Dr Christina Baxter, ceo of Emergency Response TIPS, US, and Dr Michael Logan, of the research and scientific branch, Queensland Fire and Emergency Services, Australia, on Synthetic Opioids in Operational Environments – Part I: Detection

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Since1999, the US has seen a dramatic increase in prescriptions for opioid pain relievers (OPR).[1] These include opiates derived from natural opium sources (eg, morphine and codeine), semisynthetic opioids (eg, oxycodone and hydrocodone), and synthetic opioids (eg, fentanyl). OPR treatment admissions and overdose deaths have risen in parallel with the increase in prescriptions.[1] Until 2011, most opioid overdose deaths resulted from the misuse and/or abuse of prescription opioids.[2] Since then, prescription overdoses have levelled off and heroin overdoses have soared.[2] It has become easier and cheaper for people addicted to opioid prescription drugs to switch to heroin.

In fact, people who are addicted to oxycodone are 40 times more likely to become addicted to heroin than the average person.[3] Since 2013, there has been a sharp rise in deaths related to heroin mixed with fentanyl or fentanyl analogues, often unknown to the user. In that same period, drug overdoses have become the leading cause of death for Americans under 50.[4] In 2017, the White House labelled the opioid epidemic a national public health emergency.[5] Sadly, the US is not alone in facing this epidemic. Canada is fighting the epidemic in parallel, and Europe and Australia are quickly seeing its early stages.

Fentanyl and fentanyl analogues are predominantly a respiratory hazard to first responders. While they are also a dermal hazard, the speed at which the material penetrates the skin and moves into the blood stream is very slow and is not a likely source of a toxic dose. In the case of fentanyl, for an average 75kg (165lb) person, the dose required for an analgesic effect is estimated to be 2.5micrograms, an anaesthetic effect ranges between 25 and 125micrograms, and the lethal dose is 2.5milligrams.

How does this relate to CBRNE?

In October 2002, some of the materials that are ravaging the US and Canada in the current drug epidemic were used by the Russian federal security service in an attempt to resolve the hostage crisis in the Melnikov Street theatre. The UK's Defence Science and Technology Laboratory (Dstl) compared open literature publications by government scientists from around the world both before and after the siege, and have shown an increased interest in the use of synthetic opioids as incapacitating agents.[6] While there are many synthetic opioids, the most commonly discussed are fentanyl and fentanyl analogues. Originally developed by Janssen Pharmaceuticals as OPRs in 1960[7], the fentanyl class of compounds have become drugs of abuse more recently. There are approximately 1,400 possible fentanyl derivatives, of which approximately 500 would have toxicities suitable for clandestine use, over 200 are known to have been known to been produced, and over 30 have been seen in the current drug trade.

Detecting the threat

As the synthetic opioid crisis evolves, detection technologies are being enhanced to ensure that synthetic opioids can be detected, categorised, and/or identified. Prior to beginning any detection regime, it is firstly important for responders to apply a risk based approach to ensure that they are properly protected from the material they are detecting, and so prevent accidental exposure or contamination. The protective posture may include respiratory protection with chemical protective clothing or be as simple as interrogating the sample within a glove box or laboratory type portable fume hood.

Once the responders' safety is managed, the next step will be determining the amount of material available and its form for detection. Trace detection techniques are required for samples which are less than 1 microgram in available materials. Trace samples are generally residues on surfaces, outside packages, at interfaces, etc. Bulk detection technologies are only used with samples of visible amounts of material. This paper describes considerations the operator can use to choose the appropriate detection equipment for their operations. It does not cover all currently available detectors, just a sample subset.

Choosing a trace detector for field operations

The two detection technologies capable of detecting fentanyl and its analogues at trace levels (less than a microgram) in operational environments are mass spectrometry (MS) and ion mobility spectroscopy (IMS). Table 1 compares some commercially available products using characteristic which are important in the operational environment. These include system size/weight, selectivity, sensitivity, logistics, speed of sample

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	Size / Weight	Selectivity	Sensitivity	Logistics	Sample Speed	Set Up Speed	Mixtures	Library	Cost USD
908 Devices MX908	8.7lb	MS: Drug Hunter Mode able to identify isobaric ions	10 - 100ng	Swabs	Seconds	< 1 min		20+ synthetic opioids	55K
FLIR Griffin 510	36lb	MS with Gas chromatography separation	10ng	Carrier gas, columns	Minutes	< 15 min	GC separation	10+ synthetic opioids	110K
Smiths Guardion	32lb	MS with Gas chromatography separation	10 - 10ng	Carrier gas, columns, SPME fibers	Minutes	< 5 min	GC separation	10+ synthetic opioids	110K
Bruker RoadRunner	7.7lb	IMS	1 - 10ng	Swabs, sieves, filters	Seconds	< 30 min		7 synthetic opioids	30K
Smiths IONSCAN 600	23lb	IMS	1 - 10ng	Swabs, sieves, filters	Seconds	< 10 min		9 synthetic opioids	45K

Table 1. Comparison of commercially available products for trace detection of synthetic opioids.

processing, speed of instrument set-up, ability to resolve mixtures, on-board libraries and cost. For the trace detection technologies, most commercial products measure in the mid-nanograms range which is well below the toxicity threshold for an analgesic effect.

Each of the products listed have different capabilities which make them of high interest to the operational community. The MX908, a high-pressure approach to mass spectrometry, released a software update in December 2017. This incorporates the new drug hunter mode allowing the operator to uniquely identify synthetic opioids in mixtures down to 1% of total product while also providing unique identification of the analogues. It is the only system that identifies the molecular ions of the synthetic opioids and can differentiate between materials with the same molecular weight. It incorporates a platform-specific library as a result of this unique high pressure MS approach.

The other MS approaches incorporate gas chromatography (GC) where chemical separation is utilised with an MS detector. The FLIR Griffin 510 which uses a strong electron ionisation technique, followed by quadrupole detection and library matching is an example of a GC-MS. It does not allow for identification of the molecular ion of a species, but it will provide for consistent library matching and can use widely available electron ionisation libraries, such as that developed by NIST, thereby greatly increasing its operational utility. The Inficon Hapsite GC-MS system follows the same concepts as the FLIR Griffin 510. Smiths Guardion is another GC-MS system, but it uses an ion trap detector. This system is widely deployed in the defence community.

The Smiths IONSCAN 600 is an IMS system that is widely used in aviation security around the world. Bruker's handheld RoadRunner is likely the newest IMS on the market. Recent additions of synthetic opioids to the libraries have greatly increased their utility for border security applications. As the IMS systems add more synthetic opioids to their libraries, they will continue to see more operational utility in the narcotics detection trade space. Unlike many commercial IMS instruments, both the Smiths IONSCAN 600 and the Bruker RoadRunner do not use radioactive ion sources, therefore they do not require periodic testing for radioactivity and do not have the logistics burden associated with many older IMS models.

Another consideration which is more applicable to trace detectors is the time required for the system to turn on and be ready for operations. Of the instruments studied, the MX908 takes approximately one minute, the Guardion takes five minutes, the IONSCAN 600 takes up to 10 minutes, the Griffin 510 takes 15 minutes, and the RoadRunner takes up to 30 minutes.

Choosing a bulk detector for field operations

The technologies that are suitable for the bulk detection of synthetic opioids (greater than a microgram) include Raman spectroscopy, infrared spectroscopy, and colorimetric chemistries. For bulk detection, the commercial products are measuring in the microgram range which is well below the lethal dose.

Raman spectroscopy instruments can further be divided into spatially offset Raman spectroscopy (SORS) and

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standard Raman spectroscopy. The only commercial SORS product is the Resolve from Cobalt Light Systems, a part of Agilent Technologies. SORS provides the unique capability of seeing through opaque and non-opaque containers up to several millimetres in thickness, except for metals, in addition to the standard vial-based and surface detection techniques. The Cobalt Light Resolve is a handheld SORS product that utilises a 830nm laser. Many other Raman systems on the market utilise other laser wavelengths, with the most common being 785nm and 1,064nm. The 785nm wavelength provides the lower limits of detection and the 1,064nm wavelength provides less interference from sample fluorescence. Other enhancements such as the surface enhanced Raman spectroscopy TacPac Adaptor with the B&W Tek TacticID and the H-kit with the Thermo TruNarc in addition to the 1,064nm wavelength in the Rigaku Progeny ResQ, allow for the operational evaluation of heroin and other highly fluorescent materials with a standard Raman spectrometer.

Infrared spectroscopy is another vibrational spectroscopy, like Raman spectroscopy, but it does not have issues with fluorescence. The sample preparation required to utilise infrared spectroscopy can be a drawback for field use. The DHS SAVER programme

	Size / Weight	Selectivity	Sensitivity	Logistics	Sample Speed	Set Up Speed	Mixtures	Library	Est. Cost (USD)
Cobalt Light Resolve	4.9lb	Spatially Offset Raman (830nm)	Mid-microgram		Seconds to minutes	< 1 min	Problematic < 10%		55K
Rigaku Progeny ResQ	3.5lb	Raman (1064nm)	Mid-microgram		Seconds to minutes	< 1 min	Problematic < 10%		50K
Thermo TruNarc	1.25lb	Raman (785nm)	Mid-microgram		Seconds to minutes	< 1 min	Problematic < 10%		25K
B&W Tek TacticID	2lb	Raman (785) with SERS	Mid-microgram		Seconds to minutes	< 1 min	Problematic < 10%		25K
Thermo First Defender	2.0lb	Raman (785nm)	Mid-microgram		Seconds to minutes	< 1 min	Problematic < 10%		45K
Thermo Gemini	4.2lb	Raman (785nm) and Infrared	Low to Mid-microgram		Seconds to minutes	< 1 min	Problematic < 10%		85K
Thermo TruDefender FTX	3.1lb	Infrared	Low microgram		Minutes	< 1 min	Problematic < 10%		45K
Smiths Hazmat ID Elite	5.1lb	Infrared	Low microgram		Minutes	< 1 min	Problematic < 10%		45K
Mistral Security Fentanyl test kit		Colour	High microgram		Seconds	< 1 min		n/a	<$2/ sample
DetectaChem Fentanyl test kit		Colour	High microgram		Seconds	< 1 min		n/a	<$2/ sample

Table 2. Comparison of commercially available products for bulk detection of synthetic opioids.

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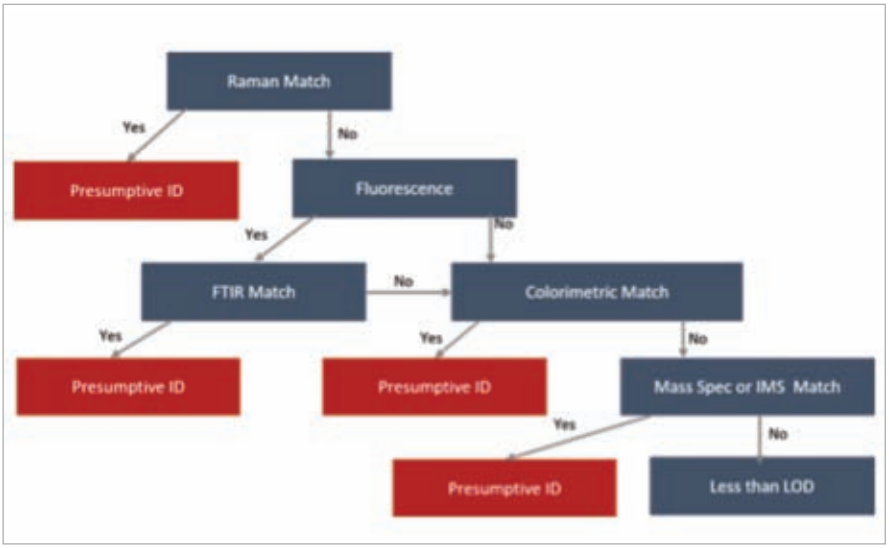
evaluated infrared spectroscopy technologies in 2016 and found the following systems to be the highest performers: Thermo Fisher Scientific Gemini, Thermo Fisher TruDefender FTX, and the Smiths Detection HazmatID Elite. The Gemini received the highest usability rating of all three and has the added capability of integrated Raman spectroscopy within the same instrument.

When determining the best system for your operational needs, it is imperative that the operator understands the materials contained within the library on the system and the reach-back support provided by the vendor. If your team has scientific support readily available, technical reach-back may not be as important. For any library based system, the ability to add new threats and the work required to gather library spectra is important. For example, in the MX908, all forms of fentanyl (hydrochloride, oxalate, citrate, free base) are converted to the free base form prior to identification, therefore only one library spectrum is required. For Raman and infrared based systems, all the forms must be in the library.

Finally, colorimetric chemistries are available which are specific to fentanyl. Two commercial products include the Mistral security fentanyl test kits and the DetectaChem fentanyl test kits. Both systems can differentiate fentanyl from other opioids, cocaine, and methamphetamine. While there are many other colorimetric chemistries on the market, they generally use the Marquis reagent (cross sensitive to methamphetamine) or the nitric acid reagent (cross sensitive to heroin).



An example of a sample that was identified following a similar detection scheme can be viewed at: https://vimeo.com/246311939/9b9dc08498. The sample in this case is a low percentage mixture of heroin and fentanyl, thereby ruling out the use of Raman and infrared spectroscopy.

A decision logic for detecting synthetic opioids

If you are part of an operational response team that has the luxury of a broad inventory of detection technologies, there are several ways you can address the synthetic opioid threat and take best advantage of your technologies. The following example is meant to quickly identify synthetic opioid threats while minimising samples required. First, a 'point and shoot' sample can be acquired for Raman spectroscopy, if the sample is less than 10% of the target material or it fluoresces (especially if heroin is present), then an infrared match is obtained. If the sample is less than 10% of the target material, then the user is pushed towards a colorimetric technique. Finally, when all else fails, the mass spectral or IMS trace technique is utilised to see if trace amounts of the target material are present. Note: if you are going straight to the mass spectrometry or IMS approach, be sure to minimise the total sample presented to the instrument (by taking a swab of a swab of a swab).

As with any high threat material, once a presumptive identification is determined in the field, it is best to package up the remaining material and send it to the laboratory for final identification.

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