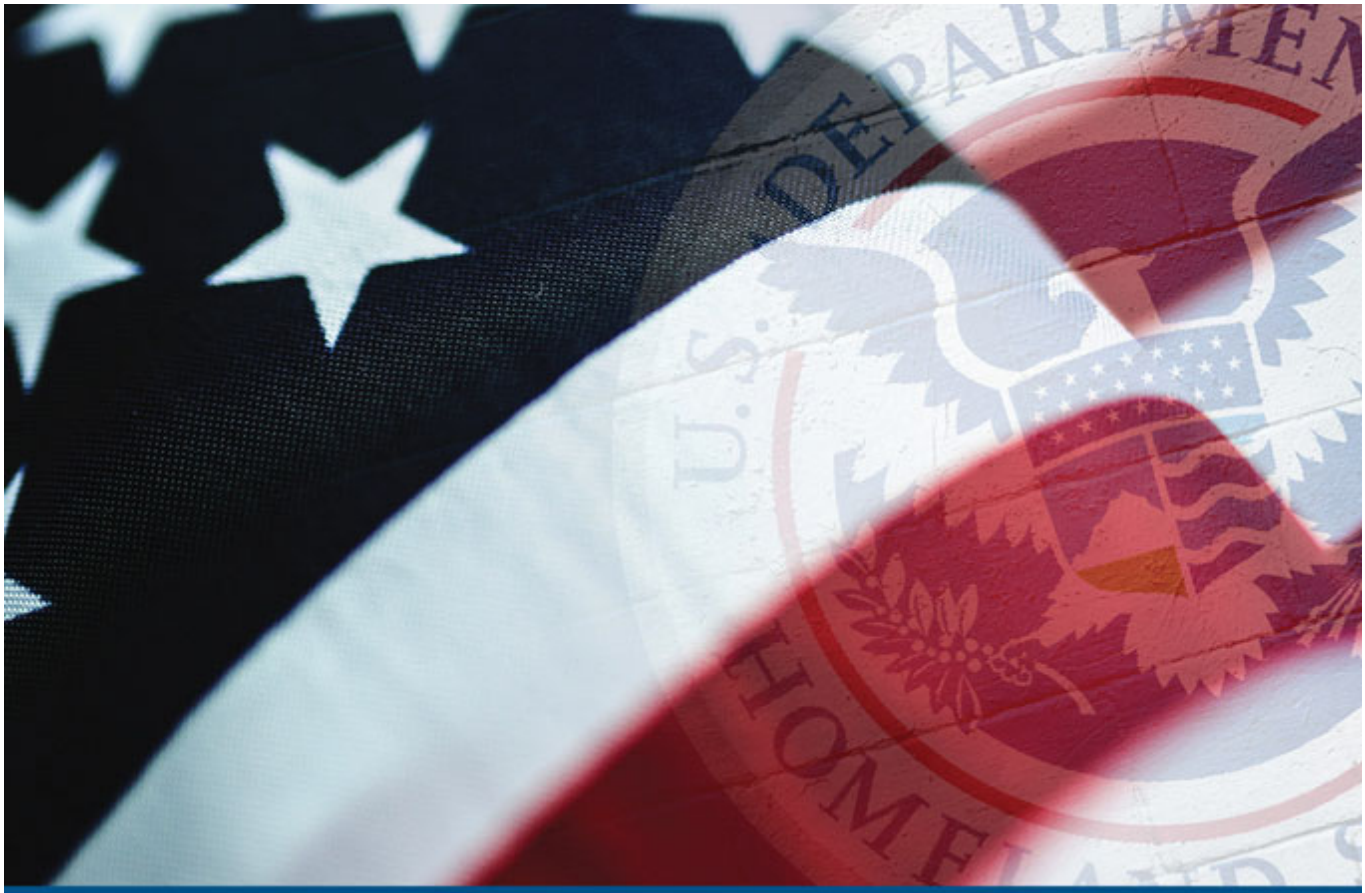

Master Question List (MQL) for Synthetic Opioids

CSAC 21-013

September 2021

Science & Technology

For comments or questions related to the contents of this document, please contact the DHS S&T Chemical Security Analysis Center at csacinfo@st.dhs.gov

Approved for public release. Distribution is unlimited; October 2021.

Master Question List (MQL) for Synthetic Opioids

Introduction

Background: Abuse of synthetic opioids is devastating communities, endangering public health, and overwhelming the response professionals who protect American communities. Between 2019 and 2020, U.S. drug overdose deaths reached the highest number ever recorded, with synthetic opioids, like illicit fentanyl, largely responsible. [1] While understanding of synthetic opioids has grown exponentially, important knowledge gaps impact our ability to make informed operational recommendations and decisions across a range of topics, from deploying effective personal protective and detection equipment to developing safe and effective decontamination protocols.

Purpose: The Department of Homeland Security (DHS) Science and Technology Directorate (S&T)* has developed this Master Question List (MQL) to serve two primary objectives:

- **Response communities**: Provide a simple interface of consolidated, scientifically vetted information in the context of daily operations.
- **Research and development communities**: Highlight the remaining critical knowledge gaps to focus investments with high operational priority and utility.

Across federal government, industry, and academia, compelling research programs continue to expand our knowledge of critical chemical and physical properties of synthetic opioids and the hazards they pose. This MQL document will serve as a living repository of ongoing research on synthetic opioids, to be updated annually or as key information emerges. This first version of the MQL focuses on synthetic opioids commonly found in the illicit drug trade. Further additions will include more synthetic opioids as information becomes available. Additional information, such as classified annexes, will be made available upon request. To request support related to this document, contact DHS S&T Chemical Security Analysis Center (CSAC) at csacinfo@st.dhs.gov.

*The Opioid MQL is a collaborative partnership among DHS S&T:

- Office of Mission and Capability Support, Opioid Program and Probabilistic Analysis for National Threats Hazards and Risks (PANTHR) Program
- Office of Innovation and Collaboration, Office of National Labs, CSAC
- Office of Science and Engineering, Hazard Assessment and Characterization Technology Center.

TABLE OF CONTENTS

List of Abbreviations and Acronyms

ABBREVIATIONS/ ACRONYMS	DEFINITION
ALEC	Anita C. Leight Estuary Center
APR	air purifying respirator
CARC	chemical agent-resistant coating
CDC	Centers for Disease Control and Prevention
CSAC	Chemical Security Analysis Center
DART-MS	direct analysis in real time mass spectrometry
DHS	Department of Homeland Security
DI	deionized
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FFR	filtering facepiece respirators
FTIR	Fourier Transform Infrared
GC	gas chromatography
GC-IRD	GC-IR detection
GC-MS	gas chromatography mass spectrometry
IM	intramuscular
IMS	ion mobility spectrometry
IR	infrared
IV	intravenous
LC-MS	liquid chromatography mass spectrometry
LC-MS-MS	liquid chromatography-tandem mass spectrometry
LD_{50}	lethal dose for 50% of the population
MQL	Master Question List
NFPA	National Fire Protection Association
NIOSH	National Institute for Occupational Safety and Health
OSHA	Occupational Safety and Health Administration
PAL	Provisional Advisory Level
RSDL®	Reactive Skin Decontamination Lotion
S&T	Science and Technology Directorate
SC	subcutaneous

List of Abbreviations and Acronyms (Cont.)

ABBREVIATIONS/ ACRONYMS	DEFINITION
SCBA	self-contained breathing apparatus
SERS	surface enhanced Raman spectroscopy
STEL	short-term exposure limit
TWA	time weighted average
U.S.	United States
UV	ultraviolet
UHPLC-MS-MS	ultra high-performance liquid chromatography-tandem mass spectrometry
USP	U.S. Pharmacopeial

<table>
<tr><th colspan="3">Responder / Operator Summary</th></tr>
<tr><th colspan="3">Overview</th></tr>
<tr><td colspan="3">• Synthetic opioids may be present in various forms.
• Inhalation of powder is the most likely route that leads to harmful and immediate effects.
• Skin contact may occur but is not expected to lead to harmful effects.
• Personal protective equipment is effective protection when worn properly.
• Respiratory depression, drowsiness, unresponsiveness, and constricted pupils are signs consistent with opioid intoxication.
• Naloxone is an effective medication to reverse the effects.</td></tr>
<tr><th>Detection</th><th>Protection</th><th>Clean Up / Decontamination</th></tr>
<tr><td>• White powder, tablets, pills, rocks, on scene
• Cutting agents (e.g., lactose, mannitol)
• Other related equipment (e.g., milling equipment, pill presses)</td><td>• Nitrile gloves
• Eye protection
• National Institute for Occupational Safety and Health (NIOSH)-approved P100 respirator
• Gown</td><td>• Wash skin with cool water and soap.
• Decontaminate surfaces and equipment with department approved cleaners.</td></tr>
<tr><th colspan="3">Identifying exposure</th></tr>
<tr><td colspan="3">• Changes in level of consciousness (drowsiness, unresponsive)
• Changes in respiratory patterns (slow breathing, no breathing)
• Changes in pupillary state (constricted, pin-point pupils)</td></tr>
<tr><th colspan="3">What to do if exposed</th></tr>
<tr><th colspan="2">Life-Threatening Exposure</th><th>Non-Life-Threatening Exposure</th></tr>
<tr><td colspan="2">• Notify dispatch / request Emergency Medical Services (EMS) and backup.
• Move away from source / remove exposed individual from the source.
• Administer naloxone according to your department guidelines.
• Perform resuscitation as needed.</td><td>• Do not touch eyes, mouth, nose, or skin.
• Wash skin with cool water and soap if available.
• DO NOT use hand sanitizers.
• Wash hands thoroughly.
• Follow department guidelines regarding disposition of contaminated clothing.</td></tr>
</table>

Physical Properties – What are the physical properties of synthetic opioids?

What do we know?

Synthetic opioids are solids at room temperature. The melting points and boiling points are specific to each analog and free base or salt form.

- Fentanyl free base, fentanyl hydrochloride, fentanyl citrate, and fentanyl oxalate are all white solids at room temperature. [2] [3]

Fentanyl compound	Free base	Hydrochloride	Citrate	Oxalate
Melting point, °C	84 [4]	220.5 [5]	154.5 [6]	188 [7]

- Fentanyl free base is stable up to 350 °C; further increases in temperature result in the decomposition of the analyte due to charring. [4]
- While boiling points for fentanyl compounds are often listed, they are generally estimated values from computations. Organic materials tend to char at temperatures above 350 °C, rather than boil. Charring is a thermal decomposition process including the removal of organic vapor and volatile organic compounds from the material, whereas boiling is a change of state of the material. [5] For example, the estimated boiling point for fentanyl free base is 391 °C [6] and 466 °C for fentanyl citrate; [7] however, these chemical compounds are likely to decompose before they would boil. [4] [5]
- Carfentanil free base and carfentanil hydrochloride are white solids at room temperatures, [8] while carfentanil citrate is a clear, crystalline solid. [9]

Carfentanil compound	Free base	Hydrochloride	Citrate	Oxalate
Melting point, °C	189 [10]	Not found	153 [11]	Not found

- Furanylfentanyl hydrochloride is a white powder [12] with a melting point of 235 °C [13] in its pure form.
- Isotonitazene is a yellow, brown, or off-white powder [10] [11] with a melting point of 172.5 °C. [11] Decomposition due to charring is likely to occur at temperatures above 350 °C, despite the estimated boiling point of 584.7 °C. [11]

Synthetic opioids have varying water and alcohol solubilities that are specific to the analog and the salt form.

- Fentanyl free base has limited water solubility (0.2 mg/mL at 25 °C) [14], while fentanyl hydrochloride and fentanyl citrate both have a higher solubility of 25 mg/mL at 25 °C. [2] [15] Conversely, fentanyl free base is more soluble in alcohol than water, while fentanyl citrate is only slightly soluble in alcohol. [15]
- Carfentanil citrate water solubility is 3.16 mg/mL at 21 °C. [16]
- Furanylfentanyl has little solubility in water but is highly soluble in methanol. [12]
- Isotonitazene is predicted to be slightly soluble (1.0 g/L) at a temperature of 25 °C and pH 7. It was soluble in methanol for chromatographic analysis. [17]

Synthetic opioid particles have particle sizes around 2 microns. However, the particle size distribution may increase based upon preparation methods and inclusion of adulterants.

- Particle sizes of illicit drugs vary depending upon the drug, adulterants, and preparation methods. [18]
- Fentanyl free base, fentanyl citrate, and fentanyl oxalate all produce particles with a 0.05–2 microns aerodynamic diameter. [19]
- Fentanyl citrate, when rapidly heated, produces a particle size distribution ranging from 1 to 3.5 microns. [20]

- Particles in the size range of fentanyl (1–3 microns) settle from still air in 1.5 hours (3 microns) to 12 hours (1 micron). Particles that are 3 microns and 1 micron settle in turbulent air with a half-life of 1.5 and 12 hours, respectively. Scrubbing surfaces where synthetic opioids are present results in a turbulent air flow situation. [21]
- Fentanyl, like many organic molecules, when dispersed as an aerosol, results in particles that are highly charged due to electrostatic effects. These particles all have the same polarity resulting in aerosol expansion due to particle-particle repulsion. The electrostatic particle-particle interaction is highly dependent upon humidity and time in the air; the electrostatic effects will gradually decrease after about 30 minutes. [21]
- In general, particles in a powder are in close contact and tend to agglomerate, resulting in increased total mass, and when aerosolized, the time these particles stay in the air is decreased. [21] Synthetic opioid powders behave accordingly.

Why does this matter operationally?

- Synthetic opioids are solids with a particle size around 2 microns. They decompose at elevated temperatures (above 300 °C). Therefore, the operational threat in the natural environment is the inhalation of aerosolized particles, not vapor phase material.
- **Due to the small particle size (< 5 microns), the particles penetrate deep into the lungs**. The synthetic opioid particles with higher water solubility (salt forms) will move into the blood stream from the lungs faster than those with lower water solubility (free base forms). While both would likely result in a similar dose, the effects of the dose will be seen more rapidly with higher solubility forms.
- Synthetic opioids with higher water solubility will be readily absorbed through mucous membranes.

What are the knowledge gaps?

- Melting Points
  - What is the melting point of carfentanil hydrochloride?
- Solubilities
  - Are more details on furanylfentanyl hydrochloride solubility available?
- Particle Size
  - The particle size distribution of synthetic opioids needs to be evaluated based upon the specific drug, adulterants, and production methods.

Exposure – What are the routes of exposure and the levels of interest?
What do we know?
Significant systemic absorption of synthetic opioids can occur via inhalation, ingestion, injection, ocular, and dermal routes, as well as via mucosal membranes. The dose and time required for a given effect vary depending on the synthetic opioid, its chemical form (freebase or salt), route of exposure, and drug concentration or purity. Effects range from altered mental state or sleepiness to loss of consciousness, severe respiratory depression, and death. • Synthetic opioids toxicity data must be derived from primate sources as dose effect levels derived from rodent studies have been shown to be very different from those observed in humans. For example, the intravenous (IV) lethal dose for 50% of the population (LD_{50}) for fentanyl is 3 mg/kg in rats, [22] but 0.03 mg/kg in monkeys. [23] The human LD_{50} has not been established, but severe to life-threatening respiratory depression has been observed in humans at IV doses as low as 0.007 to 0.015 mg/kg (7 to 15 µg/kg) in opioid-naïve individuals. [24] [25] • There are other opioids, such as carfentanil, that are significantly more toxic than fentanyl. The estimated IV lethal dose of carfentanil is around 0.3 µg/kg. [26] [27] • In humans, an intramuscular (IM) or IV bolus injection of fentanyl citrate at a dose of 50–100 µg (approximately 0.7 to 1.4 µg/kg) is recommended for control of post-operative pain. Onset of analgesia is rapid (minutes to effect) and may be adequate for one to two hours depending on the dose. Higher doses can be used during surgical procedures but only when ventilatory support is provided. [28] • For a specific opioid, the dose required and time for a given effect (such as pain relief) depend on the route of exposure. • Nebulizers and inhalers have been used for pain relief and have been effective at doses from 1.3 µg/kg [29] to 15 µg/kg [30]. The latter value is much higher than the required IV or IM dose, indicating limited bioavailability or inefficient delivery. In both cases, pain relief occurred in a few minutes. More recently, studies with an optimized fentanyl nebulizer and inhaler indicated rapid drug uptake and blood concentrations similar to that from a comparable IV dose (bioavailability of 78% or greater). [20] [31] • Fentanyl by mouth is most often given as transmucosal lozenges, sublingual tablets, or buccal tablets. Administered in this manner, some fraction of the fentanyl is absorbed directly through mucosal membranes, and the remainder is swallowed and is absorbed in the gut. Mucosal transfer is more complete and rapid, with effects seen in 30 minutes or less. [32] Transfer through the gut is more gradual and is subject to metabolism in the liver, reducing bioavailability. The bioavailability for the sublingual, oral transmucosal, or buccal forms is estimated to be 47–76%. [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] • For fentanyl given as an oral solution, mucosal transfer is minimal, and the bioavailability is only 30%. [36] [38] • In intranasal administration of fentanyl, absorption through the nasal mucosa is rapid (5–16 minutes to peak blood concentration) and bioavailability is 55–89%. [32] [47] [48] [49] [50] [51] • Fentanyl transdermal patches are designed to deliver fentanyl gradually and over a long period of time. Pain relief occurs only after 8–16 hours and is sustained for up to 72 hours, at which time the patch must be replaced. [52] [53] [54] [55] • Fentanyl citrate solution applied to the skin is absorbed faster than from transdermal patches, but it is likely that at least 2 hours are required before an appreciable amount of fentanyl

reaches the bloodstream. [56] Incidental skin contact with fentanyl powder is unlikely to produce immediate adverse effects and would allow time for removal. [57]

Synthetic opioids can penetrate intact skin but do so slowly as compared to other routes such as intravenous or inhalational administration. The rate of penetration can increase with skin temperature, solvents (such as gasoline, turpentine), and the pH of any solution put on the skin.

- The free base of fentanyl displays greater skin penetration ability than the salt form and a higher steady state penetration rate of fentanyl in solution (with 50% isopropanol) compared to powder on dry skin. [58]
- Sweaty skin increases the penetration rate of fentanyl applied as powder or solution (50% isopropanol). [58]
- The skin penetration rate of free base fentanyl increased significantly as the solution pH increased from 3 to 9. [59]
- Pre-application of alcohol-based hand sanitizers increased skin penetration of the free base fentanyl but not the hydrochloride salt. [58]
- Skin decontamination using soap and water appears to be an adequate decontamination procedure. [58] Currently, the U.S. Centers for Disease Control and Prevention (CDC) recommends avoiding decontamination with hand sanitizer or bleach. [60] [61]

There are currently no published Occupational Safety and Health Administration (OSHA)/NIOSH exposure levels; however, the U.S. Environmental Protection Agency (EPA) has published Provisional Advisory Level (PAL) recommendations for 24-hour not-to-exceed levels for fentanyl exposure, and the U.S. Pharmacopeia has published a recommended 8-hour time weighted average (TWA) and a 15-minute short-term exposure limit (STEL) for fentanyl exposure.

- PALs for Hazardous Agents are health-based guidelines used to inform decisions regarding inhalation and oral exposures to hazardous agents. They are based upon 24-hour, 30-day, 90-day, and two-year exposure durations. PAL-1 values are developed for mild, transient, reversible effects; PAL-2 values address serious, irreversible, and/or escape-impairing effects; and PAL-3 values represent lethality, morbidity, or life-threatening effects. [62]
- Inhalation PALs for fentanyl include a PAL-2 of 0.0037 $\mu g/m^3$ for ≤ 24-hour exposure and a PAL-3 of 0.011 $\mu g/m^3$ for ≤ 24-hour exposure. [7]
- The Industry Operational Exposure Limit (inhalation) for an 8-hour TWA is 0.1 $\mu g/m^3$ for fentanyl. [63] U.S. Pharmacopeial (USP) recommends the same 8-hour TWA, [64] while Mallinckrodt Pharmaceutical Company uses a 0.7 $\mu g/m^3$ exposure level for an 8-hour TWA. [65] Both USP and Mallinckrodt recommend 2.0 $\mu g/m^3$ STEL (15 min). [64] [65] Cambrex, Inc. uses an 8-hour TWA of 0.04 $\mu g/m^3$ for carfentanil inhalation. [66]
- Fentanyl ingestion PALs for ≤ 24-hour, 30-day and 90-day exposures are 0.03 mg/L (PAL-1) and 0.23 mg/L (PAL-2). [7]
- Carfentanil ingestion PALs for ≤ 24-hour are 0.007 mg/L (PAL-2) and 1.1 mg/L (PAL-3). EPA also publishes PALs at similar levels for 3-methylfentanyl and α-methylfentanyl. [7]

Why does this matter operationally?

- Synthetic opioid **exposure can occur via several different routes**; however, **inhalation is the exposure route of greatest concern for emergency responders**. NIOSH currently recommends respiratory protection if powdered illicit drugs are visible or suspected. [55] [60]
- While **synthetic opioids can penetrate the skin, they do so slowly as compared to inhalation and injection routes**. The rate of penetration is higher on sweaty or damaged skin and with the free base form of the opioid. Skin damage might render responders much more susceptible to effects of skin exposure.

- Handwashing is an effective skin decontamination technique. The use of high pH soaps (e.g., pH greater than 10) should be avoided as skin penetration increases with increasing solution pH; however, the typical handwashing time (30 seconds) is likely not enough contact time to create a concern.
- NIOSH recommends that emergency response personnel avoid using hand sanitizers that contain ethanol or isopropanol in situations which might involve direct contact with illicit drugs, including fentanyl. [60]

What are the knowledge gaps?

- OSHA, NIOSH, and American Conference of Governmental Industrial Hygienists (ACGIH) levels of concern need to be established for at least the top 10 fentanyl-related substances.
- **LD_{50} data need to be measured in primates.**

Personal Protective Equipment (PPE) – What PPE is effective, and who should be using it?
What do we know?
NIOSH-approved respirators providing at least N/R/P100 ratings provide operators with the appropriate level of protection when dealing with small amounts of airborne synthetic opioids. Higher levels of protection are required when dealing with large amounts of airborne synthetic opioids. Care should be taken during donning and doffing clothing, as particulates may reaerosolize, creating an inhalational hazard. There is a potential hazard if a vigorous movement causes dust to rise. • CDC/NIOSH recommends the use of disposable N100, R100, or P100 filtering facepiece respirators (FFRs) for pre-hospital patient care, law enforcement routine duties, investigations, evidence collection, special operations, and decontamination in situations where small amounts of illicit drugs in powder or liquid form are visible. [60] • CDC/NIOSH recommends the use of air-purifying respirators (APRs), powered APRs, or self-contained breathing apparatus (SCBAs) for investigations, evidence collection, special operations, and decontamination in situations where large amounts of illicit drugs in powder or liquid form are visible. [60] • Fentanyl-related substances have a particle diameter of 1–3.5 microns. [20] **Protective clothing meeting the National Fire Protection Association (NFPA) 1994 Class 4 standard for chemical protective clothing or the NFPA 1999 Single or Multiple Use Ensemble requirements for emergency medical clothing [67] (NFPA 1999) provides the necessary protection from airborne synthetic opioids for operators when the risk of exposure is high.** • CDC/NIOSH recommends the use of particulate hazard protective ensembles (i.e., NFPA 1999 single use/multiple use ensembles or NFPA 1994 Class 4 ensembles) for special operations, investigations, evidence collection, and decontamination in situations where large amounts of illicit drugs in liquid or powder form are visible. [60] ○ Fentanyl concentrations greater than 0.1 µg/m^3 were able to deposit on the operator's skin underneath Tyvek coveralls. Fentanyl was detected in the urine of the operator 39% of the time. This is believed to be due to dermal penetration as the operators were wearing full face masks fitted with P3 filters. [63] **Powder-free nitrile gloves should be worn with a minimum thickness of 5 ± 0 2 mil (i.e., 0.127 ± 0.051 mm) when the risk of exposure to synthetic opioids is minimal or moderate.** • CDC/NIOSH recommends the use of powder-free nitrile gloves with a minimum thickness of 5 ± 2 mil (i.e., 0.127 ± 0.051 mm) in situations where minimal amounts of illicit drugs may be present, but are not visible, or where small amounts of illicit drugs in liquid or powder form are visible. [60] • Twelve disposable glove models were tested against fentanyl and carfentanil hydrochloride solutions using a modified ASTM D6978-19 standard test method. No nitrile glove models showed permeation rates above the threshold criterion of 0.01 µm/cm^2/min during the 240-minute test. Latex and vinyl glove materials exhibited fentanyl and carfentanil permeation above this threshold. [68]
Why does this matter operationally?
• **N/R/P100 FFRs** provide appropriate protection when dealing with small amounts (milligrams) of visible aerosolized vs settled/sedentary particles of illicit drugs. When the amounts are larger (grams), **air purifying respirators (with P100 filter) or powered air purifying respirators (with high efficiency particulate air [HEPA] filter), or a SCBA** should be used. • **Powder-free nitrile gloves** with a minimum thickness of 5 mil are recommended for minimal and moderate risks of exposure.

• While fentanyl exposure via the skin is a minor route relative to inhalation in the total exposure profile for an emergency responder, it is recommended that the skin and clothing be protected to minimize the potential for secondary exposures via inhalation and should adhere to prevention protocol. When the amounts of illicit drugs are larger (grams to kilograms), **particulate-tight protective clothing** is recommended.
What are the knowledge gaps?
• Does the presence of cutting agents change the recommended level of protection? • Does glove fit, specifically wearing gloves that are too small for the hand and cause extreme stretch on the material, affect permeation rates? • **Does the practice of wearing multiple gloves decrease potential exposures? (i.e., should it be considered a best practice?)**

Personnel Decontamination – What methods can be used to remove opioids from skin?
What do we know?
Fentanyl is decontaminated by Reactive Skin Decontamination Lotion (RSDL®). • Fentanyl on chemical agent-resistant coating (CARC) was decontaminated using RSDL® kit. Fentanyl citrate in a 50% methanol aqueous solution, was placed as a 5x5 matrix of droplets that were 1–3 µL in size for a total dosing of 0.1 g/m^2 on CARC panel. The decontamination time was 2 minutes, and the decontamination efficiency was 99.86%. [69]
Why does this matter operationally?
• **Skin exposed to synthetic opioids should be decontaminated using soap and water**.
What are the knowledge gaps?
•

Detection – What technologies can detect, classify, or identify synthetic opioids?
What do we know?

HAND-HELD AND PORTABLE INSTRUMENTATION

Raman and Infrared Spectroscopy techniques can detect and identify, but not quantify, synthetic opioids down to the low microgram level in pure samples and down to 3% within mixed samples while demonstrating low false positive rates and higher false negative rates.

- The limit of detection for fentanyl in Raman and Fourier Transform Infrared (FTIR) spectroscopy instruments is less than 10 µg for a pure sample. [70]
- While fentanyl mixed in heroin has, on occasion, been detected at concentrations down to 1%, it is more commonly found to be detectable down to 3–4% with low false positive rates and high false negative rates (especially in mixed samples). [70]
- Raman and FTIR spectral libraries are readily available for high threat significant opioids. [71]
- IR can be used as the detector component for gas chromatography (GC). [72]

Surface enhanced Raman spectroscopy techniques can detect and identify mixtures at trace levels and with lower purity in mixtures.

- Surface enhanced Raman spectroscopy (SERS) techniques can distinguish as low as 1% fentanyl in heroin/fentanyl mixtures, but only as low as 5% fentanyl in cocaine/fentanyl mixtures due to similarities in the cocaine and fentanyl spectra. [73]
- Limits of detection for fentanyl using SERS detection are 5 ng/mL in solution or 500 pg. [73] [74] [75]

Variants of Raman spectroscopy that use different optical collection strategies can be used to detect opioids within packaging.

- Spatially offset Raman spectroscopy (SORS) is well suited for detecting a sample within translucent packaging by collecting light scattering from a point offset from the path of the excitation laser. **[76] [77] [78] [79]**
- Transmission Raman spectroscopy instrumentation is capable of identifying the bulk contents of pills and capsules by collecting forward scattered light rather than back-scattered light. **[80] [81] [82] [83]**

Thin layer chromatography can detect synthetic opioids down to 3 micrograms, but the analysis of mixtures can be problematic.

- The Dragensdorff reagent shows best specificity between analogs, but Rf values show overlap and may be difficult to decipher in mixtures. [84]

Colorimetric test kits for opioids may give false positive results in the presence of common interferants, such as sugar and Excedrin™. [85] [86]

- The use of a more definitive test to verify the presence of a drug is recommended. [71]

Ion mobility spectrometry-based instrumentation is commonly used for presumptive detection of opioids in the field due to the simplicity of the approach. [87]

- Limits of detection of single to tens of nanograms have been reported. [88]
- However, the target analytes do not have perfectly unique ion mobilities and can be susceptible to false positives. [89] [90]
- Detection of fentanyl in the presence of heroin can be difficult for low resolution ion mobility spectrometry (IMS) instrumentation due to formation of combination peaks. [91]

LABORATORY BENCH SCALE INSTRUMENTATION

GC mass spectrometry (GC-MS) and liquid chromatography mass spectrometry (LC-MS) are both able to separate mixtures and provide a high rate of specificity between synthetic opioids. [70]

- Instrument configurations that use electron impact ionization and single mass analysis such as quadrupole mass filters can have difficulty distinguishing structural isomers of the same mass. This can be overcome with other techniques or mass analyzers that can perform tandem, that is, multiple mass analyses, such as triple quad or ion trap instruments. [92] [93]
- Limits of detection of fentanyl and analogs using a laboratory ultra high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS-MS) in biological samples was reported to be 0.5 ng/mL and 0.1 ng/mL for carfentanil. [94] A study of 262 overdoses involving carfentanil using liquid chromatography-tandem mass spectrometry (LC-MS-MS) measurements found a range of 10.2 to 2,000 ng/L (pg/mL) in whole blood. [95]
- Direct analysis in real time mass spectrometry (DART-MS) can detect fentanyl and analogues and is a form of atmospheric pressure ionization. Ionized helium atoms react with atmospheric components and the resultant products react and ionize with the sample. [96]
- Thermal desorption DART-MS and IMS are effective methods for identifying very small amounts (<ng) of fentanyl and analogues, with detection possible from complex mixtures and as an adulterant (≥ 0.1%) in the presence of heroin. [96]
- GC-IR Detection (GC-IRD) has been reported as a complementary method of opioid detection with GC-MS. Unique molecular signatures in the IR spectrum are used to identify opioids. [72]

Why does this matter operationally?

- Positive detection and identification of synthetic opioids using **Raman or FTIR is an indicator of a high purity material** as optical systems do not readily detect less than 10% of the product in mixtures (which makes it difficult to see street level/cut drugs and conduct advanced sample processing).
    - According to the U.S. Drug Enforcement Administration, during 2018 large volumes of fentanyl were seized at the southwest border but were generally less than 10% pure on average. Conversely, the smaller volumes seized in mail shipments arriving from China had purities greater than 90%. [97]
- **Thin layer chromatography techniques can detect high purity synthetic opioids**; however, the process tends to be labor intensive, and mixtures are difficult to evaluate. [84]
- **Colorimetric Lateral Flow Immunoassay detection technologies exist for synthetic opioids**; however, cross-sensitivities must be monitored. [98] [99] Mixtures do not tend to be problematic as the immunoassay is only targeting the synthetic opioid.

What are the knowledge gaps?

- Are portable GC-MS units suitable for the detection and analysis of opioids? At what mass ranges do these work best? Are mixtures of opioids with cutting agents analyzed well by these units? [100]
- There are limited accurate presumptive field tests for fentanyl and many of its analogues. [101]
- Carfentanil can be toxic at low concentrations such that sensitivities of pg/mL are necessary in forensic laboratories to detect. [102]
- New handheld technologies and versions of bench scale instruments are becoming available and need to be characterized.

- Electrochemical detection of opioids is becoming available in wearable or even disposable formats; [103] [104] though the performance of these methods remains to be characterized under field relevant conditions.
- Electrodes impregnated with nano-sized molecularly imprinted polymers (MIPs) have been reported to detect fentanyl and its analogues. [105]

- The performance of micro or mini gas chromatography instruments against opioid samples remains to be characterized. [106]

Decontamination and Destruction of Synthetic Opioids

What do we know?

The fate of remifentanil oxalate and fentanyl citrate on soils were studied using spiking, extraction, and LC-MS-MS techniques.

- The soils tested, which had calcium chloride solution added to them before use, were: Sassafras sandy loam, Pennsylvania Ernest silt loam, North Dakota loam, and Utah Timpie loam. [107] [108]
- Recovery of fentanyl citrate from the various soils was 20–55% in 24 hours, and 20–50% after 12 weeks. [107]
- Recovery of remifentanil from the various soils was 52–76% in 24 hours, and 0–70% after 11 weeks. 5–10% of an opioid degradation product named R26, CAS Registry Number (CASRN) 132875-68-4, was observed in the first 12–18 hours. [108]

The fate of remifentanil oxalate and fentanyl citrate in various waters were studied using spiking, extraction, and LC-MS-MS techniques. [108] [107]

- The waters used were: Ground water (initial pH 5.1) from the Anita C. Leight Estuary Center (ALEC; Harford County, MD); 4 g of NaCl in 100 mL of deionized (DI) water (simulates ocean water.); 8 g of NaCl in 100 mL of DI water; and 16 MΩ water. [107]

Fentanyl citrate

- The recovery of fentanyl citrate from various waters was 95–115% in 24 hours, and from salt water was 80–96% after 7 weeks. [107]
- No mention of the presence, absence, or conditions of fentanyl degradation products in soil or water was made. [107]

Remifentanil oxalate

- The recovery of remifentanil oxalate from various waters after 1 hour was: 40% for ALEC ground water, 73% from DI water, 59% from 4% salt water, and 49% from 8% salt water. After 4 days, no remifentanil was detected in either saltwater solution. After 7 days, there was no remifentanil recovered from the ALEC water, and 4% was recovered from the DI water. **[108]**
- Recovery of remifentanil from a pH 4.0 citrate buffer is 80% in 28 days; from a pH 7.3 buffer is 13% in 1 day, and recovery from a pH 8.5 buffer is 4% in 1 day. [108]
- One degradation product, which formed in all buffered solutions, and then decayed within 5 days in the pH 7.3 and 8.5 buffers, was detected. [108]

Fentanyl is stable following exposure to ultraviolet (UV) and fluorescent lights.

- Fentanyl did not degrade after 7 days of light exposure to UV light at 365 nm and white, fluorescent light under ambient conditions. [109]

Fentanyl can be incinerated; however toxic byproducts, such as pyridine, in the resultant smoke must be managed appropriately.

- A study experimentally determined temperatures involved in recreational fentanyl smoking to range from 200 °C to roughly 450 °C and reported the corresponding pyrolysis profile for this temperature range in 50 °C increments. Fentanyl, pyridine, styrene, benzaldehyde, aniline, phenylacetaldehyde, and *N*-phenylpropionamide were consistently detected at all six temperature increments. The only additional pyrolytic product observed was 3-methylpyridine at 452 °C. [110]
- Thermal degradative studies offer meaningful data for the incineration of disposable contaminated items or the bulk solid by highlighting potential respirator and environmental hazards. [110]

Fentanyl is thermally stable up to 200–350 °C, depending upon the duration of heat exposure and the sample surface area. [4] [110]

Oxidative degradation of fentanyl can be accomplished using commercially available laboratory chemicals.

A one-hour study of 8 peroxide solutions at 0.2 M concentrations of oxidant and 1 mg/mL fentanyl showed that >90% degradation occurred in three cases: [110]

- Peracetic acid, CH_3CO_3H, pH= 8, 95.1% degraded
- Sodium percarbonate + *N,N,N,N*-tetraacetylethylene diamine (SPC+TAED), pH=8, 98.6% degraded
- Sodium percarbonate + *N,N,N,N*-tetraacetylethylene diamine (SPC+TAED), pH=10, 93.0% degraded

A one-hour study of two hypochlorite solutions that had available chlorine of 0.2 M and 1 mg/mL fentanyl had widely different results: [110]

- Trichloroisocyanuric acid (TCCA, $C_3O_3N_3Cl_3$), pH=5, 99.5% degraded
- Calcium hypochlorite, $Ca(ClO)_2$, pH=12, 36.9% degraded

Fentanyl hydrochloride powder was placed on coupons of stainless steel, laminate, acrylic, and painted drywall. The coupons were sprayed with solutions of tap water, OxiClean™ Versatile Stain Remover, bleach, pH adjusted bleach solutions, DF200®, or Dahlgren Decon™. The spray remained on the coupon for 1 hour before analysis. [111]

- After 1 hour of tap water, 5–38% of the fentanyl was left on the coupons, and 33–80% was found in the runoff water. [111]
- After 1 hour of Oxiclean™ solution, 22–50% of the fentanyl was left on the coupons, and 32–66% was found in the runoff water. [111]
- After 1 hour of pH 7 bleach solution, ~9–41% of the fentanyl was left on the coupons, and 2–25% was found in the runoff. The data indicated ~68% degradation of the fentanyl across surfaces. [111]
- After 1 hour of pH 5 bleach solution, ~3–6% of the fentanyl was left on the coupons, and 2–5% was found in the runoff. The data indicated ~93% degradation of the fentanyl across surfaces. [111]
- After 1 hour of pH 5 bleach solution modified with surfactants, ~1–6% of the fentanyl was left on the coupons, and 1–2% was found in the runoff. The data indicated ~95% degradation of the fentanyl across surfaces. [111]
- After 1 hour of DF200™, ~1–7% of the fentanyl was left on the coupons, and 0.1–9% was found in the runoff. The data indicated ~94% degradation of the fentanyl across surfaces. [111]
- After 1 hour of Dahlgren Decon, ~0.5–14% of the fentanyl was left on the coupons, and none was found in the runoff. The data indicated ~95% degradation of the fentanyl across surfaces. [111]

Fentanyl hydrochloride powder mixed with the cutting agents lactose, mannitol, or ascorbic acid (5%/95%) was placed on laminate coupons. The coupons were sprayed with solutions of Dahlgren Decon™ or pH 5 bleach with surfactant. The spray remained on the coupon for 1 hour before analysis. [111]

- The coupons sprayed with Dahlgren Decon™ with no additive, lactose, and mannitol had 2–10% fentanyl remaining on the coupon, compared to 34% for the ascorbic acid. The data indicated ~60% degradation of the fentanyl when ascorbic acid was present and 90–98% for the other samples. [111]
- The coupons sprayed with pH 5 bleach with no additive, lactose, mannitol, and ascorbic acid had 9–18% fentanyl remaining on the coupon. The ascorbic acid sample had ~35% fentanyl in

the runoff; the others had only ~2%. The data indicated around 50% degradation of the fentanyl when ascorbic acid was present and 80–90% for the other samples. [111]

- Smooth interior surfaces (e.g., acrylic, laminate, painted drywall, stainless steel) that have been contaminated with fentanyl can be cleaned using pH 5 adjusted bleach (contact time 1 hour), then wiped with a dry wipe followed by two isopropanol wipes, resulting in a 2.5 log reduction in fentanyl mass on the surface. Of this amount, 1.2 log of the fentanyl is degraded by the pH 5 bleach. Similarly, these types of surfaces can be cleaned using Dahlgren Decon (contact time 1 hour) and wiped with dry and isopropanol wipes, resulting in a better than 3.8 log reduction in fentanyl mass on the surface. [111]
- Remifentanil will persist in environmental soil for many months without significant degradation or transport, even during rainy weather. [108]

Why does this matter operationally?

- Synthetic opioids are stable in soil; if material is spilled, the **contaminated soil should be removed, or the residual opioid should be destroyed,** to minimize potential for secondary contamination.
- Synthetic opioids are **stable in water**; if water is used during decon, efforts should be made to capture the runoff and send it to a hazardous wastewater facility.
- Synthetic opioids can be **destroyed using incineration,** but the gases produced must be managed appropriately.
- **Decontamination of areas may be performed using commercially available peracetic acid, pH 5 adjusted bleach solutions, or with pool chemicals dichloroisocyanuric or trichloroisocyanuric acid**. The required contact time between the synthetic opioid is dependent upon the amount present as well as the concentration of decontaminant available in the solution.
- The use of scrubbing to aid in the removal of fentanyl is not advised since the scrubbing of surfaces may increase the exposure risk to personnel due to issues arising from particle interactions (see Physical Properties). [110]

What are the knowledge gaps?

- What are the effects of cutting agents, other drugs, degradation productions, or adulterants on decontamination efficacy?
- What are the toxicities of the environmental and decontamination degradation byproducts?
- What are the reaction stoichiometries required for each degradation pathway and the kinetics associated with the reactions?

Medical Countermeasures for Synthetic Opioids

What do we know?

Naloxone, supplied as intravenous (IV), intramuscular (IM), subcutaneous (SC), and nasal spray applications, is the standard treatment for synthetic opioid overdoses.

- Naloxone rapidly reverses the respiratory/central nervous system depression effects of opioid overdoses and is the standard treatment for synthetic opioid overdose. [112]
- Naloxone was initially approved in 1971 as a solution labeled for IV, IM, or SC uses. [113]
- In 2018, there were eight naloxone products that were being marketed. One was a nasal spray at 4 mg/0.1 mL. Another was an auto injector, available with 4 mg/0.4 mL and 2 mg/0.4 mL. The remaining six products were injections, available as 0.4 mg/mL, 2 mg/2 mL, or 4.0 mg/10 mL packages. [114]
- In 2021, the U.S. Food and Drug Administration (FDA) approved a naloxone hydrochloride nasal spray product that delivers 8 mg of naloxone per nasal cavity; previous approvals were for 2 mg and 4 mg of naloxone hydrochloride. [115]

Naloxone dosage and bioavailability is dependent upon the mode of application.

- Pharmacokinetic studies of Narcan® Nasal Spray, (4 mg/0.1 ml naloxone hydrochloride) yielded a dose-adjusted bioavailability of approximately 47% compared to naloxone administered by IM injection. [116]
- A single administration of Narcan® Nasal Spray, (4 mg/0.1 ml naloxone hydrochloride), rapidly achieves plasma exposure to naloxone approximately five times greater than that achieved by a single 0.4 mg naloxone by IM injection. [116]
- The rate of absorption and time to reach effective levels of Narcan® Nasal Spray is as fast as naloxone administered by IM injection. [116]
- Narcan® Nasal Spray 4 mg dose has a higher plasma concentration than the 0.4 mg naxolone IM injection. [116]
- Pharmacokinetic studies of Evzio® auto injection, (0.4 mg/0.4 mL naloxone hydrochloride auto-injector) achieved equivalent exposure to 0.4 mg naloxone administered by SC or IM injection. [116]
- The most rapid onset of action is achieved by IV administration. [117] IM administration of naloxone hydrochloride produces a longer plasma concentration of naloxone than IV administration. [117]
- The duration of action of naloxone may be shorter than that of some opioids and the effects of the opioid may return as the effects of naloxone dissipate. [117]

The effective dose of naloxone is dependent upon the quantity and type of opioid used and route of administration, as well as the individual factors including other drugs present in the person, underlying diseases, opioid tolerance, genetics (e.g., CYP2D6) and environmental (e.g., stimulatory) factors.

- There is no single effective dose for all opioid overdoses.
- FDA-approved labeling for injected naloxone recommends an initial dose of 0.4 mg to 2 mg naloxone by the IM or IV route of administration, followed by repeat doses up to a total dose of 10 mg. [116]

Adverse effects of naloxone treatment

- In the presence of opioid dependence, withdrawal symptoms will appear within minutes of naloxone administration and will subside in about 2 hours. The severity and duration of the withdrawal syndrome are related to the dose of naloxone and to the degree and type of dependence. [117]

- Abrupt postoperative reversal of opioid depression may result in adverse cardiovascular effects, primarily in patients who have preexisting cardiovascular disorders or received other drugs that may have similar adverse cardiovascular effects. [116]

Why does this matter operationally?

- Naloxone rapidly reverses the respiratory/central nervous system depression effects of an opioid overdose.
- The duration of action of naloxone may be shorter than that of some opioids, and the effects of the opioids may return as the effects of naloxone dissipate.
- Intranasal administration has demonstrated equivalent effectiveness to IM or SC administration.
- IV naloxone administration provides the fastest onset of action, while IM administration has a more prolonged reversal of respiratory depression.

What are the knowledge gaps?

Several medical countermeasures are currently being tested for opioid overdoses.

- Intranasal nalmefene is a competitive, reversible opioid receptor antagonist with a longer duration of action than naloxone. It competitively antagonizes the effects of opioids at μ-, κ-, and δ-receptors. [118] A new drug application for nalmefene is planned for submission in 2021. [119]
- Methocinnamox (MCAM) is a novel opioid receptor antagonist with a long duration of action. MCAM might be effective in protecting against (prophylaxis) opioid poisoning. MCAM prevents renarconization and the effects of administered opioids for a week or longer. Based on studies in rats, MCAM would be expected to cause withdrawal symptoms in opioid-dependent patients. [119]
- Covalent naloxone nanoparticles, in which naloxone is covalently bonded to a polymer, are being studied. This class of long-acting opioid antagonists will have a linear “low and slow” delivery approach that might be useful for sustained reversal of synthetic opioid overdose after an initial use of another countermeasure for rapid reversal. [119]
- Serotonin (5-HT)1A receptor agonists have demonstrated utility as respiratory stimulants and could be useful to treat opioid-induced respiratory depression. [119]
- Fentanyl-binding cyclodextrin scaffolds could potentially serve as capturing hosts for fentanyl and its analogues. [119]
- Detoxifying biomimetic “nanosponge” decoy receptors can potentially cause antagonist pharmacological effects by rapidly reducing the free concentration of opioids in plasma. [119]
- Antibody-based strategies involve development of vaccines that can generate antibodies that selectively prevent the distribution of free synthetic opioid drugs reaching the brain and reduce the drug-induced behavioral and pharmacological effects. [119]

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