluntary, and not probabilistic (Maghsoudi et al., 2022; Palamar et al., 2021a). While acknowledging that the samples analyzed are not representative of nor generalizable to national or local drug markets, it is important to recognize that from an epidemiologic perspective, no credible sampling frame is known for collecting a "representative" sample of street drugs across a large country (Dasgupta and Figgatt, 2022), including from law enforcement sources (Peterson et al., 2016). Crime lab drug seizure data are biased towards reportable substances for obtaining the harshest criminal penalties but are still routinely used for population level inference (Cottler et al., 2020; O'Donnell et al., 2017; Palamar et al., 2021b; Pitts et al., 2023). Nevertheless, our findings are consistent with estimates derived from law enforcement data (Jones et al., 2022). Our design is an effort to employ the Evidence Making framework, which blends sentinel surveillance and crowdsourcing, common in infectious disease and drug trend monitoring, to allow rapid reporting and utilization of findings (Alvaro et al., 2015; Dasgupta et al., 2013). Despite limitations to generalizability mail-in and other community based drug checking services are one of the only timely, ethically acceptable, and scientifically defensible sources of information on drug composition trends(Green et al., 2022).

5.   CONCLUSION

In this sample of unregulated stimulant drugs sent to a drug checking service, fentanyl was detected in 9.1% samples. Crystalline forms were significantly less likely to contain fentanyl than

powder forms. Xylazine reduced donors' ability to accurately identify the presence of fentanyl. These findings suggest test strip and naloxone distribution, regulated stimulant supply interventions, and polysubstance risk reduction education should be expanded to people who use cocaine and methamphetamine, and that point-of-care drug-checking services that can identify unanticipated adulterants (including, but not limited to fentanyl) should be scaled up. Careful evaluation of supply-side interventions is crucial to avoid unintended effects (e.g., driving the demand for powder stimulants which have a higher probability of containing fentanyl relative to crystalline forms).

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Table 1. Adulterant substances detected in methamphetamine and cocaine, by stimulant type.

	N	Top other substances detected (n)*	Average Number of Substances Detected by GCMS (95% CI)	Difference (t-test)
Powder methamphetamine	182	- fentanyl (39) 4-ANPP (33) - heroin (12) - phenethyl 4-ANPP (10) - xylazine (8) 1,3-Diacetin (7) - dimethyl sulfone** (7) - caffeine (6) - N,N-Dimethylamphetamine (5) - ethyl-4-ANPP (5) - p-fluorofentanyl (5)	2.01 (1.74, 2.28)	t=8.1, df 456, p<0.001
Crystal methamphetamine	276	- dimethyl sulfone (6) - N,N-Dimethylamphetamine (2) - fentanyl (2) - ketamine (2)	1.07 (1.03, 1.11)	
Powder cocaine	207	- fentanyl (56) 4-ANPP (38) - heroin (22) - xylazine (19) - methyl ecgonidine (15) - caffeine (11) - phenethyl 4-ANPP (10) 6-monoacetylmorphine (9) - acetylcodeine (8) - lidocaine (8) - phenacetin (8) - levamisole (7) - benzoylecgonine (6) - p-fluorofentanyl (6) - despropionyl p-fluorofentanyl (5)	2.39 (2.08, 2.71)	t=4.1, df 258, p<0.001
Crack cocaine	53	- levamisole (1) - methyl ecgonidine (1) - norcocaine (1) - tropacocaine (1)	1.07 (1.00, 1.23)	

* Top 10 or occurring at least 5 times
** Dimethyl sulfone is also known as methylsulfonylmethane (MSM)
Abbreviations: 1-ANPP= 4-anilino-N-phenethylpiperidine; CI=confidence interval; df=degrees of freedom; GCMS=gas chromatography-mass spectrometry

Table 2. Fentanyl positivity in street stimulants, adjusting for confounding, 96 United States counties, May 2021 to June 2023.

Condition	N	Fentanyl Positivity (95% CI)		
		Overall	Methamphetamine	Cocaine
Unadjusted	718	13.5%	8.9%	21.5%
Confounders Evaluated Individually				
Remove "weird" samples	633	13.1%	8.3%	21.3%
Community samples only*	437	17.6%	12.1%	26.0%
Non-swab samples	588	11.7%	8.1%	18.4%
Not consumed before testing	314	10.2%	4.6%	19.7%
No xylazine**	680	9.1%	7.1%	12.9%
Fully Adjusted Model***				
Adjusted for location, time, and 5 covariates above	711	9.1% (3.2%, 15%)	6.2% (1.1%, 11.2%)	12.6% (2.4%, 22.8%)

* Excluding samples from 16 FTIR-based confirmatory/complementary drug checking programs.

** Xylazine detected by GCMS in primary or trace abundance.

*** Seven samples were excluded because county location was not known and adjustment for geographic clustering could not be taken into account.

Table 3. Classification statistics for presence of fentanyl in stimulants, comparing sample donor expectations with laboratory results

	All	Texture		Xylazine	
		Powder Methamphetamine	Powder Cocaine	No Xylazine	With Xylazine
Sample size	718	182	207	680	38
Correctly Classified by donor	89.1%	82.4%	81.6%	91.8%	42.1%
Sensitivity	60.8%	74.4%	53.6%	71.0%	42.9%
Specificity	93.6%	84.6%	92.0%	93.8%	33.3%
LR+	9.44	4.83	6.74	11.5	0.643
LR-	0.419	0.303	0.504	0.309	1.71
False Positive*	6.4%	15.4%	7.9%	6.1%	67.7%
False Negative**	39.2%	25.6%	46.4%	29.0%	57.1%
ROC Area (95% CI)	0.77 (0.72, 0.82)	0.79 (0.72, 0.87)	0.73 (0.66, 0.80)	0.82 (0.77, 0.88)	0.38 (0.04, 0.71)

* Expected fentanyl circled on sample submission card, but not detected in primary abundance using GCMS.
** Fentanyl detected in the lab in primary abundance by GCMS, but not circled as expected on sample submission card.
Abbreviations: CI = confidence interval; LR = likelihood ratio; ROC = receiver operating curve

SUPPORTING INFORMATION

Sample Collection

Harm reduction programs, drug user unions, and public health departments were eligible to send samples. Programs applied to use the service through the website https://streetsafe.supply and were vetted to prevent collusion with law enforcement. Most harm reduction programs were fixed site or mobile syringe service programs. Programs were required to review an instructional video (https://vimeo.com/571816432) and sent sample collection kits, which contained:

- surgical drape to provide a clean surface and prevent contamination
- pair of nitrile gloves
- packet of 2 swabs
- non-static 10mg plastic scoop
- biodegradable bioplastic spatula
- 1 screw-top vial containing 1.5 mL acetonitrile (sealed with Parafilm)
- 2 pieces of Parafilm to reseal the vial
- Instruction and data collection card
- card with QR code for accessing results to provide to donor
- golf pencil
- pre-addressed and prepaid return FedEx Ground mailers
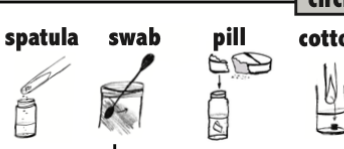
Sample donors were anonymous to the lab, but program identities were known. Results were returned to participants (a condition of service utilization) using a QR code linking to a website with anonymized public results. Data collection card and instructions are shown below.

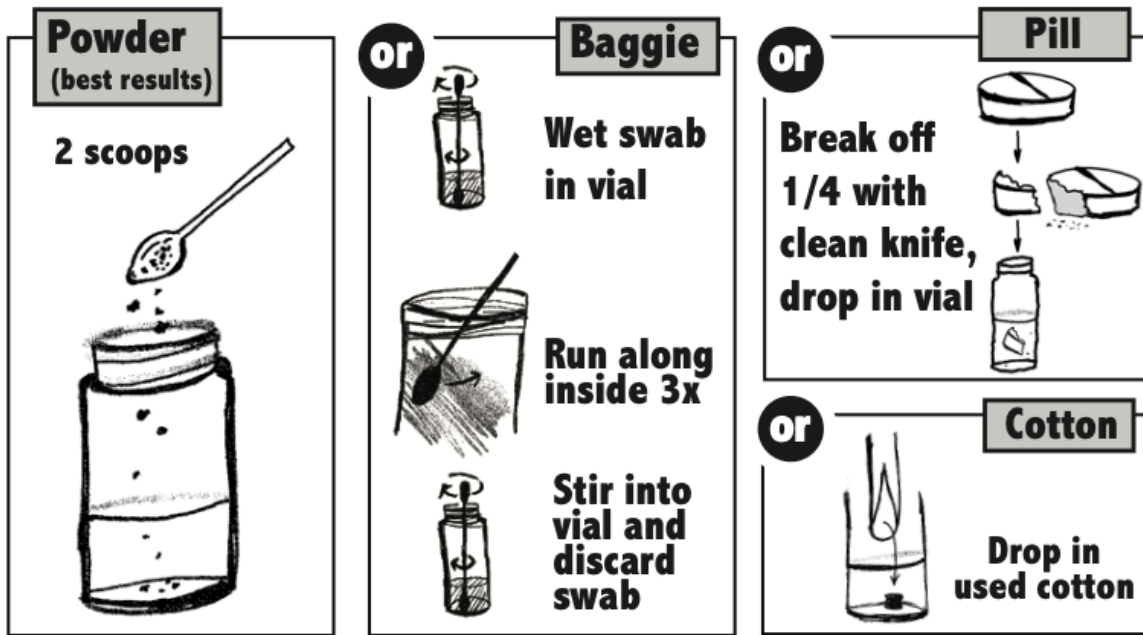**1** Unfold paper cloth, lay out supplies.

2 Unpeel wax tape to unscrew vial.

3 Wear gloves to prevent contamination.

Powder (best results)

2 scoops

or **Baggie**

Wet swab in vial

Run along inside 3x

Stir into vial and discard swab

or **Pill**

Break off 1/4 with clean knife, drop in vial

or **Cotton**

Drop in used cotton

4 Close vial <u>tightly</u>. Seal using wax tape.

Hold tape in closed fist to warm up for 3 seconds.

Remove tape from white backing.

hold   stretch

wrap
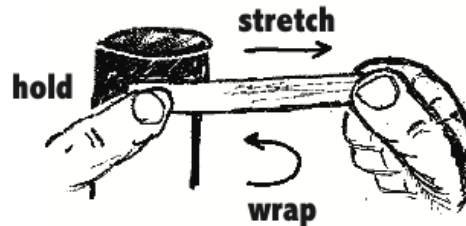
5 Complete back of this card.
Card and vial go back in bag.

6 Give QR code to donor for results.
Enter sample ID to track results in 2-5 days https://streetsafe.supply

Sample Collection

In North Carolina, programs were solicited for participation in the drug checking service through outreach in collaboration with the NC Department of Health and Human Services and by word of mouth. Outside North Carolina, programs sought out the service through word of mouth referrals and from publicity through conference presentations and news media.

Programs in North Carolina were able to submit samples for free, thanks to funding from a private foundation and the NC General Assembly. Outside North Carolina, drug user unions were eligible to avail the service for free. Harm reduction programs and health departments were provided 5 free starter kits and then charged a sliding scale fee for subsequent samples ($20-$60). Harm reduction programs and health departments also used the service as confirmatory/complementary testing for point-of-care FTIR drug checking; about 60% of samples came from these FTIR sites, but the UNC lab was blinded to FTIR results. Dissolving drug samples in acetonitrile rendered them "unusable" by federal controlled substance standards, allowing them to be stored and mailed more easily. Sample originating locations (e.g., where obtained) could have been different from the location of the program collecting the sample.

Laboratory Methods

a. Sample preparation
i. Samples were sent to the laboratory in 4.0-mL vials containing the sample dissolved in 1.5mL acetonitrile. Samples were evaluated based upon participant-provided information of the expected substance. If necessary, the sample was diluted, or an appropriate extraction was performed following standard practices in forensic chemistry. Samples were provided as either: powder (approximately 10 mg); residue swabbed from the inside of an empty bag or used pipe or syringe; a fraction (approximately ¼) of a tablet; or a used cotton.

ii. Approximately 500μL of the extract was filtered into a 2.0-mL autosampler vial.

b. Analytical method
i. Samples were analyzed with a ThermoScientific Exactive GC with an electron ionization (EI) source. Compounds in the drug samples were identified qualitatively using a Thermo Scientific Q Exactive GC Orbitrap GC-MS System with a TriPlus RSH Autosampler. Gas chromatography separation was performed using a Thermo TraceGOLD TG-5SilMS column (30 m x 0.25 mm × 0.25 μm). One microliter injections were carried out in split mode using a 20:1 ratio mode with Helium as a carrier gas (constant flow 1.5mL/min). The GC oven temperature programming started at 100°C and was ramped to 300°C at a rate of 30°C/min, with a 9-min hold time. The total run time was 17 minutes. The inlet temperature was 280°C, while the ion source was 230°C and the MS transfer line was set at 280°C. The AGC target was set to $1×10^6$. A 2.3-minute filament delay was used. Samples were acquired in positive mode in full SCAN mode with a range of m/z 40–500 and a resolution of 60,000.

ii. Xcalibur Qual Browser Version 4.5.445.18 (ThermoFisher, Breman, Germany) was used to analyze the data. Compound identification was performed using mass spectral libraries for fragmentation pattern analysis: SWGDRUG MS Library Version 3.10 (Scientific Working Group for the Analysis of Seized Drugs), Cayman Chemical (Ann Arbor, MI) and NIST 20 (National Institute of Standards and Technology, 2020 Version). If necessary, the retention time of compounds was compared to analytical reference standards. Standards were purchased from Cayman Chemical Company and Cerilliant Corporation (Round Rock, TX).

APPENDIX TABLE 1. Classification count tables for presence of fentanyl in stimulants, comparing sample donor expectations with laboratory results

ALL SAMPLES

Lab Confirmed Fentanyl

		Yes	No	
Expected Fentanyl	Yes	59	40	99
	No	38	581	619
		97	621	718

POWDER METHAMPHETAMINE

Lab Confirmed Fentanyl

		Yes	No	
Expected Fentanyl	Yes	29	22	51
	No	10	121	131
		39	143	182

POWDER COCAINE

Lab Confirmed Fentanyl

		Yes	No	
	Yes	30	12	42
Expected Fentanyl	No	26	139	165
		56	151	207

NO XYLAZINE

Lab Confirmed Fentanyl

		Yes	No	
	Yes	44	38	82
Expected Fentanyl	No	18	580	598
		62	618	680

WITH XYLAZINE

Lab Confirmed Fentanyl

		Yes	No	
	Yes	15	2	17
Expected Fentanyl	No	20	1	21
		35	3	38

DISCLOSURES

ND serves on the Scientific Advisory Board of the non-profit RADARS System of Denver Health and Hospitals Authority, which had no knowledge of or involvement in this manuscript. ND is also on the Board of Directors of the non-profit organization Remedy Alliance For The People.

CODE AND DATA SHARING STATEMENT

All study materials, including pre-registration, codebook, analytic code, data collection materials, protocols, notebook, dataset, GCMS chromatogram spectra for each sample are available at: https://osf.io/ev7nw/ with DOI: 10.17605/OSF.IO/EV7NW

TRIAL REGISTRATION

This investigation was pre-registered (https://osf.io/qkf57).

CONTRIBUTORSHIP STATEMENT

ND, PF, KP, KW conceptualized the study. CM, MN, ET, ND conducted sample collection. ET conducted the laboratory analyses. ND conducted the statistical analysis. All authors contributed to result interpretation and manuscript development.