Dr Christina Baxter, CEO of Emergency Response TIPS and partner in Hazard3 and Dr. Michael Logan, Director of Research and Scientific Branch, Queensland Fire and Emergency Services revisit Synthetic Opioids In Operational Environments

Some more sugar in my bowl…

In 2017 and 2018, we brought you a series of three articles covering detection[1] decontamination[2], and protection[3] from synthetic opioids. This article is a follow up to the threat of synthetic opioids in operational response to narcotics or terrorism related events. Unfortunately, the opioid epidemic has continued to take its toll across the world despite the pandemic - both as a drug epidemic and as an elevated terrorism threat due to increasing availability.

To illustrate these changes, the US Drug Enforcement Administration and US Customs and Borders Protection have recognised that since 2019 fentanyl has increasingly been manufactured and sourced in Mexico instead of China[4]. The amount seized originating from Mexico has also increased. It was typically high volume, low purity loads, however, they have found that purity has also increased by more than 10% from a low level (c 8%), while seizures of smaller packages of high purity fentanyl (often above 90%) sent by air have decreased[4]. These evolving illicit importation approaches have implications globally for all border protection agencies and demonstrate that supply diversification is occurring.

Physical properties

Synthetic opioids are crystalline particulates with a median size of two microns; however, size distribution is dependent on such factors as product purity, production method, and adulterants or cutting agents in the final product[5,6,7]. In addition, the vapour pressure is negligible. Why is this important? Synthetic opioids are a respiratory threat as a result of the fentanyl particulates, not by vapour phase. Synthetic opioids tend to have estimated boiling points above 350°C and decompose thermally instead of changing from a liquid to a gas[8,9,10,11,12]. Therefore, at high temperatures they degrade into other chemicals reinforcing that the vapours are not a significant threat.

The threat to responders is primarily to the respiratory system from inhalation of airborne particles. Synthetic opioids particulates on surfaces can be readily resuspended in air. Many factors affect the lifetime of such suspended fentanyl particulates, including electrostatic properties, humidity and particle agglomeration[13]. Particles in the one to three micron size range can stay airborne for 1.5 to 12 hours in still air and longer in turbulent air, which can be caused by open windows, air conditioning etc.

The solubility of synthetic opioids is also important as it drives toxicology and decontamination considerations. Different analogues and salt forms can have very different solubilities[12,14,15,16,17]. Generally, hydrochloride salts tend to be more water soluble than citrate and oxalate salts while the free base tends to be the least water soluble. The opposite is often seen with alcohol solubility.

Toxicology

It is important to understand that synthetic opioids are inhalation, ingestion and dermal absorption hazards. While inhalation is the predominant route of exposure of concern to emergency responders, ingestion and dermal absorption should not be ignored and these routes must be minimised or eliminated. The early symptoms of opioid exposure include lethargy, decreased respiratory rate and pinpoint pupils which can then progress into a coma, apnea and death[18].

While occupational exposure standards are not currently available internationally, the US Pharmacopeia, a non profit scientific organisation that develops and disseminates pharmaceutical standards, has published a recommended eight hour time weighted average value (TWA) of 0.1 µg/m3 and a 15 minute short term exposure limit (STEL) of 2.0 µg/m3 for fentanyl exposures[19]. Cambrex Inc uses 0.04 µg/m3 for an eight hour TWA for carfentanil exposure[20]. In addition, the US Environmental Protection Agency has published provisional advisory level (PAL) recommendations that include: 24-hour not to exceed levels for fentanyl inhalation are 0.0037 µg/m3 for serious, possibly irreversible health effects and 0.011 µg/m3 for lethal effects[11].

As inhalation is the predominant entry route, it is important to note that synthetic opioid particles will penetrate deep into the lungs due their small particle size. The salt forms will be readily absorbed and dispersed faster through the blood stream due to high water solubility, but the free base forms will also make their way into the blood stream over time[21]. The salt forms therefore give higher doses more quickly, but salts and free bases can have long-lasting effects. Synthetic opioids with higher water solubility will also be readily absorbed into mucous membranes.

Synthetic opioids can penetrate intact human skin, but this route of transmission is very slow, taking hours[22]. The penetration rate is affected by the fentanyl form (free base faster than salts), state (liquid faster than solid), skin temperature (sweaty faster than dry skin), skin pH (higher pH faster than lower pH), and the presence of alcohol based sanitisers (more influence on free base forms)[22,23]. Due to the slow dermal penetration rates, the best solution is to adopt working practices and PPE to prevent skin contact, and wash skin with soap and water as soon as possible after contact.

Detection

There have been plenty of reports on research into fentanyl detection, especially in the field, but much remains the same for responders. Mass spectrometry is still the go-to for trace level detection, while Raman, FTIR, immunoassay, and colorimetric technologies are used for bulk detection. As the targeted synthetic opioids have evolved, the libraries for highly specific spectroscopy and spectrometry instruments have evolved in parallel. The biggest change in trace detection since our last paper has been the addition of an aerosol interface for the

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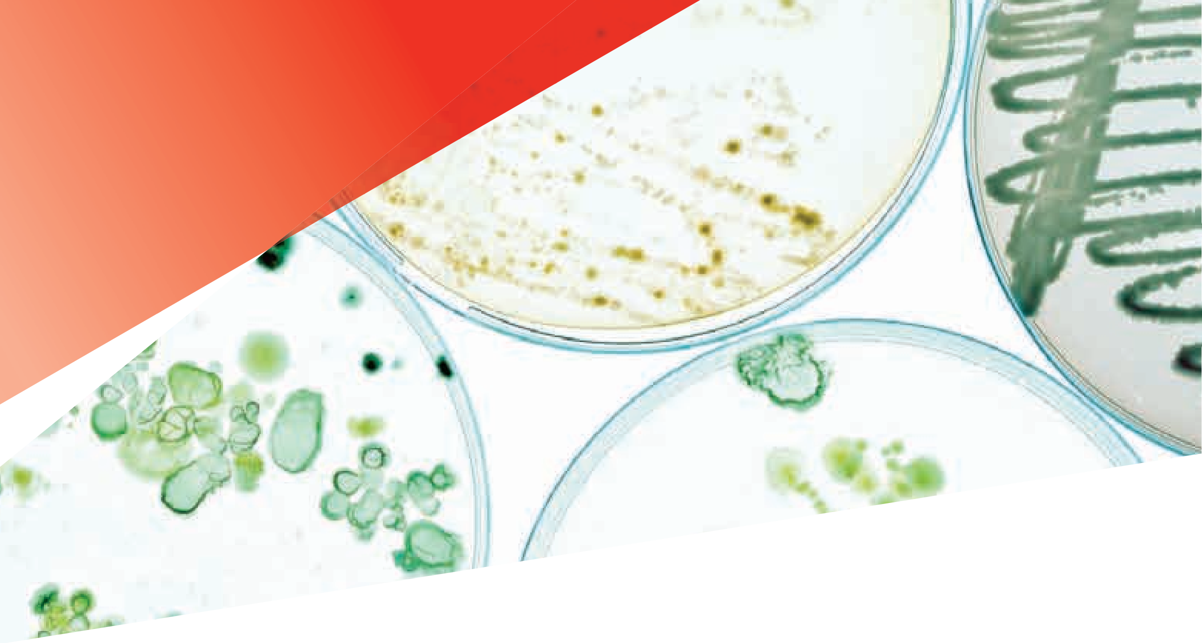

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high pressure mass spectrometry system (MX908) which allows for the collection and continuous monitoring of the environment for gas, vapour, and particulate threats. The team from 908 Devices has continued to grow its high hazard threat library to include the newer synthetic opioids and has developed a reach back capability to predict the structure of new synthetic opioids to assist in investigations. The FLIR G510 gas chromatography mass spectrometry product was relatively new during our first suite of papers on this topic. Since then considerable strides have been made in automated sampling protocols and instrument routines to make the system much easier to use and more sustainable in the operational environment.

Surface-enhanced Raman spectroscopy (SERS) exploits the interaction between the molecule of interest and a metal surface (generally gold or silver), resulting in an enhanced Raman signal, which can overcome the signal attributed to molecular fluorescence[24]. The approach has much potential and is receiving more and more attention; there is a considerable amount of research ongoing in this space with a few commercial products highlighted below. In operations involving synthetic opioids, this can be critical as materials such as heroin and many cutting agents tend to have high fluorescence. Limits of detection for fentanyl using SERS can be as low as five nanograms/mL or 500 picograms making this technique suitable for ultra trace detection[25,26,27]. More importantly, SERS can detect fentanyl in as low as 1% mixture with heroin or 5% mixture with cocaine[25].

The first SERS capability in the emergency response market was the H-kit from Thermo Scientific which was utilised with the TruNarc product to overcome heroin fluorescence. More recently, Thermo Scientific has expanded the H-Kit applicability to the Gemini product as well. The next product to market was the B&W Tek TacticID TacPac Adaptor which Metrohm has since procured. Metrohm also offers a SERS capability with its Mira product line. Serstech's recent introduction to the market features a disposable magnetic sample interface to ensure proper seating, a quick sample preparation step, and then attaches directly to the standard sample interface where it is rotated and vibrated. The evolution of SERS products into easy to use systems makes it a viable growth area in the marketplace. Keep an eye on this space as it is evolving rapidly, the applications are expanding, and the libraries are getting larger to allow for detection of mixtures or highly fluorescent materials in operational environments.

Raman and FTIR technologies continue to be mainstays in emergency response detection and identification, with many products on the market. These include Bruker, Agilent/Cobalt Light resolve, the Rigaku Progency ResQ and CQL, the Thermo First Defender and Gemini to highlight a few, familiar to most responders. The more recent entries into the Raman market take advantage of newer techniques to set themselves apart. For example, the Pendar X10 utilises differential Raman spectroscopy to reduce fluorescence and provides a proximity stand off capability up to two metres away from the sample. The Pendar algorithms for library matching and mixtures analysis utilise a chemometrics approach making them highly accurate. The Thermo Scientific FirstDefender 1064 joins the Rigaku in the market for longer wavelength products. Market consolidation has also occurred, as illustrated by Metrohm's Mira product line, which has benefited from this. It includes a variety of attachments for SERS and proximity detection enhancements.

The only change in the FTIR marketplace since our last paper has been the introduction of the RedWave ThreatID which provides solid, liquid, and gas capabilities in one instrument with easy to swap interfaces. The ThreatID software as well as its mixture algorithms provides operators with enhanced capabilities. The Thermo TruDefender FTX, the Thermo Gemini, and the Smiths Hazmat ID Elite continue to provide excellent solid and liquid detection capabilities.

All the commercially available systems, whether Raman or FTIR, have continuously updated their products, and libraries in parallel with new synthetic opioids being identified, developed new applications, and in the case of Raman, have developed new SERS capabilities. For further information on the detection of synthetic opioids, please see our paper in *CBRNe World*, December 2017.

Protection

The recommended respiratory protection for operational responses to events involving synthetic opioids is unchanged - a P100 respirator when up to one gram of product is visible and upgrading to self-contained breathing apparatus for larger amounts or high purities. The chemical protective clothing required for synthetic opioids also remains the same - nitrile gloves and duty uniforms at the low levels (grams) and particle tight ensembles for larger amounts or high purities. The protective clothing and accessories chosen should meet suitable standards (NFPA 1994 in the US) and should be selected considering the task, its duration, location, situation, hazard, and potential for contact.

Decontamination

The single most important factor when dealing with synthetic opioids is to protect the respiratory tract. This is closely followed by protecting mucous membranes such as the eyes, nose and mouth. The skin should also be protected and opportunities for contact with synthetic opioids minimised.

From a decon perspective, if contamination of the eyes and mucous membranes is suspected, they should be flushed immediately with copious amounts of saline solution or water to remove all the contaminant and minimise the dose. Immediate medical support should then be provided.

Areas of direct skin contact with any residue suspected of containing synthetic opioids should be immediately washed with copious amounts of water As soon as feasible, skin surfaces should be washed again with soap and water, using a skin-safe, low-pH soap with a sponge or wash cloth and applying

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minimal pressure. Next, rinse the body with clean water using a low-pressure application; and wiping all body surfaces with a towel until they are dry.

If no expedient decontamination method is available, use a non alcohol based, low-pH wipe to remove as much potential contamination as possible as an emergency decon procedure. It should be noted that the efficacy of wipes for removing threat materials, including synthetic opioids, has not been well characterised. Response agencies should review the policies and ensure that field decontamination approaches are proportionate to the operational context.

Summary

While the synthetic opioid epidemic has continued, the specific threat materials have evolved, scientific studies have been performed, and new products have entered the market, operational guidance for safely responding to synthetic opioids is unchanged. A safe and effective response to events involving synthetic opioids includes:

- Minimising opportunities to generate airborne particulates.
- Minimising opportunities for unexpected exposures.
- Wearing appropriate respiratory and dermal protection.
- Ensuring appropriate field expedient decontamination is available and minimising exposure by flushing mucous membranes or washing skin as soon as practical after exposure.

Training, using medically accurate information, has been shown to mitigate the promulgation of the myth that dermal exposure can result in an overdose[28]. Review your agency and allied responder approaches to ensure they are up to date and appropriate for your operational context. To help, follow the Department of Homeland Security's master question list (MQL) for synthetic opioids for future updates[21].

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