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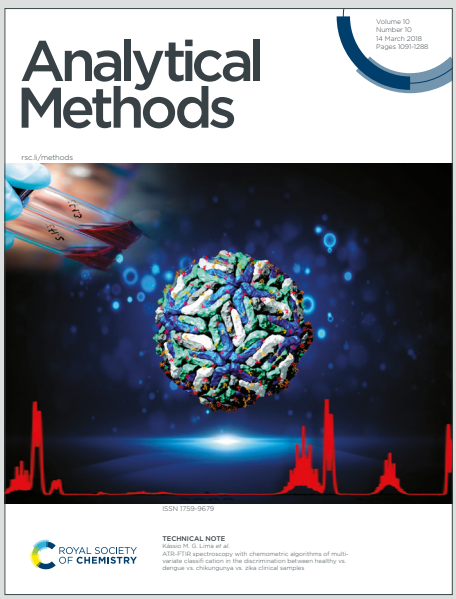

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Method for Evaluating Ion Mobility Spectrometers for Trace Detection of Fentanyl and Fentanyl-related Substances

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Abstract

Continuing efforts to combat the opioid crisis in the U.S. require technologies that can detect the presence of fentanyl and fentanyl-related substances for multiple applications, including law enforcement and border protection. Ion mobility spectrometry (IMS) technologies have a potential role here, and agencies will require robust methods to evaluate instrument performance for what are very challenging detection requirements. A suite of commercial instruments configured for general drug and/or explosives detection was used to determine baseline performance for detection of fentanyl and 15 fentanyl-related substances to guide the development of a method. Detection of all 16 compounds and reproducibility in reduced mobilities (K_0) of ± 0.01 $cm^2\ V^{-1}\ s^{-1}$ indicate that product ion formation is the same across instrument platforms, and a strong correlation with molecular weight (R^2=0.99) allows for the prediction of reduced mobility for newly encountered fentanyl analogs. Eleven compounds representing those most frequently encountered in seized materials in the U.S. since 2015 were chosen for the proposed evaluation method. Based on the highest resolution instruments, detection windows of ± 0.003 $cm^2\ V^{-1}\ s^{-1}$ allow for 6 out of 11 compounds to be uniquely identified while the remainder are identified as pairs. The method proposes testing only 9 compounds because of the redundancies represented by the paired detections. Sensitivity measurements using ASTM E2677 for fentanyl and benzyl fentanyl indicate that all instruments are capable of nanogram detection levels, and that a common dosing level of 100 ng for all tested compounds is appropriate. Heroin, procaine, and quinine are proposed as confusants to add to fentanyl samples, based on the known presence of these materials in seized samples and baseline measurements of the effect on the detection of fentanyl. The method also includes a list of drugs that should be tested for false positives to ensure that authentic pharmaceutical compounds or other illicit drugs can be discriminated. IMS manufacturers are currently developing algorithms to enable fentanyl detection in their trace detectors, and this method can apply as those instruments become available.

Introduction

Technologies are needed for detecting fentanyl and fentanyl analogs by many groups including law enforcement, the military, first responders, and customs and border protection agents.[1] Ion mobility spectrometry (IMS) technology is known for detection of contraband, including drugs and explosives, with widespread use in airports and prisons and a demonstrated capability for performing in a variety of environments with a non-technical user base.[2] A recent study demonstrated the capabilities of IMS for

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detecting fentanyl and fentanyl analogs in complex samples containing cutting agents and additional illicit substances.[3] Detection limits of a few nanograms for fentanyl and its analogs allow for the determination of the interior contents of a bag by collecting invisible traces from the exterior. This approach provides a safer alternative to sampling, eliminating the need to open bags and extract visible and potentially hazardous levels of material. The study evaluated detection performance on a single commercial instrument and demonstrated feasibility without providing a framework for testing across IMS platforms using common metrics.

Any evaluation method must consider the variety of different applications envisioned for the technology and the complexity of the targeted sample set. For example, one entry point into the U.S. for fentanyl-related substances is through direct shipments into international mail facilities, and detection of these samples would likely involve relatively pure powders and potentially novel compounds. There are over 140 known fentanyl analogs (Table S1) with the potential for more, and a recent ruling from the Drug Enforcement Administration (DEA) has placed a temporary scheduling order on all fentanyl-related substances.[4] Law enforcement activities may encounter very different types of samples, including counterfeit tablets and multi-drug mixtures where the fentanyl may be present at 0.01 mass fraction or less.[5] These samples must be discriminated against other common drugs and authentic pharmaceutical products. Regional differences in the types of opioid samples, including specific drugs, drug mixtures, and cutting agents are common and constantly in flux.[6,7] A testing framework that clearly delineates the problems inherent with different types of samples can be used to customize alarm settings for the sample suite expected.

Here we describe an approach to evaluating IMS detectors for trace detection of fentanyl and fentanyl-related substances that considers the types of samples expected in law enforcement applications, using published data on seized drugs to design the sample set. Fundamental measurements collected from a suite of commercial IMS instruments, marketed for explosives and/or drug detection but not necessarily configured for the detection of any fentanyl substances, were used to inform the development of a

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potential method. We evaluated selectivity, sensitivity, and reproducibility from the suite of instruments to determine baseline capabilities and tailor the testing method to eliminate redundancies and challenge the instruments. The selection of fentanyl-related substances included in the sample set is based on prevalence, but streamlined to use fewer, and less toxic substances where possible. Sample matrices that can result in challenges to IMS detection are proposed as part of the method, and guidance is provided for determining selectivity using selected analogs and a list of compounds that should result in true negatives.

Sample Set

The rationale for selecting specific fentanyl-related compounds for a testing protocol should include the frequency at which they are encountered, but could also consider the availability of test samples, safety concerns, and specific analytical challenges. The most commonly encountered substances were determined by surveying publicly available information on drug seizures available from the DEA's National Forensic Laboratory Information System (NFLIS), which contains data from crime labs throughout the U.S.[6] The DEA also compiles data from their own internal laboratory system to report on emerging threats, reporting the name and number of identifications of fentanyl, fentanyl-related compounds, and other new opioids.[8-10] The complete list of compounds represented by 4 recent reports are summarized in Table 1, sorted first according to their consistency (appearances in 1 report to all 4 reports) and prevalence within a report (the number of exhibits), with an overall ranking calculated from these two metrics. From this list, we chose the top 11 compounds, from fentanyl to cyclopropyl fentanyl to include as compounds that must be detected in an evaluation method. Two of the compounds in the top 11 are not fentanyl analogs; 4-ANPP (N-phenyl-1-(2-phenylethyl)-4-piperidinamine) is a precursor in the manufacture of fentanyls, and U-47700 is a synthetic opioid that is structurally different from fentanyl.

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Table 1. Fentanyl-related substances compiled from 4 reports spanning the years 2015-2018. Substances ordered by number of reports with ranking calculated according to prevalence.

Compound Name	Molecular Weight (Da)	Molecular Formula	Reports [references]	Ranking
Fentanyl	336.47	$C_{22}H_{28}N_2O$	[6, 8, 9, 10]	1
Furanyl fentanyl	374.47	$C_{24}H_{26}N_2O_2$	[6, 8, 9, 10]	2
Acetyl fentanyl	322.44	$C_{21}H_{26}N_2O$	[6, 8, 9, 10]	3
FIBF	368.49	$C_{23}H_{29}FN_2O$	[6, 8, 9, 10]	4
Carfentanil	394.51	$C_{24}H_{30}N_2O_3$	[6, 8, 9, 10]	5
4-ANPP	280.41	$C_{19}H_{24}N_2$	[6, 8, 9, 10]	6
Butyryl fentanyl	350.50	$C_{23}H_{30}N_2O$	[6, 8, 9, 10]	7
Acrylfentanyl	334.45	$C_{22}H_{26}N_2O$	[6, 8, 9, 10]	8
(±)-*trans*-3-methyl Fentanyl	350.50	$C_{23}H_{30}N_2O$	[6, 8, 9, 10]	9
U-47700	329.26	$C_{16}H_{22}Cl_2N_2O$	[8, 9, 10]	10
Cyclopropyl fentanyl	348.48	$C_{23}H_{28}N_2O$	[9, 10]	11
Methoxyacetyl fentanyl	352.47	$C_{22}H_{28}N_2O_2$	[9, 10]	12
Valeryl fentanyl	364.52	$C_{24}H_{32}N_2O$	[6, 8]	13
ortho-Fluorobutyryl fentanyl	368.49	$C_{23}H_{29}FN_2O$	[6, 8]	14
ortho-Fluorofentanyl	354.46	$C_{22}H_{27}FN_2O$	[6, 8]	15
Thiophene fentanyl	390.54	$C_{24}H_{26}N_2OS$	[9, 10]	16
Benzyl fentanyl	322.44	$C_{21}H_{26}N_2O$	[8, 9]	17
U-49900	357.32	$C_{18}H_{26}Cl_2N_2O$	[9]	18
NPP	203.28	$C_{13}H_{17}NO$	[10]	19
β-Hydroxythiofentanyl	358.50	$C_{20}H_{26}N_2O_2S$	[6]	20
Acetyl norfentanyl	218.29	$C_{13}H_{18}N_2O$	[8]	21
α-methyl Acetyl fentanyl	336.47	$C_{22}H_{28}N_2O$	[6]	22
Tetrahydrofuran fentanyl	378.51	$C_{24}H_{30}N_2O_2$	[9]	23
U-48800	343.29	$C_{17}H_{24}Cl_2N_2O$	[9]	24
Benzoylbenzyl fentanyl	370.49	$C_{25}H_{26}N_2O$	[9]	25

In addition to the top 11 compounds chosen to be detected in an evaluation method, our testing included additional compounds to aid in understanding overall instrument performance. Benzyl fentanyl (17th in the list) was included as a "safe" analog to evaluate its utility in replacing other, more toxic compounds in a test method. Benzyl fentanyl has a very low potency and is thought to be essentially inactive.[11] Recognizing that the choice of compounds to be detected may change with time or according to agency needs, a broader understanding of instrument performance was attempted by adding compounds to expand the molecular weight range and to test for differences among isomers. Specifically, acetyl

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norfentanyl (21st in the list) and norfentanyl were added to include low molecular weight compounds, crotonyl fentanyl was added as an isomer to cyclopropyl fentanyl, and valeryl fentanyl was added as another compound from the list (13th).

The sample set also included mixtures of fentanyl with heroin, procaine, and quinine, based on contents of seized materials[8-10, 12] [personal communication Amber Burns, Maryland State Police Forensic Science Division]. A suite of drugs that are generally present in instrument libraries, common in seized materials[13], or in pharmaceuticals likely to be counterfeited with fentanyl[14], were also tested for selectivity against the 11 fentanyl and fentanyl-related compounds. Other compounds commonly found in street level fentanyl samples, specifically mannitol, acetaminophen, caffeine, lactose, and inositol, do not pose matrix challenges for fentanyl detection by IMS[3, 15] and were not included in this study.

Experimental Methods

Instrumentation. Seven commercially available IMS trace detector platforms were used in development of this method, with a platform defined as a physical instrument and software configuration (Table S2). One instrument was operated both with and without a hardware adjustment provided in kit form by the manufacturer to introduce an internal calibrant, resulting in two platforms. Three instruments are from the Ionscan line of detectors (Smiths Detection*, Edgewood MD), three are from the Itemiser line (Rapiscan Systems, Torrance CA), and one is the QS-B220 (L3 Security and Detection Systems, Tewksbury, MA). The two older Ionscans (IS 500DT) are configured for illicit drug (pre-opioid crisis)

*Certain commercial equipment, instruments, or materials are identified in this paper in order to specify the experimental procedure adequately. Such identification is not intended to imply recommendation or endorsement by NIST, nor is it intended to imply that the materials or equipment identified are necessarily the best available for the purpose.

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and explosives detection or explosives detection only, and the newest model (IS 600) has a non-radioactive ionization mechanism and a pre-commercial software package designed specifically for fentanyl detection. The Itemiser platforms also include older instruments (DX) designed for explosives and pre-opioid crisis drug detection, and the newest (4DX) has a non-radioactive ionization mechanism but is not configured for fentanyl detection. The QS-B220 was designed for explosives and pre-opioid crisis drug detection. Thousands of these instruments in various platforms are deployed for screening purposes and could be repurposed for opioid detection, representing a useful population for testing purposes.

Because most platforms are not configured specifically for fentanyl detection, this study did not make any consideration of software determination of peak detection or alarms, and only the raw data was used to determine response metrics. Minor modifications in firmware settings were used, when possible, e.g., to increase the desorber temperature over the default settings employed for explosives detection. These modifications were based on our own experience and suggestions from the manufacturers but were not extensively tested and may not represent optimal conditions. The sampling time was adjusted (increased) to provide maximum removal of the sample during desorption by observing the temporal profile and ensuring a return to baseline. Details of each instrument platform including any modifications to operating conditions are given in Table S2. Given that most instruments were not marketed for fentanyl detection, the results of testing are informative to the range of possible performance results but are not meant to evaluate any given platform. As such, selected results are reported to represent the range in outcomes without linking the individual instrument platforms to specific results.

Materials and sample preparation. Samples were prepared by pipetting solutions onto the particle-collection wipe supplied with the IMS detector within the area designated as the heated area upon insertion.[16] Small volumes (< 5 μl) were deposited to confine the solution to this area, and samples were allowed to dry prior to use. Fentanyl, cocaine, oxycodone, ketamine, THC, and heroin were purchased from Cerilliant (Round Rock, TX, USA) as 1 mg mL^{-1} methanol solutions. U-47700, acetyl fentanyl,

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norfentanyl, and carfentanil were purchased as 1 mg mL^{-1} methanol solutions from Cayman Chemicals (Ann Arbor, MI, USA). *Trans*-3-methyl fentanyl, valeryl fentanyl, crotonyl fentanyl, cyclopropyl fentanyl, butyryl fentanyl, acrylfentanyl, benzyl fentanyl, furanyl fentanyl, acetyl norfentanyl, and *p*-FIBF were purchased from Cayman Chemicals as neat solids (1 mg) and diluted in 2 mL of LC/MS-grade methanol (Millipore-Sigma, St. Louis, MO, USA) to create 0.5 mg mL^{-1} methanol solutions. Solid procaine and quinine (Millipore-Sigma) were dissolved in LC-MS-grade methanol to create 1 mg mL^{-1} stock solutions. Further dilutions of stock solutions were completed volumetrically using LC-MS-grade methanol.

For measurements of reduced mobility (K_0), 25 ng to 500 ng (though typically 25 ng or 50 ng) of analyte was deposited onto each wipe depending on the specific substance and the instrument being tested. Binary mixtures containing heroin, procaine, or quinine in addition to fentanyl were prepared by co-depositing single analyte solutions serially onto the wipes. Heroin was co-deposited with fentanyl at mass ratios of 10:1 and 100:1, depositing 25 ng or 50 ng of fentanyl, depending on the instrument under test, and the corresponding mass of heroin. Procaine and quinine were co-deposited, individually, with fentanyl at 100:1, again with respect to 25 ng or 50 ng of fentanyl. Samples of fentanyl and benzyl fentanyl were prepared for sensitivity measurements, depositing from 0.25 ng to 30 ng and preparing a minimum of 20 loaded samples for each instrument. Because of the relatively large numbers of samples needed, benzyl fentanyl was included to evaluate its potential role as a substitute for fentanyl in sensitivity testing.

Safety Considerations: All instruments were operated in "particle mode", where material collected on a wipe was heated to remove the sample from the wipe as a vapor for ionization and detection. Sample vapors were drawn towards the ionization region from the desorber/inlet region during preset sampling times, which usually lasted from 5 s to 15 s. After sampling and during idle times, a countercurrent airflow, which was always present, vented through the inlet and towards the space occupied by the operator. It was possible for residual vapors to be incorporated into this exhaust, and for this reason, we

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conducted all work within a chemical fume hood. This may represent an excess of caution but was considered prudent given the total amount of material used in extensive testing of the instruments. For one instrument, tubing was added to adequately exhaust vapors from the instrument to the hood. Sampling times were increased, if necessary, to ensure complete removal of the sample and avoid continued production of sample vapors during idle times when the flow was toward the operator.

Following sample analysis, the IMS detector may contain residual contamination that could present a hazard to someone who breaches the cover of the instrument, e.g., during maintenance procedures. To return the instruments to general use after fentanyl testing, we conducted a thorough cleaning which also involved replacement of selected parts. Tubes, filters and o-rings that could have been exposed to fentanyl vapors were replaced when possible, and in consultation with the instrument manufacturers. Specific steps taken for each instrument are given in the Table S2.

Dissolution of solid standards was completed in a fume hood with the use of an N-95 respirator to reduce the risk of accidental exposure. Nitrile gloves were worn to protect hands from any contact with powders and solutions, which is considered sufficient to mitigate dermal exposure[17], and safety glasses with side shields were worn for eye protection. All samples were prepared in a dedicated area in a benchtop hood exhausted through HEPA filtration. Samples were analyzed within a few days of preparation and were disposed of in dedicated waste containers. All consumables, including pipette tips, foil-based benchtop protection, paper wipers, etc., were likewise disposed of in dedicated waste containers.

Data collection and analysis. Reduced mobilities were measured for fentanyl and 15 fentanyl-related substances on all instruments under operating conditions given in the Table S2 (7 complete datasets). Three of the instruments provided firmware calculations of K_0 based on drift time (t_d), whereas the other three did not. For the instruments that only reported t_d, K_0 was calculated by reference to cocaine according to Equation 1, where $K_0^{coc} = 1.160$ cm^2 V^{-1} s^{-1}, and t_d^{coc} was taken from the instrument library

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or measured directly. Some instruments use cocaine as a calibrant for positive ion mode and may provide updated t_d measurements for cocaine following calibration; these values were used if available.

$K_0 = (t_d^{coc} K_0^{coc}) / t_d$ Equation 1

At least 3 samples of each compound were analyzed to determine an average value of K_0, with the uncertainty calculated as the standard deviation. For fentanyl, 8 to 11 samples were analyzed over multiple days to provide a better estimate of reproducibility. Instrument responses were also measured for heroin, THC, cocaine, oxycodone and ketamine, in addition to the excipients, procaine and quinine. Methamphetamine is well separated in reduced mobility from the fentanyl-related substances[15], and was not considered a possible interference, and so was not tested here. Ketamine is found in IMS instrument libraries and may be of concern in certain applications, and so was included in our testing.

Mixtures of fentanyl with heroin, procaine, and quinine were evaluated to determine effects on fentanyl peak position and intensity. Between 3 and 5 replicates were performed for each mixture. The number of analyte peaks was noted, and the peak nearest to fentanyl was evaluated to determine any shift in K_0 from the average measured for pure fentanyl. The intensity of the fentanyl peak in the mixture was compared to the intensity measured for pure fentanyl at the same mass loading.

Estimates of the limit of detection (LOD) for fentanyl and benzyl fentanyl in each IMS detector were determined using the ASTM E2677 Web-based Standard Test Method for Limits of Detection. Most commercial IMS instruments process raw data in a way that prevents true peak intensity measurements near 0, providing what is referred to as censored data, and the statistical approach used in ASTM E2677 was designed to account for this. IMS data may also exhibit non-linear dose responses and non-uniform measurement variations across dosing levels, which were also considered in developing ASTM E2677. The method requires replicate (n = 10 or more) measurements of each compound at two dosing values near the LOD, as well as replicate measurements (n = 10 or more) of process blanks when those blanks give non-zero responses. Dose/response pairs were input to the Webtool at https://www-s.nist.gov/loda/

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under default settings, which calculated the estimate of LOD90 with alpha and beta risks both equal to 10 %. The 90 % Upper Confidence Limit (UCL) for the LOD90 was also calculated, which was a measure of uncertainty in the estimate.

Results

Reduced Mobility Values

All instruments produced a primary characteristic peak for each fentanyl-related substance, with reduced mobilities across instrument platforms reproduceable to better than ± 0.008 $cm^2\ V^{-1}\ s^{-1}$ (Table 2). This level of reproducibility was consistent with what is expected in general for IMS and implies that the product ion peak for each compound is the same across instruments. The instruments used a variety of ionization mechanisms, including Ni^{63} and corona discharge, in combination with different selections of dopant gases, and it is notable that the product ion peaks appear to be consistent. Drug compounds typically generate $[M+H]^+$ product ions in IMS[18], which was probably the case for the fentanyl compounds as the correlation between K_0 and molecular weight was strong (Figure 1). Secondary product ion peaks of lower intensity were observed for some compounds on some of the instruments, but not consistently and not across all instrument platforms. Secondary product ion peaks have also been reported by Zaknoun et al.[19] for a subset of tested fentanyl analogs on one commercial IMS instrument

Although all 11 compounds could be detected, they would not all be uniquely identified, with the number dependent upon the specific detection algorithms developed for each instrument. Detection windows are typically set at a fixed width about the expected peak position as determined for an individual instrument, wide enough to capture true peak variation while limiting false positives from compounds with similar reduced mobilities. Variability in reduced mobility arises from limitations in resolution and instabilities in instrumental operating conditions (e.g., temperature, humidity, and pressure) that are typically addressed with internal or user-prompted calibration procedures. Representative results for the reduced mobility values of fentanyl from individual instruments are given in

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Table 3 to illustrate the range in average values and uncertainties. Instrument 1 represents the lowest variability observed in reduced mobility and instrument 3 the highest. Instrument 2 had consistently lower K_0 values for all compounds compared to the average, and instrument 3 had consistently higher values of K_0.

The minimum detection window width typically used in commercial IMS instruments for reduced mobilities near fentanyl is ± 0.003 $cm^2\ V^{-1}\ s^{-1}$.[15] This width could be appropriate, e.g., for instrument 1 in Table 3, but would probably be too narrow for instruments 2 and 3, and so represents a best-case scenario. Given a detection window of ± 0.003 $cm^2\ V^{-1}\ s^{-1}$ and evaluating the data from the highest resolution instruments, only 9 detection channels would be possible. Furanyl fentanyl and FIBF would overlap, as would butyryl fentanyl and *trans*-3-methyl fentanyl, and *trans*-3-methyl fentanyl and cyclopropyl fentanyl. Instruments with less selectivity such as instruments 2 and 3 in Table 3 might have additional overlaps, e.g., ± 0.006 $cm^2\ V^{-1}\ s^{-1}$ detection windows would lead to overlaps of acrylfentanyl and fentanyl, and U-47700 and acetyl fentanyl. Additional factors such as desorption characteristics[20], peak shape, and the presence of secondary peaks, as mentioned earlier, can also be used to improve selectivity over the simple evaluation presented here.

Analysis of Binary Mixtures

Additional sample components that produce peaks in positive ion mode may cause a shift, or bias, in the position of the fentanyl (or other fentanyl-related substance) peak.[3] In the case of binary mixtures of heroin and fentanyl, only one instrument had the resolution to produce separated peaks of the two drugs; the one specifically configured for fentanyl detection. For all remaining instruments a single, combined peak was observed that was typically shifted towards heroin (instruments 2 and 3 in Table 3). This shift can be used to indicate the presence of a mixture of heroin and fentanyl, but it must be recognized and coded into the detection algorithm. Even when additional components produce peaks that are resolved from the target analyte, there may still be increased variability in peak position. For

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example, the shifts in fentanyl peak position in binary mixtures with quinine shown in Table 3 were significant for instruments 1 and 3 when compared with the variability for the pure compound. The direction of the shift due to the presence of quinine was not consistent, and the cause was unclear but indicative of problems in resolution. The intensity of the fentanyl peak, however, was relatively unaffected by the presence of quinine. Procaine, on the other hand, reduced the intensity of the fentanyl peak for all the instruments, with the reduction ranging from 80 % to 100 % (no peak observed). This is presumably due to the higher proton affinity of procaine over fentanyl, which could be addressed by changes in dopant chemistry to try to favor ionization of fentanyl.

Table 2. Average and standard deviation in measured K_0 (K_0^{meas}) from 7 instruments. K_0 values calculated from the polynomial fit in Figure 2 (K_0^{calc}). Measurements of other drugs provided to show proximity in K_0 to the fentanyl-related substances.

Compound	K_0^{meas} ($cm^2\ V^{-1}\ s^{-1}$)	Molecular Weight (Da)	K_0^{calc} ($cm^2\ V^{-1}\ s^{-1}$)	K_0^{meas}-K_0^{calc} ($cm^2\ V^{-1}\ s^{-1}$)
Ketamine	1.371 ± 0.007			
Procaine	1.301 ± 0.010			
Hydrocodone	1.18‡			
4-ANPP	1.172 ± 0.008	280.41	1.175	-0.003
Oxycodone	1.167 ± 0.004			
Cocaine	1.161 ± 0.004			
Alprazolam	1.15‡			
Quinine	1.102 ± 0.003			
U-47700	1.094 ± 0.003	329.26	1.070	0.024
Acetyl fentanyl	1.086 ± 0.005	322.44	1.083	0.003
Acrylfentanyl	1.065 ± 0.005	334.45	1.061	0.005
Fentanyl	1.056 ± 0.005	336.47	1.057	-0.001
THC	1.052 ± 0.007			
Heroin	1.044 ± 0.006			
Cyclopropyl fentanyl	1.034 ± 0.005	348.48	1.037	-0.003
trans-3-methyl Fentanyl	1.028 ± 0.006	350.50	1.034	-0.006
Butyryl fentanyl	1.027 ± 0.006	350.50	1.034	-0.007
p-FIBF	1.010 ± 0.007	368.49	1.007	0.003
Furanyl fentanyl	1.009 ± 0.006	374.47	0.999	0.010
Carfentanil	0.981 ± 0.005	394.51	0.975	0.006
Buprenorphine	0.91§			

‡From reference [15].
§From reference [3].

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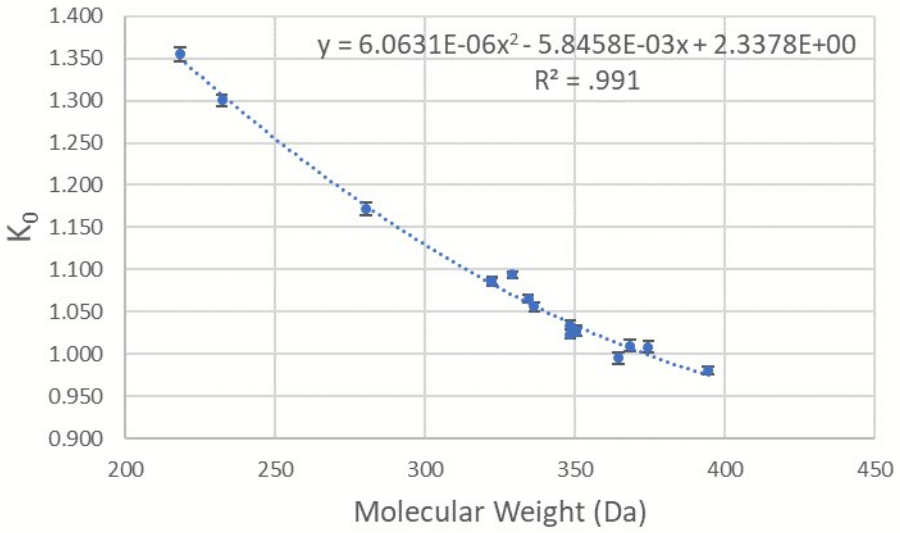

Figure 1. Average measured K_0 ($cm^2\ V^{-1}\ s^{-1}$) as a function of molecular weight for fentanyl and the 10 fentanyl-related substances reported in Table 2 and norfentanyl, acetyl norfentanyl, benzyl fentanyl, crotonyl fentanyl, and valeryl fentanyl. Measured values represent the average and standard deviation across 7 instrument platforms.

Table 3. Representative results from 3 instruments for K_0 of fentanyl (n = 10) and the shift from this value in mixtures (ΔK_0). Peak intensities for fentanyl peak in mixtures (I) relative to pure fentanyl (I_0) at the same mass loadings reported (I/I_0). 'NP' reported for samples with no fentanyl peak. Specific instruments were randomly assigned a number from 1-3.

	Inst. 1		**Inst. 2**		**Inst. 3**	
	K_0 ($cm^2\ V^{-1}\ s^{-1}$)		**K_0 ($cm^2\ V^{-1}\ s^{-1}$)**		**K_0 ($cm^2\ V^{-1}\ s^{-1}$)**	
Pure Fentanyl	1.0583 ± 0.0005		1.0518 ± 0.0019		1.0645 ± 0.0025	
Mixtures	**ΔK_0**	**I/I_0**	**ΔK_0**	**I/I_0**	**ΔK_0**	**I/I_0**
1:10 Heroin	-0.0003	0.96	-0.0081	1.02	0.0001	1.45
1:100 Heroin	0.0008	0.84	-0.0077	1.07	-0.0058	1.32
1:100 Procaine	0.0002	0.18	-0.0067	0.12	NP	0
1:100 Quinine	-0.0028	1.09	0.0029	0.84	-0.0153	0.89

Instrument Sensitivities

The LOD90s for fentanyl and benzyl fentanyl ranged from sub-nanogram to 10s of nanogram levels over all instruments studied (Table 4). Peak intensities were quite variable in these instruments

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even at single dosing levels, which led to an LOD90 value for fentanyl for instrument 1 that was higher than the highest dosing level used in the measurement (30 ng). Considering the uncertainties represented by the 90 % UCL, there was not a significant difference in sensitivity between fentanyl and benzyl fentanyl, and the results for either analyte were sufficient to characterize an instrument. Although LOD90s were not determined for the remaining fentanyl-related substances, there were no obvious differences observed in sensitivity within a single instrument for the fixed dosing levels used during the measurement of reduced mobilities.

Table 4. Representative results from 3 instruments for LOD90s and 90% UCLs for fentanyl and benzyl fentanyl. Random instrument number assignment different from Table 3.

	Inst. 1		Inst. 2		Inst. 3	
Compound	**LOD90 (ng)**	**90% UCL (ng)**	**LOD90 (ng)**	**90% UCL (ng)**	**LOD90 (ng)**	**90% UCL (ng)**
Fentanyl	51.7	87.5	7.0	13.5	0.6	1.0
Benzyl fentanyl	34.6	63.9	10.8	16.5	0.5	0.9

Proposed Test Method

Of the proposed 11 compounds for testing, three pairs would not be separable based on resolution; specifically furanyl fentanyl and FIBF, butyryl fentanyl and *trans*-3-methyl fentanyl, and cyclopropyl fentanyl and *trans*-3-methyl fentanyl. Our testing indicates that within a single instrument, there is very little difference in sensitivity with respect to compound, and therefore one compound could be chosen to represent each pair. These pairs are identified in Table 5, with the choice for the compound to use in testing appearing first in line, and the non-tested compound appearing in parentheses. The choice of furanyl fentanyl over FIBF as the tested compound is based on safety, as the potency of furanyl fentanyl is known and relatively low at 20 times relative to morphine[21] whereas the potency of FIBF has not been reported. Butyryl fentanyl and cyclopropyl fentanyl may be resolved from each other, and so should be independently tested, whereas *trans*-3-methyl fentanyl is redundant and potent (400 times relative to morphine).[21] The potential use of secondary product ion peaks or additional data

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discriminators might lead to improved resolution, which might help to separate overlapped pairs in Table 5 and lead to higher resolution. Instruments with higher resolutions than those evaluated in this study may exist or could be developed. This could be tested by simply adding in the detectable compounds considered redundant in Table 5.

The 9 compounds to be tested are fentanyl, carfentanil, furanyl fentanyl, butyryl fentanyl, cyclopropyl fentanyl, acrylfentanyl, acetyl fentanyl, U-47700, and 4-ANPP. Our data indicates that a common dosing level of 100 ng per compound using solution deposition onto instrument-specific blank substrates as detailed in the Experimental Methods is appropriate for all tested instrument platforms. Methanol solutions are compatible with all substrate types specific to these instruments, including woven and Teflon-coated substrates. After drying, each loaded sample would be inserted into the instrument to determine the presence or absence of an alarm. Depending upon user needs, the alarm could report specific compound names or provide generic results such as “threat” or “fentanyl-related”. The number of replicates is based on the level of statistical certainty desired in the results and again, would be user or application specific.

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Table 5. Elements comprising proposed method for evaluating IMS detectors for fentanyl detection. Compounds considered redundant in testing are identified in parentheses.

1) Detected Compounds[1]	2) Fentanyl Detection with Additives	3) Tests for False Positives	4) Sensitivity[2,3]
Fentanyl	1:10 Heroin	Hydrocodone	Benzyl fentanyl
Carfentanil	1:10 Procaine[2]	Oxycodone	
Furanyl fentanyl (FIBF)	1:10 Quinine[2]	Alprazolam	
Butyryl fentanyl (*trans*-3-methyl fentanyl)		Cocaine	
Cyclopropyl fentanyl (*trans*-3-methyl fentanyl)		Heroin	
Acrylfentanyl		THC[4]	
Acetyl fentanyl		Buprenorphine	
U-47700		Quinine	
4-ANPP			

[1]100 ng dosing levels
[2]Recommended but not critical
[3]Use ASTM E2677
[4]See problems addressed in text

Following analysis of the target compounds, the additives listed in Table 5 would be used to prepare mixtures with fentanyl in the stated proportions. Samples could be prepared as described in the Experimental Methods by codepositing solutions containing fentanyl with those containing heroin, procaine, or quinine. The critical issue with the additives is the possibility of a shift in fentanyl peak position or depression of the fentanyl peak, which is based on the relative proportions of fentanyl and the additives, and not the overall availability of fentanyl sample. Therefore, the amount of fentanyl can be kept at 100 ng, with corresponding levels of the additives at 1 μg, rather than reducing the fentanyl amount to 10 ng to keep the entire sample at 100 ng. The relative amount of heroin is based on case samples[12], but the same information is not available for procaine. Quinine may also be a regional additive and not appropriate for all parts of the country. For those reasons, mixtures with procaine and quinine are recommended rather than critical. To ensure that fentanyl, rather than any of the additives, are detected in

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the mixtures, alarms should be clearly identified by compound name and/or any alarms for the additives should be turned off.

All instruments follow-up a detection event with a process to purge any remaining analyte and return the system to background levels. Process blanks (substrate with methanol blank) should be used periodically to test this process during the measurements of detected compounds and fentanyl mixtures to record the false positive rate. Law enforcement applications will require additional measures of false positives to ensure discrimination against other common drugs and non-threat materials. Hydrocodone, oxycodone, cocaine, and alprazolam are commonly encountered, either in true pharmaceutical preparations that must be distinguished from counterfeit fentanyl-containing tablets or as street-level drugs. The identification of these compounds would be more diagnostic than a simple lack of an alarm, and it might be useful to add them to the detection library. Buprenorphine is found in pharmaceutical products (e.g., Suboxone) and is of concern in the opioid crisis, and it may be close enough in reduced mobility to overlap with the detection of carfentanil. Quinine is close in reduced mobility to U-47700 and should be tested for false positives if it was not already tested in mixtures with fentanyl. Samples containing 100 ng of each of the false positive compounds listed in Table 5 should be prepared and analyzed to determine the absence of an alarm for the 11 fentanyl and fentanyl-related compounds. Acceptable results include the absence of any alarm and/or the identification of the specific non-fentanyl related compound.

THC will be the compound most likely to generate false positives during testing because its reduced mobility is very close to fentanyl. Samples made from solution-deposited pure THC are likely to overestimate the false positive rate that would result from sampling marijuana plant residues, due to the relatively low concentrations of THC in the plant and the difficulties observed in detecting THC from marijuana with IMS.[15] Reproducible testing with the plant is difficult due to a lack of reference materials and sample preparation techniques. Synthetic cannabinoids are another emerging class of compounds that might be encountered in law enforcement activities and may pose an interference with fentanyl-related

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substances. These samples might present as papers, textiles, or plant materials onto which the cannabinoid was sprayed. Reduced mobilities reported from a study of 25 synthetic cannabinoids[22] range from 0.807 to 1.051 $cm^2\ V^{-1}\ s^{-1}$, representing a considerable overlap with the range reported here for the fentanyl-related substances. For THC and synthetic cannabinoids, more detailed information is needed about the form of the samples to know whether they can be easily segregated on the basis of appearance from the general population of samples and analyzed with alternate techniques, which would avoid the issue of overlaps with fentanyl-related substances.

All instruments evaluated in this study were sufficiently sensitive to fentanyl and fentanyl-related substances to warrant a common dosing level of 100 ng per compound for testing purposes. There are circumstances where a lower LOD may be required, and a test of sensitivity would be useful to discriminate among instruments. Sensitivity tests will not be needed for all applications, but where they are, we recommend testing a single analyte, benzyl fentanyl, using ASTM E2677, which was designed specifically for the processed data common to these instruments. Benzyl fentanyl yields information on sensitivity that is equivalent to measurements of fentanyl and is a safer alternative.

Modifying Detected Compounds List

The compounds seen in the opioid crisis are changing rapidly, and the list presented in Table 1 from which the 11 detected compounds were drawn is necessarily dated and skewed towards publicly available information. As new compounds arise, or existing compounds become more prevalent, the relationship between molecular weight and K_0 values given in Figure 1 can be used as a first step in adding new compounds to the detected compound list. The fit in Figure 1 was calculated from the reduced mobilities of the primary peaks for the 11 detected fentanyl-related compounds in addition to benzyl fentanyl, crotonyl fentanyl, valeryl fentanyl, acetyl norfentanyl and norfentanyl. The addition of the two metabolites was important to extending the range of molecular weights over which the prediction of reduced mobilities applies. For fentanyl-related compounds lighter than fentanyl, the measured values

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were within ± 0.007 $cm^2 V^{-1} s^{-1}$ of the predicted values, except for U-47700, which is structurally different from fentanyl. For fentanyl analogs heavier than fentanyl there was more potential for deviation from the predicted values, with crotonyl fentanyl (an isomer of cyclopropyl fentanyl) exhibiting a deviation of -0.013 $cm^2 V^{-1} s^{-1}$, and valeryl fentanyl exhibiting a deviation of -0.017 $cm^2 V^{-1} s^{-1}$. Structurally unrelated drugs, such as ketamine and THC, have reduced mobilities that deviate significantly from the trend exhibited by the fentanyl-related substances, which indicates that the model is specific to elements of the fentanyl structure.

Additional compounds from Table 1 were measured during the course of this study and could be added to Table 5 without any additional study. Valeryl fentanyl is sufficiently separated in reduced mobility from carfentanil and furanyl fentanyl that it would require separate testing. Acetyl norfentanyl would also require separate testing and would necessitate the addition of ketamine to the list of compounds tested for false positives. Benzyl fentanyl is not separated in reduced mobility from its structural analog acetyl fentanyl and would not require separate testing, particularly if it is already included as part of sensitivity testing. Fluorobutyryl fentanyl was evaluated in Sisco et al.[3] on a single instrument where it was separated in reduced mobility from FIBF and would need to be independently tested. For the remaining compounds, estimates could be made of potential overlaps based on the calculated reduced mobilities. Methoxyacetyl fentanyl, with a molecular weight of 352.47 Da, has a calculated $K_0 = 1.031$ $cm^2 V^{-1} s^{-1}$, which is likely to put it near *trans*-3-methyl fentanyl and cyclopropyl fentanyl, where there is already significant overlap. Molecular weights between 350 and 360 Da are the most common for compounds in Table 1, and common for other known fentanyl analogs (Table S1).

Conclusions

The method proposed here provides a basic level of validation for the detection of fentanyl and fentanyl-related substances by IMS by specifying 11 compounds to detect, 3 confusants to add to fentanyl samples, 8 compounds to use in false positive testing, and a single compound to use for sensitivity

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measurements. IMS manufacturers are currently developing algorithms to enable fentanyl detection in their trace detectors, and this method can apply as those instruments become available. Baseline measurements from a current suite of commercial IMS instruments indicate that all can detect the required compounds, but that differences in resolution among the instruments may affect their ability to separate the compounds from each other. The confusants, including heroin, procaine, and quinine, reflect the compositions of known samples from seizure, and can affect the ability of some instruments to detect fentanyl, either by depressing the signal or by shifting the characteristic peak. The compounds chosen for false positive testing include common illicit drugs or pharmaceuticals, all of which, with the possible exception of THC, can be separated from the list of detected compounds. All instruments were capable of nanogram level detection, with measured LOD90 values ranging from subnanogram to 10s of nanograms, and measurements of sensitivity using ASTM E2677 and benzyl fentanyl provides a metric to discriminate among instruments.

While providing a basic level of testing, the method described here does not address all expected sources of error, particularly those arising from deployed field conditions. Dirty environments that include airborne or surface contaminants can add background signal in the channels of interest for compound detection. One approach is to add a standard dirt during testing, as outlined in ASTM E2520-15 Standard Practice for Measuring and Scoring Performance of Trace Explosive Chemical Detectors. Known or expected contaminants in specific deployments could be added to the testing regime, as was done in Sisco et al.[3], e.g., to include contaminants expected on the outside of plastic bags. Another approach is to measure the contribution of environmental background to the IMS signal by analyzing large numbers of true negative samples on field-deployed instruments.[23]

The compounds chosen for false positive testing were based on seized illicit drugs and thus appropriate in general for law enforcement and border protection activities. For mail screening activities, other substances might be of concern when discriminating against fentanyl and fentanyl-related substances, including steroids and bulk supplements. It is also expected that novel fentanyl-related

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substances might be present in mail screening, including both active compounds and precursors. It is possible to open detection channels to encompass a large range of known and potential compounds, and K_0 values calculated from the range of known molecular weights could be used for this purpose. This approach would necessarily require significantly expanded tests of false positives drawing upon knowledge of the compounds expected in the environment.

Finally, the method proposed here calls for 100 ng testing levels, and a practical approach for sample preparation is by solution deposition directly onto the wipes used for each instrument. Residues of solid samples might exceed 100 ng levels, or the application may call for sampling bulk powder or pharmaceutical tablets. Introduction of large sample amounts can adversely affect instrument performance by saturating the detector and producing contamination levels that are difficult to clear down. Large samples can also shift the reduced mobility of characteristic peaks and produce additional, nonrepresentative peaks, leading to false identifications.[15] A method for appropriately sampling bulk materials using a fine needle probe was proposed in Verkouteren and Staymates [15] and adopted successfully by Zaknoun et al.[19] for field detection of bulk seized drugs containing fentanyl. For applications considering analysis of bulk samples, an extension to the method described here to include sampling from bulk powders might be useful.

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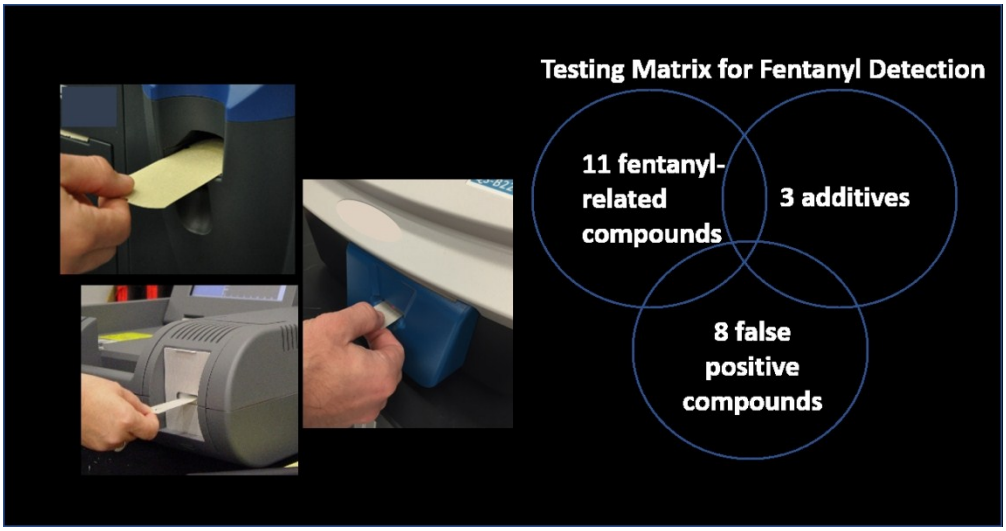

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