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NON-CONTACT DETECTION OF FENTANYL AND OTHER SYNTHETIC OPIOIDS

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EIN: / DUNS:

Project start/end date: September 29, 2019 – September 30, 2021
Award Amount: $605,696
Reporting term: Final Report
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Recipient: National Institute of Justice
Department of Justice, Office of Justice Programs
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Washington, DC 20531

Summary of the Project

The overall goal of the project is to develop a method for detecting fentanyl and related substances without manipulation or handling of the hazardous material. The significant potency of fentanyl, as well as the exponential increase in its recreational use, drives the need for a non-contact detection method. Increased instances with fentanyl pose a fatal occupational hazard for law enforcement and other first responders. Unfortunately, current protocol for detecting fentanyl require direct contact, manipulation, or destruction of the substance. Ion-mobility spectrometry (IMS) has become the standard as a detector for explosives and narcotics at ports and airports and can be utilized in vapor mode for non-contact detecting. The development of a field-portable, handheld IMS method for detection of fentanyl will provide for presumptive identification of fentanyl to increase safety for first responders. The project was conducted through the following specific aims:

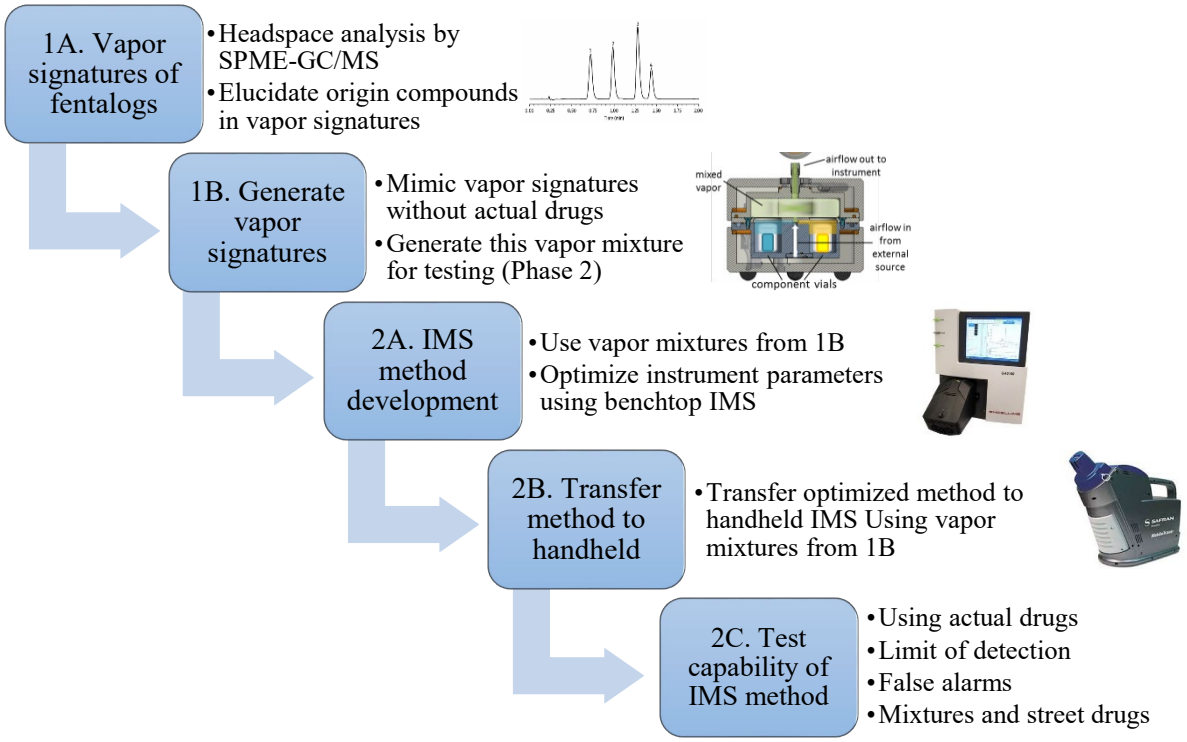
Specific Aim 1: Determination and generation of vapor signatures for fentanyl and structurally-related compounds

Aim 1 is comprised of two tasks, vapor signature determination (1A), and vapor signature generation (1B). In Task 1A, a method for the headspace analysis of fentanyl by using solid phase microextraction (SPME) coupled with gas chromatography and mass spectrometry (GC-MS) was optimized. The vapor signatures of pharmaceutical-grade fentanyl, confiscated fentanyl exhibits, and fentalogs (fentanyl analogs) were then determined using the optimized SPME-GC-MS method and compared. Common compounds in the vapor profiles were selected as target analytes for Aim 2. In Task 1B, mimic vapor signatures containing the target components were generated allowing for IMS method development without requiring the use of actual drugs.

Specific Aim 2: Detection of fentanyl vapor signature by benchtop IMS and handheld IMS

The primary goal of Aim 2 was to develop a detection method for fentanyl vapor by ion mobility spectrometry (IMS) by using the determined target analytes from Specific Aim 1. Aim 2 was divided into three tasks. In Tasks 2A and 2B, methods for fentanyl detection were developed and optimized for a high-resolution benchtop IMS, as well as a handheld IMS device, respectively. Task 2C, the optimized handheld IMS method was used for detection of pure drugs, mixtures, and street drugs, moving from pure standards to laboratory-prepared mixtures, and finally street drugs method. Limits of detection and false alarms were also assessed.

Overview of project



PARTICIPANTS & OTHER COLLABORATING AGENCIES:

Participant 1:

Name:	Lauryn E. DeGreeff, Ph.D.
Project Role:	PI
Nearest person month worked:	4
Contribution to Project:	Dr. DeGreeff has worked to develop testing and development protocols, procured all samples, overseen daily laboratory work, and reporting. She also has mentored Drs. Vaughan, Fulton and Smith as well as Ms. Forte during her summer internship experience.
Funding Support:	Support from other sponsors for other projects include DoD and DHS
Collaborated with individual in foreign country:	No

Participant 2:

Name:	Stephanie R. Vaughan, Ph.D.
Project Role:	Post-doctoral Researcher
Nearest person month worked:	15
Contribution to Project:	Dr. Vaughan has worked to optimize the headspace analysis protocols. Using this method she has performed headspace analysis of pharmaceutical-grade fentanyl, laboratory adulterated fentanyl, and confiscated fentanyl She has authored two published manuscript for the project.
Funding Support:	NRC Research Associateship Program
Collaborated with individual in foreign country:	No

Participant 3:

Name:	Kenneth Furton, Ph.D.
Project Role:	PI for Florida International University
Nearest person month worked:	2

Contribution to Project:	Oversee FIU graduate student and procurement of field-relevant samples. Dr. Furton also assists in report-writing.
Funding Support:	Faculty
Collaborated with individual in foreign country:	No

Participant 4:

Name:	Leann Forte
Project Role:	Graduate Student (Florida International University)
Nearest person month worked:	24
Contribution to Project:	Ms. Forte has worked on experiments relating to the degradation of pharmaceutical-grade fentanyl.
Funding Support:	
Collaborated with individual in foreign country:	No

Participant 5:

Name:	Charles D. Smith, Ph.D.
Project Role:	Post-doctoral Researcher
Nearest person month worked:	4
Contribution to Project:	Dr. Smith has worked on method development for the benchtop IMS. He has been successful in detecting NPPA and NPP in the liquid phase, and NPPA in the gas phase. He has authored one manuscript that is under internal review.
Funding Support:	NRC Research Associateship Program
Collaborated with individual in foreign country:	No

Participant 6:

Name:	Ashley C. Fulton, Ph.D.
Project Role:	Post-doctoral Researcher

Nearest person month worked:	9
Contribution to Project:	Dr. Fulton has completed the method development for the handheld IMS. She has authored one manuscript draft and is currently working on another manuscript.
Funding Support:	ASEE Research Associateship Program
Collaborated with individual in foreign country:	No

Partner Organization:

Organization Name:	Florida International University - International Forensic Research Institute
Location of Organization:	Miami, FL
Partner's Contribution:	Collaborative Research
More detail on partner organization:	Domestic

OUTCOMES

Significant Results

Specific Aim 1: Determination and generation of vapor signatures for fentanyl and structurally-related compounds

A standard operating procedure (SOP) was developed for handling fentanyl and pharmaceutical-grade materials were obtained from Cayman chemical. Using this material, a SPME extraction method for headspace analysis of fentanyl was developed and optimized. Extraction temperature, equilibration time at the extraction temperature, extraction time and fiber coating were optimized. All analysis was done by GC-MS (GC-MS parameters are given in the published manuscript "Identification of volatile components in the headspace of pharmaceutical-grade fentanyl", full reference below). Using the developed method, generation of a vapor profile for pharmaceutical-grade fentanyl was determined. The main vaporous components from the

headspace of pharmaceutical-grade fentanyl were identified as: heptane, styrene, benzaldehyde, aniline, N-phenylpropanamide (NPPA), Unknown, N-phenethyl-4-piperidone (NPP), and 1-phenethyl-4-propionyloxypiperidine. From this, potential targets of interest were identified as NPPA, NPP, 1-phenethyl-4-propionyloxypiperidone, and the Unknown compound. Attempts to elucidate the identity of the unknown were carried out by comparison to NIST and SWGDRUG libraries and using high resolution mass spectrometry; however, to date, the unknown has not been identified.

The headspaces of confiscated fentanyl exhibits, as well as, fentalogs was carried out in cooperation with the Maryland State Police Forensic Sciences Division Laboratory, the DEA Special Testing and Research Laboratory, and the United States Army Combat Capabilities Development Command (CCDC). Comparative analysis of vapor profiles of fentalogs, confiscated exhibits, and lot-to-lot comparisons with the pharmaceutical-grade material revealed two targets of interest: NPPA and NPP. Out of the fourteen street-grade fentanyl exhibits, ten contained NPPA in the headspace while none contained NPP. A total of six fentalogs were sampled, with three containing NPPA and two containing NPP in the headspace. It should be noted that pharmaceutical-grade fentanyl contains both NPP and NPPA in the headspace. Thus, it is thought that NPPA is a target for identification of fentanyl and related substances in vapor phase, while NPP is a target more specific to fentanyl. Of the 20 confiscated fentanyl materials and fentalogs tested, only five did not contain either NPPA or NPP. For four of these five samples, the non-detection was likely due to instrument sensitivity, as these materials were all significantly diluted by several adulterants. Details of this comparative analysis is found in the manuscript entitled "Comparative analysis of vapor profiles of fentalogs and illicit fentanyl", which has been accepted to *Analytical and Bioanalytical Chemistry* September 2021.

Specific Aim 2: Detection of fentanyl vapor signature by benchtop IMS and handheld IMS

First, a method for the detection of NPPA and NPP in solution using an Excellims benchtop IMS with electrospray ionization (ESI) was developed, followed by detection of analytes in the vapor phase using secondary electrospray ionization (SESI). In a solution of 80:20 methanol:water, 5 – 10 ppm of NPPA or NPP were detected using direct injection of the analytes in solution into the IMS. After successful detection in solution, vapor phase identification was achieved by placing the NPPA in the Mixed Vapor Generator (MV-Gen) to actively deliver analyte vapor to the IMS. When delivered in the vapor phase, NPPA required protonation by reactant ions to be detected. Here, the analyte vapor enters the instrument source by a transfer capillary. Reactant ions were delivered perpendicular to the analyte vapor stream. After testing reactant ions produced from several strong and weak acids at varying concentration, it was determined that optimal detection was achieved when a 0.5 ppm solution of HCl in methanol was injected perpendicular to the vapor stream prior to ionization. The resulting reduced ion mobility of NPPA was 1.46 (±0.01) $cm^2/V\text{-}1s^{-1}$. Further details of this approach will be included in "Detection of N-phenylpropanamide vapor from fentanyl materials by secondary electrospray ionization with ion mobility spectrometry", which is under internal security review and expected to be submitted to *Analytica Chimica Acta* in October 2021. After testing a variety of ionization mechanisms, satisfactory detection of NPP in the vapor phase was not achieved with this instrumentation.

NPP, as well as NPPA, were both readily detected by the Rapiscan MobileTrace handheld IMS. The determined drift time for NPPA and NPP was 5.896 (±0.040) ms and 6.484 (±0.040) ms, respectively. The established drift times were programmed in the handheld IMS to alert the user to the presence of either analyte. Initial testing of the system was conducted by sampling the vapor above a vial containing 5 mg of reference-grade fentanyl. The IMS alerted to both NPP and

NPPA. Further testing was accomplished using diluted reference-grade fentanyl. Common adulterants and diluents were used to determine the effects of additives on detection. NPPA was detected in all samples, however, NPP was not.

Figures of merit and other related metrics were explored for non-contact detection. To test the false alarm rate of the instrument, a multitude of over the counter as well as prescription drugs were sampled. Of the 17 substances tested none alarmed for NPP or NPPA. Limit of detection (LOD) was established in both vapor and particle sampling modes on the IMS in terms of vapor concentration and material mass, respectively. For particle mode LOD, the drop cast method was used. The LOD was established at the lowest mass of NPPA detected that gives a true-positive probability (TPP) limit of 0.8. The LOD was reached at 10 ng of NPPA in particle mode. For vapor mode LOD, the trace explosive sensor testbed (TESTbed) system was employed. The TESTbed enables the delivery of NPPA at a specific concentration where the nominal NPPA mass can be calculated. Again, the TTP limit of 0.8 was used to determine the operational LOD. Vapor mode LOD was reached at 5 ng of NPPA.

The handheld IMS was carried to the Maryland State Police Forensic Sciences Division Laboratory for sampling on two sample sets, as well as the DEA Special Testing and Research Laboratory. Of the two sample sets tested from the Maryland State Police Forensic Sciences Division Laboratory only one yielded an alert for NPPA. The poor detection of these samples was due to their heavy adulteration. Each sample was only approximately 5 mg, and all were diluted by cutting agents. The sample with the highest amount of fentanyl was correctly detected. Three samples confiscated from the U. S. border were tested at the DEA Special testing and Research Laboratory, all of which gave positive alerts for NPPA. These samples contained a higher concentration of fentanyl. The results of this study highlighted the need of a pre-concentrator on

the hand-held device to improve the detection limit. A pre-concentrator will allow for a larger mass of analyte to be trapped and then enter the detector as a bolus. Details of method optimization and testing will be outlined in "Non-contact detection of fentanyl by a field-portable ion mobility spectrometer" to be submitted to *Analytical Chemistry* in November 2021.

Additional Study: Degradation effects on fentanyl's vapor profile

A complementary research question grew from observations made in completion of Aim 1 when the abundance of NPPA was found to increase as the extraction temperature increased. This led to further investigation of how/why this would occur. It was discovered that NPPA was a degradant of fentanyl. This then prompted the question of how degradation effects the headspace of fentanyl. As a result, experiments were designed to simulate the clandestine transport of fentanyl. Humidity, oxygen level, and heat are some of the factors being manipulated in this study. As well as examining the effects of tape and plastic on the headspace. There was an increase of NPPA over time in all environments tested, as well as an increase in styrene when heat was introduced. With the addition of plastic and tape to the environments NPPA was still the prominent VOC, there were no new VOCs formed from fentanyl, and tape masks all VOCs significantly. This work will be detailed in a final manuscript to be entitled "Headspace Analysis of Fentanyl Degradation" to be completed by the end of December 2021.

ARTIFACTS

Publications

Published Manuscripts

Vaughan, S. R.; DeGreeff, L. E.; Forte, L.; Holness, H. K.; Furton, K. G.; Identification of volatile components in the headspace of pharmaceutical-grade fentanyl. *Forensic Chemistry* **2021**, 24, 100331. DOI: 10.1016/j.forc.2021.100331

Vaughan, S. R.; Fulton, A. C.; DeGreeff, L. E.; Comparative analysis of vapor profiles of fentalogs and illicit fentanyl. *Analytical and Bioanalytical Chemistry*, **2021**, *accepted.*

Pending Manuscripts

Smith, C.; Fulton, A. C.; DeGreeff, L. E.; Detection of N-phenylpropanamide vapor from fentanyl materials by secondary electrospray ionization with ion mobility spectrometry. *Analytica Chemica Acta*, **2021**, *under NRL internal review.*

Planned Manuscripts

Fulton, A. C.; Vaughan, S. R.; DeGreeff, L. E.; Non-contact detection of fentanyl by a field-portable ion mobility spectrometer. *Analytical Chemistry,* **2021**, *in progress.*

Fulton, A. C.; Forte, L.; Holness, H. K.; Vaughan, S. R.; DeGreeff, L. E.; Furton, K. G.; Degradation effects on fentanyl's vapor profile. *Forensic Chemistry*, **2021**, *in progress.*

Conferences

- Ashley Fulton, Stephanie R. Vaughan, Lauryn E. DeGreeff, Headspace Analysis of Street-Grade Fentanyl and the Development of a Non-Contact Detection Method for Fentanyl, Forensic Science Symposium, hosted by the Global Forensic and Justice Center, Virtual, June 10, 2021. (contributed, oral)
- Stephanie R. Vaughan, Lauryn E. DeGreeff, Leann Forte, Howard K. Holness, and Kenneth G. Furton. Headspace Analysis of Fentanyl and Synthetic Opioids for Development of a

Non-contact Detection Method, Louisiana State University Analytical Seminar, Virtual, March 2021. (Invited, oral)

- Lauryn DeGreeff, Stephanie Vaughan, Leann Forte, Howard K. Holness, and Kenneth G. Furton, A Characterization of the Vapor Profiles of Fentanyl and Synthetic Opioids for Instrumental and Canine Detection, AAFS Annual Scientific Meeting, Virtual, February 2021. (Contributed, oral)
- Stephanie R. Vaughan, Lauryn E. DeGreeff, Leann Forte, Howard Holness, and Kenneth Furton, A Characterization of Vapor Profiles of Fentanyl and Synthetic Opioids for Development of a Non-Contact Detection Method, Sigma Xi Annual NRL Postdoctoral Associate Symposium, Virtual, January 2021. (Contributed, oral)
- Leann Forte, Stephanie Vaughan, Lauryn DeGreeff, Howard Holness, and Kenneth Furton, The Effects of Degradative Stress on Vapor Analysis of Fentanyl, AAFS Annual Scientific Meeting, Virtual, February 2021. (Contributed, poster)
- Lauryn DeGreeff, Stephanie Vaughan, Leann Forte, Howard Holness, and Kenneth Furton, Headspace Analysis of Fentanyl and Related Analogs for Development of a Non-Contact Detection Method, NIJ R&D Symposium, Virtual, February 2021. (Invited, oral)
- Lauryn E. DeGreeff, Stephanie Vaughan, Ashley Fulton, Leann Forte, Howard Holness, and Kenneth Furton, Characterization of Vapor Profile of Fentanyl for Instrumental and Canine Detection, ASCLD FRC Lightning Talks – Fentanyl Signature Research, Virtual, July 2021. (Invited, oral)
- Lauryn DeGreeff, Stephanie Vaughan, Leann Forte, Howard Holness, and Kenneth Furton, Headspace Analysis of Fentanyl and Related Analogs for Development of a Non-Contact Detection Method, The Pittsburgh Conference and Exposition, NIJ Symposium, Virtual,

March 2021. (Invited, oral)

- Leann Forte, Stephanie Vaughan, Lauryn DeGreeff, Howard Holness, and Kenneth Furton, The Effects of Degradative Stress on Vapor Analysis of Fentanyl, The Pittsburgh Conference and Exposition, Virtual, March 2021. (Contributed, poster)