TERROR
Strengthened preparedness and response to biological and chemical terror attacks

Co-funded by the Health Programme of the European Union

WP8 Novel Threats

WP8 Synthetic Opioids- Literature Review

Authors:

Anders Östin[1], Viktor Péter Nyitrai[2], Carola Grub[3], Lara Ježić[4], Eric Deconinck[5], Jessica Jones[6]

Affiliations:

[1] Swedish Defence Research Agency; Sweden
[2] National Centre for Public Health and Pharmacy; Hungary
[3] Norwegian Defence Research Establishment; Norway
[4] Croatian Institute of Public Health; Croatia
[5] Sciensano; Belgium
[6] UK Health Security Agency; United Kingdom

Contents

This report arises from the TERROR Joint Action, which has received funding from the European Union through the European Health and Digital Executive Agency of the European Commission, in the framework of the Third Health Programme 2014-2020. The European Commission is not responsible for the content of this report. The sole responsibility for the report lies with the authors, and the European Health and Digital Executive Agency is not responsible for any use that may be made of the information contained herein. The authors are not responsible for any further and future use of the report by third parties and third-party translations.

Terms and abbreviations

ASTM	American Society for Testing and Materials
ATR-FTIR	Attenuated total reflectance (ATR), a widely used sampling methodology for Fourier transform infrared (FTIR) spectroscopy.
CBRN	Chemical Biological Radiological and Nuclear agents
CND	The Commission on Narcotic Drugs
CPR	cardiopulmonary resuscitation
CWC	Chemical Weapons Convention
DEA	USA Drug Enforcement Administration
ED50	Median Effective Dose
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EPA	United States Environmental Protection Agency
EWS	Early Warning System
GC-MS	Gas chromatography–mass spectrometry is an analytical method that combines gas-chromatography and mass spectrometry to identify different substances within a test sample.
INCB	International Narcotics Control Board
LC-DAD	Liquid Chromatography with Diode Array Detection
LC-HRMS	Liquid chromatography-high resolution mass spectrometry
LC-MS	Liquid chromatography–mass spectrometry is an analytical technique that combines liquid chromatography with the mass analysis capabilities of mass spectrometry
LC-QTOF	Liquid Chromatography Quadrupole Time-of-Flight mass spectrometry
NMR	Nuclear Magnetic Resonance
NPS	New Psychoactive Substances
NSO	Novel Synthetic Opioids
OPCW	Organisation for the Prohibition of Chemical Weapons
OUD	Opioid Use Disorder
RCA	Riot Control Agents
SCBA	Self-contained breathing apparatus
QTRAP LC-MS/MS	Quadrupole Linear Ion Trap Liquid Chromatography Tandem Mass Spectrometry
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organisation

Executive summary

This review examines the complex dangers associated with synthetic opioids with a particular focus on their potential for misuse as a tool for terrorism. It navigates recent developments in drug evolution, including drug seizure information, incident response strategies, advancements in analytical methods for new opioid detection, and provides an overview of current and prospective medical countermeasures. The core objective is to scrutinize the relationship between synthetic opioids and terrorism, noting the enhanced potency, increased accessibility, and previous instances of their deployment as weapons.

A critical concern highlighted is the immense risk synthetic opioids, especially fentanyl and its derivatives, but also others like the nitazenes, pose to first responders. The review suggests that the high toxicity of these substances necessitates improved protective protocols and response strategies to mitigate exposure risks for frontline workers.

On the analytical front, the review acknowledges challenges in swiftly and safely identifying novel synthetic opioids, especially for on-site analysis in the context of a first risk assessment. Laboratory techniques such as Gas Chromatography–Mass Spectrometry (GC-MS), Liquid Chromatography with tandem Mass Spectrometry (LC-MS/MS) and Liquid chromatography-high resolution mass spectrometry (LC-HRMS) are explored for their pivotal roles in detecting novel or emerging opioid variants, ensuring the safety of those tasked with their identification.

Medical countermeasures discussed in the review point to the complexities surrounding the diagnosis and treatment following synthetic opioid exposures. It draws attention to the intricacies of addressing mass casualty scenarios and the critical need for awareness regarding opioid overdoses, which often necessitate specialized medical responses.

While this review provides a comprehensive snapshot of the current state of synthetic opioids and their implications in terrorism and public health, it does not delve into the impact of Artificial Intelligence (AI) in the development and distribution of these drugs. Nonetheless, the authors recognize AI as a significant emerging factor that is likely to profoundly influence the landscape of synthetic opioid creation and misuse. Although AI is not covered extensively in this review, it is identified as a critical area for future monitoring due to its potential to accelerate scientific advancements in drug discovery, design, and production in ways yet to be fully understood.

Through this exploration, the review aims not only to inform but also to serve as a call to action for continuous surveillance, research, and policy development to mitigate the risks posed by synthetic opioids. Given the dynamic nature of synthetic biology, drug development, and AI, the field requires ongoing vigilance and adaptation to safeguard public health and security.

Joint Action TERROR

The European Union (EU) plays an important role in counter-terrorism activities. While primary responsibility for security measures lies with individual Member States, the EU provides a borderless perspective that encourages cooperation and coordination through numerous policy frameworks.

EU Regulation 2022/2371 (Council of the European Union, 2022) seeks to build a stronger EU health security framework by improving coordination between the European Commission and other EU agencies. The regulation was formally adopted during the lifecycle of Joint Action TERROR and repeals Decision No 1082/2013/EU on serious cross-border threats to health. It provides the framework to improve preparedness and to strengthen the response capacities to health emergencies of biological, chemical, environmental, and unknown origin.

The 2009 Commission Working document 'Bridging Security and Health' identified areas that could be strengthened. It states, among other issues, that Member States preparedness in health would benefit from sharing lessons learned and best practices in, among other issues, cross-sectoral support, and coordination.

To support this, Joint Action TERROR's main objectives were to address gaps in health preparedness and to strengthen cross-sectoral work with security, civil protection, and health sectors response to biological and chemical terror attacks.

Joint Action TERROR aimed to build upon work undertaken for the Health Programme and other relevant EU programmes and exercises in particular Joint Action "Strengthened International Health Regulations and Preparedness in the EU" (SHARP) and the Joint Action "Healthy Gateways".

Introduction

Synthetic Opioids

Synthetic opioids are man-made compounds created through chemical synthesis, designed to mimic the effects of natural opioids but are often much more potent than their natural counterparts. Natural opioids, such as morphine and codeine, are derived from the opium poppy plant and exert their effects by binding to opioid receptors in the brain and body, leading to pain relief, euphoria, and, in higher doses, sedation, respiratory depression and cardiac arrest. In contrast, synthetic opioids like fentanyl and its analogues (carfentanil, acetylfentanyl, cyclopropylfentanyl, and acrylfentanyl) (figure 1)

exhibit potent analgesic properties and can be dozens to hundreds of times stronger than morphine (Armenian et al., 2018). The potency of synthetic opioids has contributed to their widespread illicit production and use, posing a higher risk of overdose and death (Jannetto et al., 2019; Misailidi et al., 2018).

The synthetic opioid fentanyl was originally synthesised by Janssen in 1958 (Janssen et al., 1958) to be used for anaesthesia and analgesia. It proved to be 100 times more potent than morphine and became widely used in medical settings in the decades that followed. Its potency led to instances of misuse both by clinicians who overprescribed or wrongly prescribed the drug, and by criminals engaged in illegal drug manufacturing and trafficking.

New Psychoactive Substances (NPS), which include synthetic opioids, have garnered significant attention due to their emergence on the global drug market for recreational use. NPS are defined by the United Nations Office on Drugs and Crime (UNODC) as "a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions". The expression "new" refers to its emergence on the global drug market for recreational use rather than a newly created substance.

These new drugs are synthesised to mimic known illegal drugs and to evade regulation through slight changes to the chemical structure (Armenian et al., 2018). Only in countries with a generic drug legislation which regulates basic structures of molecules are these new drugs considered illegal. Furthermore, availability is not limited to illicit markets, as they can also be openly purchased online in some regions (Negri et al., 2021).

Novel Synthetic Opioids (NSO) are a more specific subset of NPS that focuses specifically on opioid-like substances. NSO are synthetic compounds that have been designed to act on opioid receptors. Some NSO have extremely high potencies even in minute quantities, which raise the concern that these compounds have the potential to be misused in antagonistic incidents. NSO feature heavily in illegal markets as a drug of abuse and an adulterant in falsified medicines and traditional narcotics (Green & Gilbert, 2016).

Synthetic Opioid Use in Europe

Synthetic opioids in Europe represent a complex and evolving challenge, distinct in nature and scale from the opioid crisis observed in the United States. The European landscape of opioid use is characterized by a lower prevalence compared to global averages, with 0.7% of the population aged 15–64, which is approximately 3.6 million individuals, engaging in opioid use, primarily heroin (UNODC, 2022).

Despite this lower prevalence, the continent faces its own set of challenges with the emergence of new psychoactive substances (NPS), including synthetic opioids. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), through its EU Early Warning System and collaborative efforts with Europol, plays a pivotal role in monitoring and mitigating the public health threats posed by these substances. Since late 2015, this surveillance has led to numerous investigations into new fentanyl analogues, highlighting the potential risks they present (EMCDDA, 2021).

According to the EMCDDA's 2021 annual report, 10 of the 67 new synthetic opioids discovered between 2009 and 2020 were first reported in Europe in 2020. Following the predominance of fentanyl in 2017, non-fentanyl opioids have dominated opioid seizures since 2019. A rise in potent synthetic opioids such as isotonitazene (figure 1), has been implicated in drug-related deaths across Estonia, Switzerland, and the United Kingdom, and observed in law enforcement data across several European countries (EMCDDA, 2019).

Despite the challenges presented by synthetic opioids, the European response has been robust, characterized by advanced monitoring systems and international cooperation. Further, the distinct difference in health-related systems between the USA and European countries including access to healthcare; access to medicines and strict advertising standards surrounding medical products, has assisted in the stabilization of drug-related deaths. The sharp increases seen in North America have not been observed in Europe which suggests a level of effectiveness in these approaches. Nonetheless, the dynamic and adaptive nature of synthetic opioid markets requires continuous vigilance and adaptation from European authorities to safeguard public health and respond effectively to emerging threats.

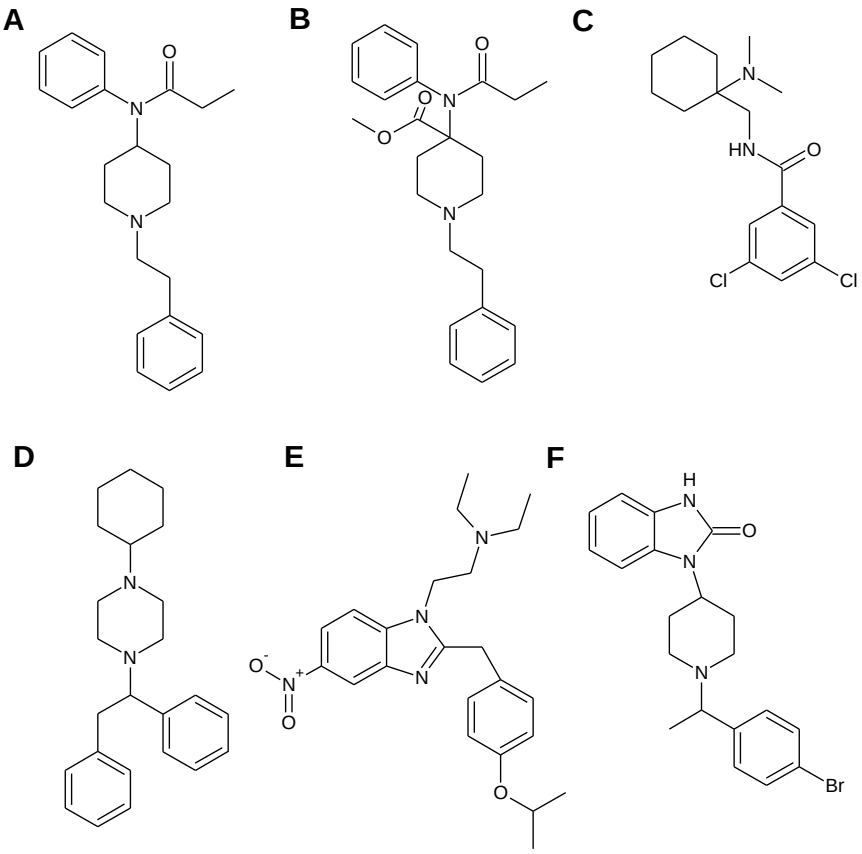

Figure 1 : New synthetic opioids emerging in Europe A) fentanyl B) carfentanil, C) AH-7921, D) MT45 E) Isonitazene F) buprenorphine (Jannetto et al., 2019)

Legislation and surveillance

The European Union's approach to synthetic opioids and drug control is shaped by a suite of legislation and regulations, each with distinct functions and oversight entities. Central to this framework is the EU Drug Strategy and Action Plans, delineating the EU's overarching drug policy, alongside the Early Warning System (EWS), managed by the EMCDDA, which plays a critical role in identifying and assessing new psychoactive substances. The Council Framework Decision 2004/757/JHA ensures the establishment of minimum standards for drug trafficking penalties across the EU, complemented by regulations governing the control of chemical precursors necessary for the production of synthetic opioids. National legislation within EU member states further refines and adapts the EU drug policy to meet local challenges.

On a global scale, the Single Convention on Narcotic Drugs of 1961, the Convention on Psychotropic Substances of 1971, and the UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, overseen by the Commission on Narcotic Drugs (CND), the World Health Organization (WHO), and the International Narcotics Control Board (INCB), provide a foundational legal basis for the classification and international control of narcotic drugs and psychotropic substances, aiming to curb illicit trafficking and misuse worldwide.

Table 1: Legislative acts relevant to the control of synthetic opioids

Legislation/Regulation	Key Functions	Territorial scope
EU Drug Strategy and Action Plans	Outlines EU's comprehensive drug policy	European Union
Council Framework Decision 2004/757/JHA	Sets minimum standards for drug trafficking penalties	European Union
EU Regulations on Precursors	Controls chemical precursors for synthetic opioids	European Union
National Legislation	Tailors EU drug policy to specific local challenges	EU Member States
Single Convention on Narcotic Drugs of 1961	Informs drug classification systems at the UN level	CND, WHO, INCB
Convention on Psychotropic Substances of 1971	Regulates international control of psychotropic substances	CND, WHO, INCB
UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988	Addresses illicit trafficking of drugs and substances	CND, WHO, INCB

Information gathering on circulating drugs

The most effective strategy for identifying previously unreported NPS molecules, such as new synthetic opioids, involves surveillance of the drug market. This can be conducted through various channels, including seizure information, analysis of drugs being sold online, information from poison

centres, syringe exchange programs, and drug testing programs, which serve the dual purpose of both harm reduction and law enforcement.

Syringe exchange program

The aim of syringe exchange programs is to reduce the transmission of blood diseases such as HIV and hepatitis. Used syringes can be sent for laboratory analysis to provide information about what drugs are being used in different areas and provide an early warning for new emerging drugs. Comparing results with self-reported data provides information regarding what drugs people believe they are using compared to what they have actually used. This approach has been in use in Norway where returned needles were analysed using the laboratory technique UHPLC-MS/MS and concluded that the most common drugs were heroin, (meth-)amphetamines and benzodiazepines which correlated with the self-reported data (Gjerde et al., 2023). Similarly, in Sydney, Australia used syringes were analysed using laboratory GC-MS which showed that heroin, methamphetamines and oxycodone were the most abundant drugs amongst people who inject (Lefrancois et al., 2020). In the USA, syringe exchange programs have been investigated in the Washington area (Evans et al., 2021) and in New York (Fiorentin & Logan, 2020). In these studies, fentanyl, fentanyl analogues as well as by-products from synthesis and degradation products were identified.

Drug testing services

Some countries offer a point-of-care service where people can submit drug samples in order to determine drug content and reduce harm from the illegal use of drugs (for example, The Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS)). To provide rapid and easy to handle analysis capability, point-of-care services are equipped with colorimetric tests, TLC, ATR-FTIR and fentanyl immunoassays. The simplified tests come with drawbacks in that only the main components will be identified while compounds present in small concentrations will be undetected. Due to the high toxicity and the use of fentanyl as an adulterant, fentanyl immunoassays are added to the analysis. For more in-depth analysis, laboratories with professional personnel and techniques such as GC-MS and LC-MS would be required (Ti et al., 2021; Tobias et al., 2021).

Synthetic opioids: Illicit drug or chemical weapon

To ensure a comprehensive understanding of NSO, particularly fentanyl analogues, as potential threat agents, it is crucial for scientists, military experts, policymakers, and lawyers to have a clear understanding of the distinctions between different groups of threat agents (Mathews, 2018). From a military viewpoint, chemical weapons were initially developed for various tactical purposes and were classified into three classes by the World Health Organization (WHO) in 1970:

- **Lethal agents**: Intended to inflict severe injury or death upon the opponent, such as nerve agents, blister agents, and blood agents.
- **Incapacitating agents**: Also known as central nervous system-acting or psychoactive substances, designed to disable the opponent for a limited time (hours or days) without requiring hospital care, e.g., BZ.
- **Harassing agents**: Also referred to as riot control agents (RCA). These irritating agents force unprotected opponents to vacate an area, examples include tear gas and pepper spray.

The Chemical Weapons Convention (CWC), enforced by the Organisation for the Prohibition of Chemical Weapons (OPCW) since April 29, 1997, is an arms control treaty. It prohibits the use, development, production, stockpiling, and transfer of chemical weapons and their precursors. As a result of this convention, the overwhelming majority of declared lethal military chemical weapons across the world have been destroyed. One notable synthetic opioid, BZ, was developed and weaponized in the past as an incapacitating agent (Ketchum, 2006), but current stockpiles of such agents are disarmed in compliance with the chemical weapons convention. According to the CWC, all the aforementioned military classes are considered toxic chemicals and are prohibited from use in conflicts between nations.

In this context, NPS, particularly fentanyl analogues, possess the potential to act as incapacitating threat agents. Historical reports indicate two instances where fentanyl substances were employed as knock-out agents. The first occurred in 1997 when the Israeli intelligence service Mossad targeted Palestinian Hamas leader Khaled Meshal, blowing toxic dust into his ear during his exile in Amman, Jordan (Gummin, 2020). Although some agents were apprehended, political pressure led to Israel providing the antidote, and Khaled Meshal eventually recovered. The second incident took place in 2002, when a Russian Special Rapid Response Unit used fentanyl analogues, specifically carfentanil (a

tranquilizer for large animals) and remifentanil (a short-acting sedative), as a knock-out gas during an assault on hostage takers at the Moscow Dubrovka theater. Medical personnel on-site were unaware of the knock-out gas, resulting in several fatalities (Riches et al., 2012). The use of central nervous system acting (CNS-acting) chemicals by the Russian response unit raises awareness of fentanyl analogues as a potential weapon, capturing the attention of other nations, criminals, and terrorists. Discussions regarding the classification and use of CNS-acting chemicals as RCAs have taken place within the OPCW, with the Scientific Advisory Board discouraging their classification and use due to the high toxicity and low safety margin of fentanyl and its analogues. The board emphasizes that law enforcement usage cannot be equated with controlled medical usage in a hospital setting (Timperley et al., 2018).

While synthetic opioids possess the potential to cause harm and have been used as incapacitating agents, they do not fit squarely within the category of chemical weapon based on traditional definitions and legal frameworks. The classification of synthetic opioids as such would depend on the specific circumstances of their use, intent, and impact, as well as international legal interpretations and enforcement.

Response to Incident

USA experience of a fentanyl epidemic

Fentanyl and its analogues are highly toxic compounds that can seriously injure responders who encounter these substances during their duties. Therefore, there is a need for universal methods to prevent themselves and others from exposure to the agent. Regardless of whether the presence of the agent is from the handling of illegal drugs or from an antagonistic incident, the risk to field responders remains the same. In the USA, the epidemic proportions of illegal use of fentanyl and its analogues have necessitated the development of national standards and recommendations in order to safely handle this type of threat. Several agencies are involved in providing support to the first responder community with information from the Department of Defense (www.defense.gov), the Department of Homeland Security (www.dhs.gov), the Department of Justice (www.justice.gov) and the National Institute for Occupational Safety and Health (www.cdc.gov/niosh) and further from

collaborative organisations such as the Interagency Board for Emergency and Response (www.interagencyboard.org).

The primary occupational hazard is inhalation of aerosolized material with a secondary dermal hazard caused by direct skin contact with visible amounts of concentrated materials. For first responders, law enforcement and emergency medical personnel, encountering illicit fentanyl or other synthetic opioids within their routine work will not present a significant threat of toxic exposure. Nevertheless, it is important that they are equipped with a proper awareness of potential risks. Fentanyl analogues and most NPS are non-volatile compounds and are found in the drug market as powders, pills, liquids, and nasal sprays. Exposure to these compounds may occur through:

- Inhalation-breathing of aerosolized powder or liquid
- Ingestion-unintentional eating from contamination on hand or contaminated food or drink
- Dermal exposure- exposure on naked skin that could be absorbed
- Touching - eyes, nose with a contaminated hand
- Handling- injury from contaminated material like needles used for drug consumption

With awareness of the risks, proper countermeasures can be taken, and proper protection and decontamination can be performed.

First responders

Anyone in an occupation where they are at risk of exposure to opiates should routinely carry and know how to use naloxone. For first responders, *e.g.*, rescue services, customs, health care and police personnel, protection levels are based on observations made on site. Basic protection, standard uniform and nitrile gloves are recommended when handling overdose incidents. If smaller amounts (grams) of potential toxic material is observed, P100 filtering facepiece respirator (a P100 filter will block 99.9% of particles 0.3 microns or larger) and safety glasses are recommended. Important factors for first responders in contaminated areas are to avoid stirring up dust and to not touch their face. Potential contamination can be removed with the use of water and soap. When decontaminating skin, the soap should preferably be neutral or have low pH since basic conditions favour salt formation which increases skin absorption. Disinfectant based on alcohol should also be avoided since alcohol increases skin adsorption (www.interagencyboard.org.2017).

Hazmat teams

If the scene includes larger amounts of potentially toxic material (kilos) in an identified bulk storage, preparation site of a suspected illegal lab or an antagonistic incident with dispersed agent the protection level must be increased. First responders may cordon off the site as a hot zone area. Special Hazmat-teams with CBRN-trained personnel can provide a higher protection level and decontamination resources for both personnel and the hot zone area (www.interagencyboard.org.2017). The authors' experience is that there are at present two different approaches in the formation of CBRN-teams. In the most common approach, Hazmat-teams consisting of personnel from rescue services, police and military that have been provided with extra CBRN-training. A less frequent approach is to provide operational training to dedicated subject specialists that form an operational Hazmat-team. Support to field personnel from subject specialist can be given in the form of instrument specialists (this can be provided from the instrument manufacturer) that can contribute with in depth knowledge of spectra analysis. Alternatively, the support to the team can be provided via subject specialists for handling the hot zone, in the literature described as reach-back/ back office. These Scientific Advisors may also be integrated in the Hazmat team in more demanding operations (NATO, AEP 66).

On-site detection and field analysis

Identification of a seizure is normally done through sampling followed by transport and laboratory analysis. Documentation of sampling and a proper chain of custody is required for evidence for law enforcement. However, during an incident, information about the current threat may be obtained with field analysis/ detection for identification of the threat and on-site detection of contaminated areas. These results will provide the on-site tactical/operative responsible responder guidance in order to take proper proportional response to the present threat. Recommended procedures for field detection and analysis were developed in the format of an international standard providing guidance for responders performing in field detection and analysis with recommendations about handling samples in the field that have been published as an ASTM standard and provides a useful model for the potential field analysis of fentanyl and other NPS (ASTM, 2021).

The quality of on-site analysis varies from detection with a simple colorimetric test to more robust field analysis using analytical techniques such as ATR-FTIR, Raman and portable GC-MS. In order to understand the quality of the analysis there are formalised scales to describe the quality of the

identification. Within NATO the scale is divided into provisional, confirmed, and unambiguous (NATO, AEP 66). This scale is mainly based on the quality of the obtained data. In contrast, U.S. Army Medicine introduced a scale in which the education level of the analyst and the place of analysis is considered. This scale ranges from presumptive, field confirmatory, theatre validation to definitive identification.

If a threat agent has been dispersed in an area, there are various detection techniques available for Hazmat teams. There are instruments that may be used for purposes ranging from the general detection of the presence of chemicals to the specific detection of agents such as chemical warfare agents, narcotics, or explosives. Fentanyl and other NPS usually have low or no volatility and two approaches for detection of dispersed material could be used 1) detection of the vapour /aerosols during dispersion of the threat agent or (2) through swab sampling and followed by thermal desorption on deposit material. Table 2 provides an overview of various field analysis techniques.

Key field analysis techniques for the detection of synthetic opioids

Technique	Application	Details	References
Flame Photometric Detection	Standard for detecting chemical warfare agents; adapted for fentanyl via swipe sampling to detect nitrogen.	Special swipe sampling device designed for nitrogen detection in opioids.	ProEngin.com
Ion Mobility Mass Spectrometry (IMS)	Drug and explosives detection; includes fentanyl in instrument library, but not all analogues.	Requires pure chemicals; useful for post-dispersion analysis via swab sampling.	(Sisco et al., 2019; Verkouteren et al., 2019)
Electrochemical Sensor	Air surveying; ongoing basic research for fentanyl specificity.	Multigas-sensor used by Hazmat teams; development of fentanyl-specific sensors in progress.	(Barfidokht et al., 2019; Glasscott et al., 2020; Goodchild et al., 2019; Mishra et al., 2020)
Vibrational Spectroscopy	Rapid field identification of chemicals.	Portable, with spectral libraries; libraries more robust and	EMCDDA/SWDRG; European Joint Research Centers;

(ATR-FTIR and Raman)		interchangeable for ATR-FTIR; Raman libraries are instrument specific.	(Kranenburg et al., 2021)
Portable GC-MS (and LC-MS)	Analysis of cutting agents and drugs including fentanyl analogues in the field.	Introduction of liquid injection or SPME-injection has expanded its use.	(Ciesielski et al., 2021; Cooman et al., 2021; Fiorentin et al., 2019; Gozdzialski et al., 2021; Li & Quintero, 2021; Sisco et al., 2019; West et al., 2021)

Table 2: The table provides an overview of available and developing field analysis techniques for the detection of synthetic opioids

Analytics section

The chemistry of synthetic opioids

For analytical investigations of new synthetic opioids (NSO), it is first necessary to define which of the detected compounds are considered to be NSO. Naturally occurring and semi-synthetic opioid derivatives are not considered NSO. Naturally occurring opioids can be divided into two chemical classes: phenanthrenes (morphine and codeine) and benzylisoquinolines (papaverine). The semisynthetic opioids are morphine derivatives. However, all opioid receptor-acting compounds produced by chemical synthesis are considered as NSO. Evidence of opioid agonist activity is the inhibition by naloxone, a competitive opioid antagonist.

NSO can be grouped in several ways, according to their use, mechanism of action and chemical structure. The NSO are grouped according to their basic skeleton, distinguishing biphenyl, morphinan, benzomorphan and phenylpiperidene opioid derivatives. NSO are used in medicine mainly as obstipative, antitussive, sedative and analgesic agents and grouped according to their ATC code as follows: N01AH Opioid anaesthetics (fentanyl, alfentanyl, sufentanyl, remifentanyl, these are otherwise phenylpiperidine derivatives), N02A OPIOIDS, N02AB Phenylpiperidine derivatives, N02AC Diphenylpropylamine derivatives, N02AD Benzomorphan derivatives, N02AE Oripavine derivatives and N02AF Morphinan derivatives. Anti-drugs authorities classify NSOs into the groups

Piperidine (e.g., fentanyl), Benzamide (acetamide) (U derivatives), Piperazine (e.g. MT-45) and Benzylbenzimidazole (e.g. etazene). A more simplified grouping distinguishes only fentanyl and non-fentanyl NSO drugs.

This high chemical diversity and the presence of a high number of structural analogues are the main factors that make the analytical detection of NSO difficult. The toxicity of new synthetic opioids is determined by their potency and their side effects on the body. Fentanyl in milligrams and carfentanyl in micrograms can cause lethal poisoning, which amounts to just two tiny carfentanyl crystals in size.

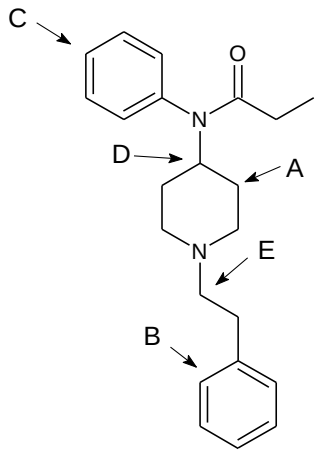

Figure 2: Modifications to the structure of fentanyl. Known potency-enhancing modifications include (**A**) the addition of a methyl group at the 3-position of the piperidine ring (particularly in the cis-position relative to the anilido group), (**B**) an hydroxyl group at the β-position of the phenethyl chain, (**C**) a halogen atom on the aniline or phenethyl rings, especially a fluorine atom at the o-position of the aniline ring, and, particularly, (**D**) a carbomethoxy or methoxymethyl group at the 4-position of the piperidine ring. (**E**) An alpha-methyl group on the phenethyl chain inhibits enzymatic degradation and so increases the duration of the effect.

Modifications to the structure of fentanyl (see figure 2) are expected to alter efficacy by altering the interaction with the opioid receptor or the duration of metabolic degradation. Known potency-enhancing modifications include the addition of a methyl group at the 3-position of the piperidine ring (particularly in the cis-position relative to the anilido group), a hydroxyl group at the β-position of the phenethyl chain, a halogen atom on the aniline or phenethyl rings, especially a fluorine atom at the o-position of the aniline ring, and, particularly, a carbomethoxy or methoxymethyl group at the 4-position of the piperidine ring. An alpha-methyl group on the phenethyl chain inhibits enzymatic degradation and so increases the duration of the effect. Combinations of these modifications can produce extremely potent materials. Carfentanil, for example, is carbomethoxy fentanyl, and the

even more potent lofentanil is 3-methyl carfentanil, while ohmefentanyl combines both the 3-methyl and β–hydroxy modifications of fentanyl. Carfentanil, lofentanil (3-methyl carfentanil) and some stereoisomers of 3-methyl fentanyl and ohmefentanyl (β-hydroxy-3-methylfentanyl), cis-fluoro-ohmefentanyl (Yong et al., 2003), are significantly more potent than fentanyl and therefore present a very severe risk of accidental overdose (Negri et al., 2021). To give an idea, post-mortem typical levels of morphine in blood after an overdose are more than 50 ng/ml, for fentanyl more than 3 ng/ml and for carfentanil more than 0.1 ng/ml (Kahl et al., 2018).

Difficulties of detection from biological samples

Once in the body, the opioid and its metabolites to be identified are often present in the nanogram range, after dilution and metabolisation. The small quantities to be detected is another factor that makes the detection of NSO difficult. It can be assumed that there are deaths where small amounts of an unknown agent are not detected after fatal NSO use, especially when a mixture of drugs has been used.

The most common biological matrices used to detect and quantify these drugs of abuse are blood and urine. However, there are also unconventional matrices such as oral fluid, hair, tissues, vitreous humour, or bile (Bergh et al., 2021; Caspar et al., 2018; Tabarra et al., 2019). Blood, if drawn from a sufficiently isolated peripheral vein, is reliable in determining concentrations and relating them to potential effects at the time of the incident. Urine is more abundant and more easily accessible than blood, does not require an invasive collection procedure, and usually contains higher concentrations of parent drugs and metabolites. The quantities and detection time in urine are influenced by several factors, including in vivo dilution, dose, urine pH, drug pKa, latency time, time between drug/drug administration, drug-drug interactions, drug-disease interactions and genetics.

Although excellent as a screening matrix, for quantification, the usefulness of urine is limited. The amount of drug measured in urine only gives a snapshot of the amount of drug present in the body and it cannot reflect the amount that was present in the body at a time of death. Opioids undergo extensive glucuronidation and/or sulphation, leading to the formation of conjugated metabolites, which can be difficult to detect by immunoassay or Mass Spectrometry. Urine samples should be collected under supervision/monitoring, to prevent sample exchange and in vitro addition of adulterants to the sample. Abundant fluid consumption is a possible masking method, although this can also be detected by measuring urine creatinine and specific gravity. Various methods for the

detection of adulterated samples have been described in literature and are now used in forensic and clinical toxicology. Drug testing in clinical laboratories uses synthetic urine to prepare controls, which unfortunately are now commercially available and can be used to "fool" a positive drug test.

Unlike blood and urine, hair provides a historical picture of drug use in previous weeks or months, depending on the length of the hair. Hair can also be used to detect drug use that occurred during pregnancy, as drugs are incorporated into the hair of the newborn baby. Hair can be segmented to examine drug exposure over a given time window, usually expressed in months. The preferred hair sampling site is the posterior vertex, where there is minimal deviation between hairs. Once drugs or metabolites are incorporated into the hair shaft, they do not undergo further metabolism or degradation (Salomone et al., 2019).

There are several limitations to the use of hair as a matrix. Certain hair treatments, such as bleaching, can affect the incorporation of drugs into hair. It is also difficult deduce recent drug use as it may take up to two weeks for hair to emerge from the skull. Although hair analytics has been in use for more than a decade, there is a lack of standardisation of pre-analytical protocols for samples for pre-treatment and handling. Because many illicit drugs can be vaporized, false positive test results may occur from passive exposure of hair to vaporized drugs in the environment. The ability to distinguish between systemic exposure and external contamination makes it difficult to provide conclusive evidence of exposure to an antagonistic attack.

Saliva is a non-invasive alternative to blood, which offers fewer opportunities for adulteration compared to urine samples. Oral fluid is the collection of saliva and other debris from food and other objects in the oral cavity. Following drug administration, drugs and metabolites are rapidly distributed to the salivary glands and passively diffuse into the saliva within minutes (Heiskanen et al., 2015). Since saliva is an ultrafiltrating substance, only the free or unbound fraction of the drug is carried by the salivary glands into the saliva. Physiochemical characteristics of the drug, such as molecular weight, lipophilicity, plasma drug-protein binding and pKa of the drug, among others, influence diffusion into saliva. The high inter-individual variability in salivary pH is a likely explanation for the variability in the ratio of salivary to plasma concentration of ionised drugs. Although there is often a significant correlation between oral fluid and plasma or blood concentrations, there is a high degree of variability within and between subjects. This variability does not allow prediction of blood concentrations from oral fluid concentrations (Bakke et al., 2020).

Analytical techniques

Immunobased methods of detection

Immunobased detection methods such as lateral flow immunoassays (LFIs), enzyme-linked immunosorbent assays (ELISAs), and enzyme multiplied immunoassay techniques (EMIT) are key techniques that can offer rapid detection of synthetic opioids. LFIs offer quick and cost-effective testing suitable for various settings, although they lack the sensitivity needed for detecting low concentrations found in post-mortem samples. ELISAs and EMIT provide higher sensitivity and specificity but require more specialized equipment and training. Other advantages of Immunobased methods These methods are crucial in scenarios where rapid screening of synthetic opioids is necessary, including health care and law enforcement settings.

Analytical testing methods

In European laboratories, the identification and quantification of NSO content in biological and non-biological samples is carried out using a combination of hyphenated techniques (such as GC-MS, LC-MS/MS, UHPLC-HRMS, NMR, LC-DAD, FT-IR) to identify NSO content in powders (Gilbert et al., 2020; Mörén et al., 2021; Vincenti et al., 2020).

Most important is the usage of liquid chromatography combined with tandem mass spectrometry or alternatively high-resolution mass spectrometry. These techniques are presented in more detail below.

Liquid Chromatography with tandem Mass Spectrometry (LC-MS/MS): Several European medical universities or institutes of forensic medicine have written articles about NSO detection using LC-MS/MS methods. This technique was used to investigate the metabolisation, distribution ante-mortem and redistribution of NSO in post-mortem biological samples and can be used for both qualitative and quantitative analysis (Freni et al., 2019; Nedahl et al., 2020).

Different variations of this technique exist, as well as different types of MS/MS detectors:

Liquid chromatography-MS/MS (LC-MS/MS): In the last 8 years, dozens of articles have been published in Europe on the detection of NSO using LC-MS/MS for hair, urine, skin surface and blood analysis. This method also enables the simultaneous detection of multiple NSO. In Sweden, a fully validated LC-MS/MS method for the determination of 26 fentanyls, including several structural

isomers, and the opioid antagonist naloxone in human whole blood was presented (Bergh et al., 2018). This method successfully separated all 27 analytes, including 7 isomers, and was validated according to SWGTOX guidelines with a very low limit of quantification (4-20 pg/ml). The applicability of the method was verified by determining fentanyl in post-mortem blood samples from 2 cases. In a 2021 study, the previously developed LC – MS/MS method was updated with some new fentanyl analogues and metabolites (sufentanil and norsufentanil, cis-3-methylnorfentanil, trans-3-methylnorfentanil, cis metabolites and transmethyl- fentanyl, beta-phenylfentanyl, phenylfentanyl, para-fluorofuranyl-fentanyl, isobutyryl-fentanyl and ocfentanil) (Mannocchi et al., 2021).

Modern LC-MS/MS instruments with triple-quadrupole analysers can simultaneously detect more than one hundred substances in just a few minutes, and generally the methods are sufficiently flexible to include new substances and more Internal Standards, for a continuously expanding set of analytes. However, intoxication cases caused by synthetic opioids may be related to new compounds for which neither reference standards nor published literature are available. In this context, the introduction of performing high-resolution mass spectrometers, can make the laboratory capable of executing a truly general toxicological analysis on biological samples, allowing factual untargeted screening and retrospective re-examination of acquired data, following the identification (or reporting from the Early Warning Systems) of new designer opioids (Gerace et al., 2018).

Liquid chromatography-high resolution mass spectrometry (LC-HRMS): LC-HRMS is a powerful analytical method for detecting synthetic opioids and a wide range of other compounds in complex samples. The main advantage of LC-HRMS is that it also offers untargeted screening with no need for any a priori knowledge of the substances you are looking for. LC-HRMS combines two essential techniques: liquid chromatography (LC) for separating compounds in a mixture and high-resolution mass spectrometry (HRMS) for accurate mass measurements of ions. LC-HRMS can detect synthetic opioids at very low concentrations, making it suitable for identifying trace amounts of these substances in various matrices, including biological samples and seized drug samples, provides high selectivity because it can differentiate between compounds with similar masses based on their mass spectra, allowing for the specific identification of synthetic opioids among complex mixtures (Montesano et al., 2017; Montesano et al., 2021). In high-resolution mass spectrometry (HRMS) the mass can be measured to many decimal places. Normal MS is supposed to measure nominal mass and

HRMS can measure exact mass so precisely that it can detect the minute differences in mass between two complexes whereas normal MS is indistinguishable. Overall, in HRMS, the mass accuracy is below 5 ppm. LC-HRMS can provide information about the molecular formula and structure of the detected compounds, aiding in the precise identification of synthetic opioids and their analogues and can simultaneously analyse multiple compounds in a single run, making it efficient for screening samples for a wide range of synthetic opioids and related substances. While the same is true for LC-MS/MS, the difference is that with LC-HRMS you don't need to know in advance what you are looking for. LC-HRMS can be used for both qualitative and quantitative analysis, allowing for the determination of the concentration of synthetic opioids in a sample. This method was, for instance, used to detect the metabolites of 4-fluoro-furanylfentanyl, isobutyrylfentanyl, MT-45 and cyclopropylfentanyl (Cutler & Hudson, 2019).

Work aimed at developing and validating a liquid chromatography–high-resolution mass spectrometry (LC–HRMS) method for screening various psychoactive substances, demonstrated its effectiveness in analysing over 17,000 urine samples and highlighted its potential as a comprehensive alternative to traditional immunochemical screening in toxicology laboratories (Stephanson et al., 2017). In the United Kingdom, an investigation was carried out into the presence of fentanyl and its analogues (e.g., carfentanil) in post-mortem samples. In the detection of fentanyl and carfentanil, the sensitivity of the LC-HRMS method was 100% for fentanyl and 89% for carfentanil. The study revealed a high prevalence of fentanyl and its analogues in the post-mortem samples of persons who died under circumstances suggestive of fentanyl poisoning, fentanyl and/or fentanyl analogues were detected in 40 cases (48%) of the 84 deaths examined. The LC-HRMS method was effective in detecting these substances with high sensitivity (Rab et al., 2019).

For high resolution mass spectrometry, there are mainly two types of analysers:

Liquid Chromatography-Quadrupole Time-of-Flight mass spectrometry (LC-QTOF): In LC-QTOF, a quadrupole mass analyser is coupled with a time-of-flight mass analyser. The quadrupole helps in the selection and filtering of ions of interest, while the time-of-flight analyser measures the accurate mass and intensity of ions in a mass spectrometry experiment. This combination of technologies provides high-resolution mass data and accurate mass measurements, making LC-QTOF a powerful tool in analytical chemistry for various applications, including the identification and quantification of compounds in complex samples. In Europe, the LC-QTOF method, like LC-HRMS, has been mainly

used for the detection of metabolites in the last 6 years as an independent analytical test. This method was used to detect the metabolites of fentanyl, acetylfentanyl, acrylfentanyl, furanylfentanyl, 4-fluoro-isobutyrylfentanyl, isobutyrylfentanyl, butyrfentanyl, ocfentanyl, ortho-, meta-, and para-fluorofentanyl and cyclopropylfentanyl (Gundersen et al., 2020; Steuer et al., 2017; Vikingsson et al., 2019; Wallgren et al., 2020; Watanabe et al., 2017). In Denmark, a targeted screening method was developed for the detection of 50 4-anilidopiperidine-related fentanyl analogues in whole blood by ultra-high-performance liquid chromatography quadrupole time-of-flight mass spectrometry in a data-independent data acquisition mode (Noble et al., 2018). A targeted screening method for 50 fentanyl analogues was successfully validated and implemented to analyse authentic blood samples, where identifying targeted fentanyl analogues was tentatively achieved without using reference standards.

Discovery of new synthetic opioids

The Slovenian National Forensic Laboratory completed analytical testing of 120 new synthetic opioid compounds by 2022. The compounds included new synthetic opioid precursors, metabolites, RM-reference materials and nearly 30 purchased or seized drugs (compounds can be viewed at https://www.policija.si/apps/nfl_response_web/seznam.php). However, the seized and chemically identified NSO provide information on drug availability only, but there are other potentially dangerous opioids with high potency in addition to the compounds thus far brought to light. Arillotta and colleagues used the NPS Finder R search program to identify a total of 426 opioids on the Internet, including 234 fentanyl analogues and 192 non-fentanyl analogues (Arillotta et al., 2020). There is concern about the large number of opioid compounds collected using the NPS Finder R search program because, although it is likely that some of the compounds are precursors and metabolites, it indicates that more opioid compounds are of interest than those seized by authorities and that there is insufficient information on the toxicology of these opioids. The analytical testing of the new synthetic opioids is carried out by drug and pharmaceutical testing laboratories in European countries with the appropriate equipment and expertise. Hospital laboratories in university hospitals and toxicology centres may also be equipped to carry out these analytical tests.

In half of the articles on European opioid analytical studies published in the last 7 years, several analytical methods were used to determine the composition of samples and the amount of components. As previously mentioned, different analytical methods are suitable for quantitative and

qualitative testing of powders and biological samples. Three deaths were studied in Sweden by using LC-MS/MS to quantify methoxyacetylfentanyl in femoral blood and LC-QTOF-MS was used to identify the metabolites in urine (Kronstrand et al., 2021). In Germany LC-QTOF-MS was used to identify cyclopropylfentanyl. The obtained mass spectrum and exact mass of the unknown compound detected by this technique referred to a fentanyl analogue. The sum formula derived from the exact mass was the same as cyclopropylfentanyl or crotonylfentanyl. LC-MS/MS analysis using appropriate reference standards clearly confirmed the presence of cyclopropylfentanyl and its nor-metabolite (Wilde et al., 2020).

Several new synthetic opioids have been fully analytically tested in Europe in recent years. These include: identification of isotonitazene in Belgium and Switzerland, using GC-MS, LC-QTOF-MS, ATR-FTIR, NMR, and GC-MS, HRMS, GC-FTIR, ATR-FTIR, NMR (Blanckaert et al., 2020; Mueller et al., 2021); identification and structure characterization of five synthetic opioids: 3,4-methylenedioxy-U-47700, o-methyl-acetylfentanyl, 2-thiophenefentanyl, benzoylfentanyl and benzoylbenzylfentanyl in Poland, using: NMR, LC–QTOF-MS (Popławska et al., 2021); identification of p-hydroxy-butyrylfentanyl in the Netherlands, using: LC-QTOF-MS, GC-MS, FTIR, NMR (Oldenhof et al., 2019); etonitazepyne in Belgium, using: GC-MS, LC-HRMS/MS, 1H NMR, and ATR-FTIR (Blanckaert et al., 2021).

If a new psychoactive substance is identified in a European Member State for the first time, the Member State concerned must report the detection along with the analytical data to the EMCDDA and Europol via the EWS. Data on new psychoactive substances is then stored in the non-public European Database on New Drugs (EDND2) database and shared between member states. In addition to the EDND2 database, public mass spectrum libraries are also available to laboratories. The sharing of knowledge relating to new substances allows Hazmat teams to update field analysis equipment with available data.

Remediation and recovery

Medical Usage

Fentanyl, introduced as a medical product over 50 years ago, has become a critical intraoperative analgesic. Its applications have expanded to managing chronic pain related to various cancers and persistent, intense noncancerous pain. Over the last two decades, several rapid onset transmucosal

fentanyl forms have been developed and popularized for treating different pain syndromes. The onset of fentanyl's effects and its concentration in the bloodstream vary based on dosage and delivery method. For instance, intravenous administration can provide analgesia in 1 to 2 minutes, while buccal transmucosal systems take around 10 to 15 minutes. Conversely, sublingual, and intranasal sprays act within 5 to 10 minutes.

Fentanyl concentrations in the blood typically peak 8 to 16 hours after applying a transdermal patch. It's notable that opioid-tolerant individuals may require higher plasma concentrations for therapeutic or toxic effects. Following intravenous or transmucosal delivery, the analgesic effects last about 2 to 4 hours. When using transdermal patches, fentanyl levels decline gradually even after removal due to continued skin absorption, persisting approximately 17 +/- 2.3 hours. Metabolized through the human cytochrome P450 (CPY3A4) isoenzyme system, co-administration with drugs affecting CPY3A4 activity can alter plasma concentrations, potentially resulting in prolonged opioid effects or, in severe cases, fatal respiratory depression (Stanley, 2014).

An increase in the use of prescription opioids has been observed across several European nations, including Germany, France, the UK, Spain, Poland, and the Netherlands (Kalkman G. A. & Schers H. J., 2022). Various factors contribute to this escalation. An essential aspect is the aging demographic, grappling with more persistent pain concerns and the need for palliative care. The proportion of individuals aged over 80 surged from 3.9% to 5.4% between 2004 and 2016 and continues to rise. Notably, oxycodone and fentanyl, among the array of prescription opioids, face lesser stigma (EMCDDA, 2023). Patients often lack awareness that these opioids are within the same substance class as morphine, promoting their acceptance and heightened utilization. In medical practice, they are often introduced through patches, nasal sprays, and lollipops, which both patients and physicians may perceive as safer alternatives to tablets or injections.

In France, individual fentanyl use within the general populace experienced a substantial increase (+74%) from 2004 to 2017, while remaining stable among strong opioid users (35-32%, $p > 0.05$). (Chenaf C & N., 2019). In Germany, the prevalence of fentanyl treatment surged from 0.17% to 0.58% between 2000 and 2010 (Schubert et al., 2013). Furthermore, an analysis of trends in hospital analgesic consumption in Spain after the implementation of a pain performance improvement plan in 2018 revealed a noticeable rise in fentanyl consumption, escalating from 8.1 to 12.1 defined daily dose per

100 bed-days, positioning fentanyl as the most widely consumed opioid in hospitals in 2015 (Monje B. & M., 2018).

In Poland, fentanyl emerged as the second most prevalent strong opioid in 2000, constituting approximately a quarter of their 83.1 mg oral morphine equivalents (OME) per capita. Consumption surged significantly until 2003 and then stabilized up to 2015, maintaining usage at 13.0 mg OME per head. Since 2003, fentanyl transdermal formulations have represented the predominant opioid analgesics in terms of usage. The availability of diverse medicinal products from 2000 onwards has broadened treatment options for healthcare professionals. Notably, fentanyl and buprenorphine patches are the most extensively used opioid formulations in Poland (Dzierżanowski & Ciałkowska-Rysz, 2017).

Fentanyl Exposure Risks and Remediation

Due to its potency, fentanyl poses significant risks in both accidental exposure and deliberate misuse, such as in a terrorist or organized attack. The Center for Disease Control and Prevention (CDC) outlines various dissemination methods for fentanyl, including airborne release, contamination of water, food, and agricultural products. Exposure to fentanyl can occur through inhalation, ingestion, or skin/mucous membrane absorption, making it critical to adopt precautionary measures (EPA, 2021; NIOSH, 2011).

Overdose may also result from handling strong synthetic opioids without the precautions that prevent the substance from being inhaled or absorbed through the skin or mucous membranes. Contact with fentanyl or its analogues is so hazardous that both Canada and the USA recorded incidents of hospitalization of law enforcement officers that carried out seizures of such chemicals. The USA Drug Enforcement Administration (DEA) released safety alerts on fentanyl and carfentanil, advising on steps to follow in situations where such drugs might be present, including the immediate application of naloxone in case of exposure (UNODC, 2017).

The United States Environmental Protection Agency (EPA) developed Voluntary Guidelines for Methamphetamine and Fentanyl Laboratory Clean-up (2021) which offers information on hazards present in places where fentanyl is manufactured, packaged, or stored. Presented information on the remediation process can be used after the use of fentanyl in a terrorist attack. EPA suggests gross chemical removal as a first step before the remediation process. While conducting remediation work a ‘’buddy system’’ is recommended, meaning no one should enter alone, and additionally, air quality

monitoring is required to ensure the atmosphere is safe for entry. Personal protective equipment is required based on site-specific conditions. Conditions, hazards, and risks should be assessed on a case-by-case basis. Non-specialist personnel is advised not to touch or open any packages and not to ventilate the scene, immediately leave the scene, call for specialist support, e.g. chemical response team/hazardous area response teams, quarantine the scene to prevent others from entering, follow procedures if exposure is suspected, and follow procedures if personnel shows signs of poisoning.

General response measures for law enforcement, fire, rescue, and emergency medical services should include guidelines on how to protect personnel from exposure, on proceedings in the case of exposure, and on actions that should be taken if personnel show signs of poisoning.

In response to fentanyl exposure, four protective equipment levels (A, B, C, D) are employed based on the assessment of contamination risk:

Level A: Maximum protection for unknown chemical hazards. Includes a full-face-piece self-contained breathing apparatus (SCBA), a Chemical Protective suit, gloves, and chemical-resistant boots.

Level B: High respiratory protection with lesser skin protection. Involves a non-encapsulating, splash-protective suit with a SCBA or supplied air hose respirator.

Level C: Respiratory protection when the contaminant and its concentration are known. Utilisation of Air Purifying Respirators or Powered Air Purifying Respirators along with a chemical-resistant suit.

Level D: Basic protection with coveralls or work clothes, boots, and gloves.

All remediation workers must be aware of the fentanyl exposure symptoms, which may include the following: slowed, shallow breathing; pale, clammy skin; decreasing consciousness, increasing drowsiness, confusion; low blood pressure; pinpoint pupils; euphoria. If experiencing some or all symptoms it is important to seek medical attention (EPA, 2021). In 2018, the EMCDDA together with Europol issued an advisory for reducing the risk of occupational exposure to fentanyls. It is emphasized that many fentanyls, particularly new fentanyls, may not be detected by commercially available tests based on immunological and chemical techniques or by some analytical methods and techniques currently used by forensic laboratories. Personnel expected to encounter fentanyls should be trained

to recognise the signs of poisoning in themselves and others. They should have sufficient knowledge to respond to poisoning, which may include first aid training, basic life support (cardiopulmonary resuscitation (CPR) and CPR with rescue breaths) and the administration of naloxone. It is recommended to carry naloxone kits with syringes or pre-packaged naloxone applicators containing enough doses and individual applicators for all personnel on-site in case of acute intoxication (EPA, 2021).

Medical Countermeasures

Medical challenges

Opioids with their high abuse potential have been a major threat to public health for decades, but in recent years, their possible use as a chemical weapon has been recognized. While morphine derivates such as heroin are mainly known as drugs causing addiction, newer synthetic opioids developed as effective painkillers also have a high abuse potential in addition to quite narrow safe dosage intervals. Fentanyl and its effects are well examined in humans and it is approved as a therapeutic painkiller by several state drug agencies in the world. Carfentanil is only approved as an analgesic for wild animals (Zawilska et al., 2021). The analgesic and anesthetic effects and dosage safety features are not established for humans. It is known that carfentanil, similar to several other synthetic fentanyl-like opioids, is highly toxic for humans in microgram dosages with long lasting effects that can be difficult to antagonize and re-narcotization with potential respiratory arrest is a severe challenge (Tuet et al., 2019). As a consequence, it is not licensed for use in humans.

Legally produced opioids are safer to use than illegal synthesized compounds since the drug concentration and purity is known and it is at least theoretically possible to administer the desired dosage. Nevertheless, opioids are known for their rapid build-up of tolerance but also their rapid decrease if the substance is not used for a while. This can lead to (fatal) overdoses in people who have been abstinent and thought they titrated the dose according to their previous habits. The clinical symptoms of synthetic opioid intake are the same, regardless of production methods, and it is more or less independent from the route of uptake.

Toxidrome

The complete clinical picture of opioid poisoning symptoms is known as opioid toxidrome. Patients usually first experience drowsiness, followed by loss of consciousness with the potential for airway compromise. The pupils are observed to be pinpoint sized. As intoxication progresses further,

depression of autonomous nervous system occurs with initial bradypnoea developing until respiratory arrest. Hypotension, central hypothermia, and bradycardia can be observed during the progress. In some cases, depressed gut motility leads to lack of bowel sounds in clinical examination and depressed urinary bladder tone causes urinary retention (Gummin, 2020).

Antagonistic attacks may include highly toxic compounds where some synthetic opioids can be used as chemical warfare agents. Unfortunately, the opiate toxidrome and the toxidrome caused by nerve agents have several similarities in clinical appearance. This is a problem as the emergency antidotal treatment is completely different. Patients exposed to nerve agents might get confused or anxious at the beginning of exposure if the exposure dose is low enough. Without treatment or after exposure to a higher dose nerve agent the patient will fall unconscious, with or without seizures. The clinical picture is similar for patients with opioid intoxication, although they will not experience signs of seizure or anxiousness but will fall immediately unconscious due to the central depressive opioid effect. Both cause pinpoint pupils and in high enough doses or longer exposure time, respiratory depression. Nerve agents will initially lead to a tachypnea due to stress and high secretion in the airways causing a lack of oxygen retention, but without antidotal treatment respiratory depression and respiratory arrest will set in rapidly.

Secretion, including sweating is one major clinical difference between nerve agent and opioid intoxication, which might help a first responder to distinguish and chose the right antidote. On the other hand, in opioid overdoses non-cardiogenic pulmonary edema can, when untreated, cause a sign described as a "cone of death". This frothy secretion from the mouth and nose again may lead an inexperienced first responder to the conclusion of nerve agent intoxication (Gummin, 2020).

Another difference can be the rigidity of the chest wall in opioid intoxicated patients, especially when the initial dose was high or administrated intravenously (Burns et al., 2016). The drawback, even when recognized, is that the time window for life saving treatment is short when chest rigidity appears, and treatment is not covered by the education of traditional first responders from anything other than medical branches, since it is, in addition to antidote, muscle relaxation and immediate intubation. This effect is described for medical use and abuse of drugs and cannot necessarily be transferred to a CBRN-attack setting, although chest wall rigidity seems to be associated with an initial severe high synthetic opioid dosage to parts of the central nervous system (Burns et al., 2016).

The opioid toxidrome is diagnostically specific when patients are intoxicated by smaller to moderate doses and will easily be recognized by trained first responders. Higher doses, which may be likely in a CBRN-attack setting which aims to kill, not to sedate, the victims (as in the Moskva theatre), can cause severe symptoms quickly. Then the fulminant symptoms alone will not be enough to choose the right antidote and it is important to have the support of point of care tests, intelligence information and solid leadership in the field.

Treatment of victims exposed to New Synthetic Opioids

Respiratory support is a critical intervention for opioid overdose that may be lifesaving on its own. Therefore, it is recommended to begin CPR, depending on the rescuer's level of training. Moreover, individuals that are experiencing an opioid overdose should be ventilated with oxygen before naloxone is administered to reduce the risk of acute lung injury. Naloxone is a medicine that binds opioid receptors and is the antagonist of choice for the reversal of acute opioid toxicity. It should be administered to every person that presents signs of opioid overdose or when opioid overdose is suspected. Naloxone can be administered intranasally, intramuscularly, subcutaneously, or intravenously. In life-threatening situations, it can also be used in pregnant women (Ordean & Tubman-Broeren, 2023). After naloxone administration, it is important to further monitor the person for re-emergence of signs and symptoms of opioid toxicity for at least 4 hours following the last dose of naloxone (Rzasa Lynn & Galinkin, 2018). Most people respond to naloxone by returning to spontaneous breathing, with mild withdrawal symptoms. The response generally occurs within 2 to 3 minutes after administration. It is important to continue rescue breathing while waiting for the naloxone to take effect. Duration of effect of naloxone depends on the dose and route of administration of the substance which induced the overdose. The goal of naloxone therapy should be the restoration of adequate spontaneous breathing. In some cases, it is necessary to use more than one dose of naloxone to revive a person. Therefore, it is essential to get the person to an emergency department or other source of acute care as quickly as possible, even if the person revives after the initial dose of naloxone and seems to feel better. If a person does not respond to naloxone, an alternative explanation for the clinical symptoms should be considered. Support via ventilation, oxygenation, and blood pressure should be sufficient to prevent the complications of opioid overdose and should be given the highest priority if the patient's response to naloxone does not occur quickly.

A fentanyl overdose generally requires more doses of naloxone than is used for treating respiratory depression from heroin overdose because of the increased potency. While using naloxone, it is important to note that it has an expiration date, which is important to check and replace as needed (SAMHSA, 2018).

Withdrawal symptoms induced by naloxone can be unpleasant. Some people show signs of agitation or confusion, which may improve by providing reassurance and explanation of what is happening. Physically dependant people on opioids experience more symptoms that are very uncomfortable but not life threatening unless vomiting and diarrhoea result in extreme dehydration (SAMHSA, 2018).

Antidotes to fentanyl

Antidotes to opioids, including fentanyl, have been developed over several decades. Naloxone, naltrexone and nalmefeme are the most well-known ones. It has been observed that renarcotization can occur after naloxone or naltrexone antagonization of carfentanil sedation in wild animals (McCranor et al., 2020). In order to learn more about the effects of aerosolized carfentanils and the antagonizing characteristics of the traditional antidotes, naloxone and naltrexone, mice were exposed to aerosolized carfentanil (Tuet et al., 2019). Antidotes were given as prophylaxis and as a treatment, while respiratory parameters were observed over time. Naltrexone was superior to Naloxone in counteracting carfentanil respiratory depression. Prophylactic administration of both antidotes prevents severe intoxication effectively, meaning that a prophylactic dose for first responders in a setting with synthetic opioid release might be a future option.

A naloxone efficacy study on green monkeys elucidated the challenge of carfentanil intoxication treatment in an animal model suitable for pharmacological comparison to human physiology (Langston et al., 2020). The study revealed a tight safety interval and demonstrated that doses of carfentanil causing intoxication (SC ED50 of carfentanil for bradypnea and/or loss of posture in the male African green monkey to be 0.71 µg/ kg (95 % CI: 0.58-0.87 µg/kg) are equivalent to a 2mg lethal dose in humans. The dose antagonized some monkeys and proved deadly for some individuals even when treated with Naloxone in time. The study also showed that the time from mild intoxication to severe live-threating intoxication is very short, often just minutes. Naloxone as an antidote treatment affects carfentanil intoxication immediately when given in high enough doses, but a clear dose dependency is lacking. Independently of the dosage, the authors also observed symptoms of re-intoxication up to some hours after initial treatment and recovery, which made it necessary to treat

with a second dose of naloxone. There was no clear dosage-effect relation in these cases either. Naloxone has a double half –lifetime (t ½) than carfentanil in humans (90 vs. 45 min.) The prolonged and highly unpredictable carfentanil effect is assumed to be related to the pharmacological distribution patterns in the lipid body compartments. The authors prove that a 355 µg/kg dose of naloxone is efficacious against their 1.15 µg/kg carfentanil challenge; however, the effect level of this dose of carfentanil is currently unknown and the precise sufficient dose of naloxone as an antidote for immediate or delayed rescue in cases of supra-lethal doses of carfentanil or other fentanyl analogues should be evaluated (Tuet et al., 2019).

Active and passive immunization for treatment to sudden opioid overdose

Immunization against synthetic opioids involves both active and passive strategies to combat opioid use disorder (OUD) and prevent opioid overdose. Active immunization (vaccination) involves inducing the immune system to develop antibodies against small molecule opioid haptens bound to carrier proteins, which help block the opioids from crossing the blood-brain barrier and mitigating their effects (Baehr et al., 2020). Passive immunization entails administering pre-made antibodies to immediately counteract opioids' effects, useful for emergency responses or prophylaxis in high-risk situations like first responders encountering fentanyl (Hicks et al., 2022).

These immunization methods, while promising, are not yet a standard treatment due to challenges in achieving the high antibody titers necessary to counteract overdose effectively and the potential for vaccines to interfere with pain management using therapeutic opioids. Despite these hurdles, vaccines and antibody therapies are under development, aiming to provide targeted protection against specific synthetic opioids without affecting other opioids used medically.

Summary of Medical Countermeasures

There have been developed several medical countermeasures the recent years, some of them are older products, which were now tailored to meet new drug challenges, while others are completely new concepts.

Type	Common name	Mode of action	Duration of action	Blood brain barrier	State of developement	Reference
Traditional antidotes in use as MCM against synthetic opioids	Naltrexone	Reversible μ, κ and δ competitive antagonist	> 72 h	molecules pass	FDA & EMA	(Coussens et al., 2019)
	Naloxone	Reversible μ, κ and δ competitive antagonist	1-2 h	molecules pass	FDA &EMA	(Coussens et al., 2019)
Active immunization	Synthetic opioid vaccines	antibody-opioid complex neutralizes opioids in vivo	not finally explored, at least several months	opioid antibody-complex does not pass	animal model	(Baehr et al., 2020; Townsend et al., 2021)
Passive immunization	Monoclonal antibodies	antibody-opioid complex neutralizes opioids in vivo	21 days	opioid antibody-complex does not pass	animal model	(Hicks et al., 2022)

Type	Common name	Mode of action	Duration of action	Blood brain barrier	State of developement	Reference
	Chimeric antibodies	antibody-opioid complex neutralizes opioids in vivo	21 days	opioid antibody-complex does not pass	animal model	(Ban et al., 2021; Hicks et al., 2022)
Opioid receptorantagonist	Nalfeme intranasal	competitive, reversible opioid receptor antagonist	> 7 hours	molecules pass	clinical studies	(Krieter et al., 2019)
	Methocinnamox	Pseudo-irreversible μ, not competitive antagonist 2, reversible κ, δ competitive antagonism	5 days to 2 weeks	unknown, needs further studies	animal modell	(Coussens et al., 2019; Jordan et al., 2022; Maguire et al., 2020)
	Covalent binding naloxone on nanoparticles	low and slow naloxone release	4 days	Naloxone passes after release from nanoparticle	animal model	(France et al., 2021)
Serotonin receptor agonist	Serotonin (5-HT)1A receptor agonists	5-HT neurons activation stimulates respiration	< 24 h	molecules pass	animal modell	(Blier & Ward, 2003; France et al., 2021)

Type	Common name	Mode of action	Duration of action	Blood brain barrier	State of developement	Reference
Scavenger molecules	Cyclodextrin scaffolds	captures opioids in its hydrophobic interior 3D structure	7 days	different molecules sizes under development, passage of BBB depends on size and coating of molecule	in vitro studies	Gosselet 2021, France 2021, Mayer 2023
	NarcoBond	irreversible fentanyl-μ-opioid receptor binding in the "nanosponge"	24 h	molecules of nanosponge does not pass	animal modell	France 2021

Table 3: Summary of available and developing medical countermeasures to treat opioid intoxication

Protection of working dogs

Fentanyl and its derivatives can cause severe intoxication not only in humans but also in animals. Working dogs, particularly those used by law enforcement for narcotics detection, are especially vulnerable due to the nature of their duties (Essler et al., 2019). In case of exposure to an overdose, these K9 officers, like their human counterparts, are treated with Naloxone. Given the significant investment of time and money in training a narco-dog, it is crucial to ensure that exposure to the narcotic antidote Naloxone does not affect the dogs' training outcomes. The reliability of a K9's narcotics detection is critical since these results are often used in legal proceedings.

A cross-over trial was conducted to determine whether repeated exposure to narcotics or treatment with Naloxone impacts the odor detection abilities of K9 officers. The study, which used both intramuscular and intranasal administration of Naloxone, found no impairment in the dogs' olfactory senses (Essler et al., 2019). Although the study involved only a small number of animals, the results suggest that treatment with Naloxone does not compromise the dogs' ability to accurately detect narcotics.

As the development of more potent fentanyl analogs, such as carfentanil, continues, further research is necessary to understand the clinical effects of these substances and explore possible modes of antagonization in both humans and animals. Additionally, alternative solutions need to be explored to enhance safety and efficacy in handling such potent substances.

Conclusion

Synthetic opioids have emerged as a significant concern due to their extreme potency and potential for misuse. The widespread illicit production and use of these drugs have led to an alarming increase in overdose incidents and fatalities necessitating a coordinated response from health and law enforcement agencies worldwide. The established presence of synthetic opioids on the illegal recreational drug market signifies that synthesis and transportation routes for these potent drugs are already in place. While these channels are primarily intended for the illegal drug market, they also

have the potential to be exploited to disseminate these substances as weapons of terror, thus amplifying their threat manifold.

One of the most significant challenges is the emergence of New Psychoactive Substances (NPS). These substances are not currently controlled by international drug conventions and pose a unique challenge to drug enforcement and public health agencies. Often designed to evade existing drug laws through minor chemical modifications, NPS are legally ambiguous and difficult to regulate. Their availability both through illicit channels and online markets complicates efforts to monitor and control these drugs.

Effective surveillance and data gathering are integral to the fight against synthetic opioids. EMCDDA's Early Warning System plays a vital role in identifying and assessing the drugs circulating in various communities and programmes such as syringe exchange and drug testing services complement these surveillance activities and assist in harm reduction. These early warning systems are essential for informing national and international response strategies.

In terms of operational response, Europe could benefit from establishing standardised protocols similar to those developed in the US for the safe handling of synthetic opioids. This includes comprehensive training and appropriate personal protective equipment to ensure the safety of those on the front lines, minimising the risk of exposure. Harmonising these standards across EU member states would ensure a consistent approach, enhancing the effectiveness and safety of first responders across different regions.

Additionally, the integration of advanced on-site detection technologies, such as portable GC-MS and Raman spectroscopy, could significantly improve the capability of European first responders to assess and manage incidents involving synthetic opioids. Investing in these technologies, along with the necessary training for personnel, would provide first responders with the tools needed to respond swiftly and safely to opioid-related emergencies.

In the laboratory, technological advancements have greatly enhanced detection capabilities. Techniques such as LC-MS/MS and high-resolution mass spectrometry are advantageous for the detection and quantification of synthetic opioids. These methods are particularly valuable when handling complex sample types or detecting multiple substances simultaneously. Particularly for HRMS methods, pre-existing knowledge of the methods looked at is not needed, a necessary feature given the rapid evolution of synthetic opioids in the drug market.

Challenges extend beyond just detection; the sheer number of NSO and their analogues, constantly changing due to slight modifications by manufacturers to evade legal restrictions, complicates standardization of detection methods. This dynamic nature of NSO production and use necessitates continual updates to testing protocols and equipment, ensuring that first responders and medical professionals can accurately identify and respond to opioid-related incidents.

The ability of synthetic opioids to cause widespread harm is particularly concerning in scenarios of mass exposure, where the rapid identification and response to such events are hindered by current clinical practices that are accustomed to handling opioid overdoses on a much smaller scale. In such events, the immediate availability of medical countermeasures like naloxone becomes critical. However, the uncertainty surrounding hospitals' capacity to handle mass casualty events with sufficient supplies of antidotes like naloxone underscores the need for robust healthcare preparedness and response strategies.

Looking ahead, the advent of Artificial Intelligence (AI) in drug discovery poses a double-edged sword; while it may accelerate the development of new synthetic opioids, it also holds promise for advancing detection methods and improving diagnostic capabilities. The integration of AI could revolutionize how we detect and diagnose drug exposure, enhancing our ability to respond to overdoses and potential terrorist use of these drugs more effectively.

In conclusion, the potential use of synthetic opioids as weapons of terror represents a formidable challenge that requires an integrated and innovative approach across various sectors. The ease with which these substances can be diverted from the illegal drug market to be used nefariously adds a layer of complexity to already strained regulatory and enforcement frameworks. It is crucial for international collaborations and partnerships to strengthen, enhancing the sharing of intelligence, best practices, and technological advancements to mitigate the risks posed by these potent substances. Furthermore, the development of global standards for the rapid response and treatment of synthetic opioid exposure can significantly reduce the potential for widespread harm.

As we advance, the role of technology, especially AI, will be pivotal in shaping future strategies against the misuse of synthetic opioids. By enhancing our analytical capabilities and improving early detection systems, we can better anticipate and counteract the evolving threat landscape. However, as much as technology offers solutions, it also presents new challenges that must be addressed to prevent these powerful tools from becoming facilitators of misuse. The journey to effectively

managing the risks associated with synthetic opioids is complex and ongoing, demanding vigilance, innovation, and international cooperation to safeguard public health and security.

Methods

A literature search was conducted, targeting literature published between January 2016 and February 2022 using PubMed, Web of Science and Scopus. Search terms are detailed in Table 4.

We aimed for a transparent and systematic process, whilst also ensuring a pragmatic approach in the light of available resources of time and funding.

Literature and data from relevant reports or protocols were included based on authors' prior knowledge and experience. Reference lists of included papers were also researched for relevant articles.

"synthetic opioid" AND (terrorism OR weapon OR threat OR attack)
Fentanyl AND (terrorism OR weapon OR threat OR attack)
carfentanil AND (terrorism OR weapon OR threat OR attack)
"synthetic opioid" AND (DIY OR "do it yourself" OR do-it-yourself OR homemade)
Fentanyl AND (DIY OR "do it yourself" OR do-it-yourself OR homemade)
carfentanil AND (DIY OR "do it yourself" OR do-it-yourself OR homemade)
"novel psychoactive substances" AND (terrorism OR weapon OR threat OR attack)
"novel psychoactive substances" AND (DIY OR "do it yourself" OR do-it-yourself OR homemade)
"synthetic opioid" AND (illegal OR illicit) AND (production OR trade)
Fentanyl AND (illegal OR illicit) AND (production OR trade)
carfentanil AND (illegal OR illicit) AND (production OR trade)
"novel psychoactive substances" AND (illegal OR illicit) AND (production OR trade)

"synthetic opioid" AND (LC-MS OR GC-MS OR "Gas chromatography mass spectrometry" OR "liquid chromatography mass spectrometry")
Fentanyl AND (LC-MS OR GC-MS OR "Gas chromatography mass spectrometry" OR "liquid chromatography mass spectrometry")
carfentanil AND (LC-MS OR GC-MS OR "Gas chromatography mass spectrometry" OR "liquid chromatography mass spectrometry")
"novel psychoactive substances" AND (LC-MS OR GC-MS OR "Gas chromatography mass spectrometry" OR "liquid chromatography mass spectrometry")
(nitazene OR isotonitazene OR methodesnitazene OR etonitazene OR methonitazene OR etazene OR protonitazene) AND (terrorism OR weapon OR threat OR attack)
(nitazene OR isotonitazene OR methodesnitazene OR etonitazene OR methonitazene OR etazene OR protonitazene) AND (illegal OR illicit) AND (production OR trade)
(nitazene OR isotonitazene OR methodesnitazene OR etonitazene OR methonitazene OR etazene OR protonitazene) AND (LC-MS OR GC-MS OR "Gas chromatography mass spectrometry" OR "liquid chromatography mass spectrometry")
(sufentanil OR remifentanil OR afentanil) AND (terrorism OR weapon OR threat OR attack)
(sufentanil OR remifentanil OR afentanil) AND (illegal OR illicit) AND (production OR trade)
(sufentanil OR remifentanil OR afentanil) AND (LC-MS OR GC-MS OR "Gas chromatography mass spectrometry" OR "liquid chromatography mass spectrometry")

Table 4. Search terms used to interrogate PubMed; Web of Science and Scopus. Dates from 2016 to February 2022.

Inclusion and exclusion criteria

Literature was included if it met the following criteria: 1) Described data related to the identification of emerging threats; 2) detailed risks posed by synthetic opioids and their potential use as a terrorist weapon; 3) described illegal/illicit production: state-wide and rogue individuals; 4) detailed response to incidents involving synthetic opioids including detection and treatment; 5) Published data between January 2016 and the February 2022. Papers published before 2016 were included on a case-by-case basis if discovered opportunistically and deemed relevant; 6) Presented data from original articles. Letters to the editor, abstract publications, conference proceedings, non-systematic reviews (narrative reviews etc.), and editorials were excluded. Additional literature was included on a case-by-case basis. The following exclusion criteria were applied: 1) Duplicated data, 2) not in English or language of JA partner, 3) not about the topic and 4) other reasons, including papers not relevant.

Search results

The selection of relevant papers is depicted in a PRISMA flow diagram (Figure 3). In summary, 1037 papers were screened, 80 of these met the inclusion criteria and 59 were referenced in the review. Additional material was included from organisational websites such as NATO, EMCDDA, UNODC, etc (n = 11); papers published after initial search complete (n = 5); and papers selected by authors either through signposting from reference lists or to exemplify a discussion point (n = 25). Most of the 100 references (91%) were published after 2016.

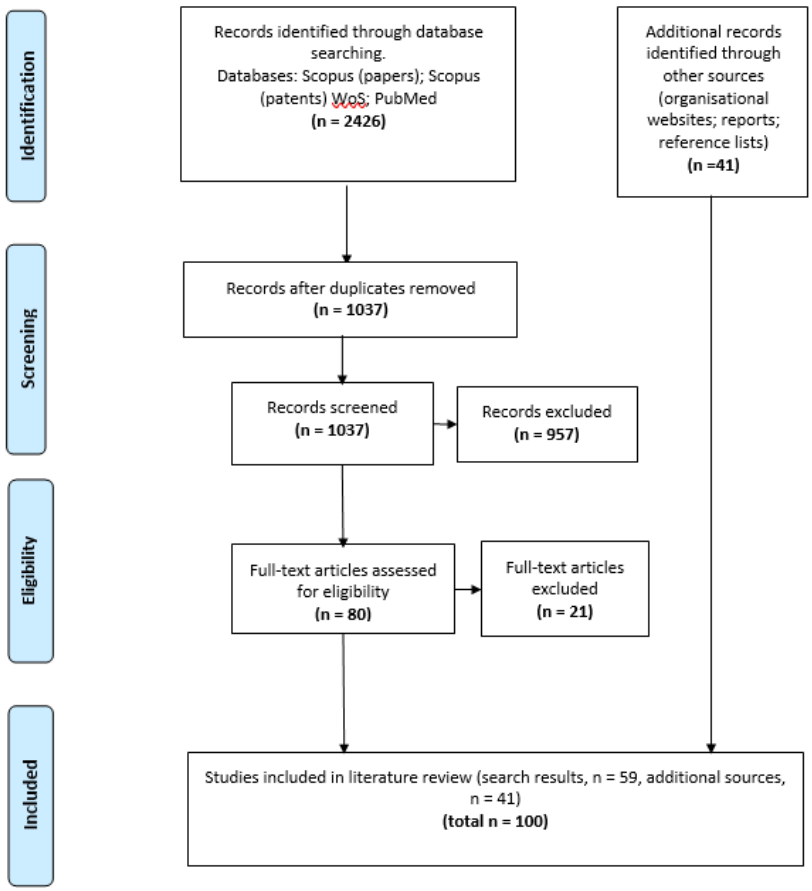

Figure 3. Flowchart to describe results of literature search

Limitations (methodological)

- There are many ongoing advancements in the field of synthetic opioids and making a complete list of developments is beyond the reach of this review, since prediction of the future of such a broad field is by definition predestined to be incomprehensive.
- Search results of the literature review are restricted by the search strategy, e.g., selection of search terms, the time frame of the search as well as the inherent limitations of only examining open-source literature.
- Artificial Intelligence (AI) has become a new and powerful tool as this review is being finalised. It is the opinion of the authors that this technology will accelerate both scientific advancements, but also increase the risks regarding drug development in the future.

References

Arillotta, D., Schifano, F., Napoletano, F., Zangani, C., Gilgar, L., Guirguis, A., Corkery, J. M., Aguglia, E., & Vento, A. (2020). Novel opioids: systematic web crawling within the e-psychonauts' scenario. *Frontiers in neuroscience*, *14*, 149.

Armenian, P., Vo, K. T., Barr-Walker, J., & Lynch, K. L. (2018). Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review. *NEUROPHARMACOLOGY*, *134*, 121-132.

ASTM. (2021). Standard guide for using equipment and assays for field detection of fentanyl and fentatanyl-realted compounds. In (Vol. Designation: E3289-21, pp. 1-37). www.astm.org: ASTM international.

Baehr, C., Kelcher, A. H., Khaimraj, A., Reed, D. E., Pandit, S. G., AuCoin, D., Averick, S., & Pravetoni, M. (2020). Monoclonal Antibodies Counteract Opioid-Induced Behavioral and Toxic Effects in Mice and Rats. *JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS*, *375*(3), 469-477. https://doi.org/10.1124/jpet.120.000124

Bakke, E., Høiseth, G., Furuhaugen, H., Berg, T., Arnestad, M., & Gjerde, H. (2020). Oral Fluid to Blood Concentration Ratios of Different Psychoactive Drugs in Samples from Suspected Drugged Drivers. *Ther Drug Monit*, *42*(5), 795-800. https://doi.org/10.1097/ftd.0000000000000760

Ban, B., Barrientos, R. C., Oertel, T., Komla, E., Whalen, C., Sopko, M., You, Y. J., Banerjee, P., Sulima, A., Jacobson, A. E., Rice, K. C., Matyas, G. R., & Yusibov, V. (2021). Novel chimeric monoclonal antibodies that block fentanyl effects and alter fentanyl biodistribution in mice. *MABS*, *13*(1). https://doi.org/10.1080/19420862.2021.1991552

Barfidokht, A., Mishra, R. K., Seenivasan, R., Liu, S., Hubble, L. J., Wang, J., & Hall, D. A. (2019). Wearable electrochemical glove-based sensor for rapid and on-site detection of fentanyl. *Sens Actuators B Chem*, *296*. https://doi.org/10.1016/j.snb.2019.04.053

Bergh, M. S.-S., Bogen, I. L., Wilson, S. R., & Øiestad, Å. M. L. (2018). Addressing the fentanyl analogue epidemic by multiplex UHPLC-MS/MS analysis of whole blood. *Therapeutic Drug Monitoring*, *40*(6), 738-748.

Bergh, M. S., Øiestad Å, M. L., Baumann, M. H., & Bogen, I. L. (2021). Selectivity and sensitivity of urine fentanyl test strips to detect fentanyl analogues in illicit drugs. *Int J Drug Policy*, *90*, 103065. https://doi.org/10.1016/j.drugpo.2020.103065

Blanckaert, P., Balcaen, M., Vanhee, C., Risseeuw, M., Canfyn, M., Desmedt, B., Van Calenbergh, S., & Deconinck, E. (2021). Analytical characterization of "etonitazepyne," a new pyrrolidinyl-containing 2-benzylbenzimidazole opioid sold online. *DRUG TESTING AND ANALYSIS*, *13*(9), 1627-1634. https://doi.org/10.1002/dta.3113

Blanckaert, P., Cannaert, A., Van Uytfanghe, K., Hulpia, F., Deconinck, E., Van Calenbergh, S., & Stove, C. (2020). Report on a novel emerging class of highly potent benzimidazole NPS opioids: chemical and in vitro functional characterization of isotonitazene. *DRUG TESTING AND ANALYSIS*, *12*(4), 422-430.

Blier, P., & Ward, N. M. (2003). Is there a role for 5-HT1A agonists in the treatment of depression? *Biological psychiatry*, *53*(3), 193-203.

Burns, G., DeRienz, R. T., Baker, D. D., Casavant, M., & Spiller, H. A. (2016). Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse? *Clinical Toxicology*, *54*(5), 420-423.

Caspar, A. T., Kollas, A. B., Maurer, H. H., & Meyer, M. R. (2018). Development of a quantitative approach in blood plasma for low-dosed hallucinogens and opioids using LC-high resolution mass spectrometry. *Talanta*, *176*, 635-645. https://doi.org/10.1016/j.talanta.2017.08.063

Chenaf C, K. J., Delorme J, Pereira B, Mulliez A, Zenut M, Delage, & N., A. D., Eschalier A. and Authier N. (2019). Prescription opioid analgesic use in France: trends and impact on morbidity-mortality. In: Eur J Pain.

Ciesielski, A. L., Wagner, J. R., Alexander-Scott, M., & Snawder, J. (2021). An optimized method for sample collection, extraction, and analysis of fentanyl and fentanyl analogs from a non-porous surface. *Talanta*, *228*, 122210. https://doi.org/10.1016/j.talanta.2021.122210

Cooman, T., Ott, C., Dalzell, K., Burns, A., Sisco, E., & Arroyo, L. (2021). Screening of seized drugs utilizing portable Raman spectroscopy and direct analysis in real time-mass spectrometry (DART-MS) [Article]. *FORENSIC CHEMISTRY*, *25*, Article ARTN 100352. https://doi.org/10.1016/j.forc.2021.100352

Regulation (EU) 2022/2371 on serious cross-border threats to health and repealing Decision No 1082/2013/EU, (2022).

Coussens, N. P., Sittampalam, G. S., Jonson, S. G., Hall, M. D., Gorby, H. E., Tamiz, A. P., McManus, O. B., Felder, C. C., & Rasmussen, K. (2019). The opioid crisis and the future of addiction and pain therapeutics. *JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS*, *371*(2), 396-408.

Cutler, C., & Hudson, S. (2019). In vitro metabolism of the novel synthetic opioid agonist cyclopropylfentanyl and subsequent confirmation in authentic human samples using liquid chromatography-high resolution mass spectrometry. *DRUG TESTING AND ANALYSIS*, *11*(8), 1134-1143. https://doi.org/10.1002/dta.2611

Dzierżanowski, T., & Ciałkowska-Rysz, A. (2017). Accessibility of opioid analgesics and barriers to optimal chronic pain treatment in Poland in 2000–2015. *Supportive care in cancer*, *25*, 775-781.

EMCDDA. (2019). European drug report 2019: trends and developments. *Luxembourg: Publications Office of the European Union*.

EMCDDA. (2021). European Drug Report 2021: Trends and developments. In. Luxembourg: Publications Office of the European Union.

EMCDDA. (2023). Older people and drugs: health and social responses. In.

EPA. (2021). Voluntary Guidelines for Methamphetamine and Fentanyl Laboratory Cleanup. In: United States Environmental Protection Agency

Essler, J. L., Smith, P. G., Berger, D., Gregorio, E., Pennington, M. R., McGuire, A., Furton, K. G., & Otto, C. M. (2019). A Randomized Cross-Over Trial Comparing the Effect of Intramuscular Versus Intranasal Naloxone Reversal of Intravenous Fentanyl on Odor Detection in Working Dogs. *ANIMALS*, *9*(6). https://doi.org/10.3390/ani9060385

Evans, A., Krause, M., Leach, S., Levitas, M., Nguyen, L., & Short, L. (2021). Analysis of drug residue in needle-exchange syringes in Washington, DC [Article]. *FORENSIC SCIENCE INTERNATIONAL*, *329*, Article ARTN 111083. https://doi.org/10.1016/j.forsciint.2021.111083

Fiorentin, T., Krotulski, A., Martin, D., Browne, T., Triplett, J., Conti, T., & Logan, B. (2019). Detection of Cutting Agents in Drug-Positive Seized Exhibits within the United States [Article|Proceedings Paper]. *JOURNAL OF FORENSIC SCIENCES*, *64*(3), 888-896. https://doi.org/10.1111/1556-4029.13968

Fiorentin, T., & Logan, B. (2020). Analytical findings in used syringes from a syringe exchange program [Article]. *INTERNATIONAL JOURNAL OF DRUG POLICY*, *81*, Article ARTN 102770. https://doi.org/10.1016/j.drugpo.2020.102770

France, C. P., Ahern, G. P., Averick, S., Disney, A., Enright, H. A., Esmaeli-Azad, B., Federico, A., Gerak, L. R., Husbands, S. M., & Kolber, B. (2021). Countermeasures for preventing and treating opioid overdose. *CLINICAL PHARMACOLOGY & THERAPEUTICS*, *109*(3), 578-590.

Freni, F., Bianco, S., Vignali, C., Groppi, A., Moretti, M., Osculati, A. M. M., & Morini, L. (2019). A multi-analyte LC–MS/MS method for screening and quantification of 16 synthetic cathinones in hair: Application to postmortem cases. *FORENSIC SCIENCE INTERNATIONAL*, *298*, 115-120.

Gerace, E., Salomone, A., & Vincenti, M. (2018). Analytical approaches in fatal intoxication cases involving new synthetic opioids. *Current Pharmaceutical Biotechnology*, *19*(2), 113-123.

Gilbert, N., Mewis, R. E., & Sutcliffe, O. B. (2020). Classification of fentanyl analogues through principal component analysis (PCA) and hierarchical clustering of GC-MS data. *FORENSIC CHEMISTRY*, *21*. https://doi.org/10.1016/j.forc.2020.100287

Gjerde, H., Bretteville-Jensen, A. L., Bache-Andreassen, L., Hanoa, K., Furuhaugen, H., Brochmann, G.-W., & Vindenes, V. (2023). Which illicit drugs are injected in Oslo? A study based on analysis of drug residues in used injection equipment and self-reported information. *Scandinavian journal of public health*, *51*(1), 21-27.

Glasscott, M., Vannoy, K., Fernando, P., Kosgei, G., Moores, L., & Dick, J. (2020). Electrochemical sensors for the detection of fentanyl and its analogs: Foundations and recent advances [Review]. *Trac-Trends in Analytical Chemistry*, *132*, Article ARTN 116037. https://doi.org/10.1016/j.trac.2020.116037

Goodchild, S., Hubble, L., Mishra, R., Li, Z., Goud, K., Barfidokht, A., Shah, R., Bagot, K., McIntosh, A., & Wang, J. (2019). Ionic Liquid-Modified Disposable Electrochemical Sensor Strip for Analysis of Fentanyl [Article]. *ANALYTICAL CHEMISTRY*, *91*(5), 3747-3753. https://doi.org/10.1021/acs.analchem.9b00176

Gozdzialski, L., Aasen, J., Larnder, A., Ramsay, M., Borden, S. A., Saatchi, A., Gill, C. G., Wallace, B., & Hore, D. K. (2021). Portable gas chromatography-mass spectrometry in drug checking: Detection of carfentanil and etizolam in expected opioid samples. *Int J Drug Policy*, *97*, 103409. https://doi.org/10.1016/j.drugpo.2021.103409

Green, T. C., & Gilbert, M. (2016). Counterfeit medications and fentanyl. *JAMA internal medicine*, *176*(10), 1555-1557.

Gummin, D. D. (2020). Potent opioids and implications for national defense. *TOXICOLOGY LETTERS*, *321*, 90-94. https://doi.org/10.1016/j.toxlet.2019.12.017

Gundersen, P. O. M., Astrand, A., Green, H., Josefsson, M., Spigset, O., & Vikingsson, S. (2020). Metabolite Profiling of Ortho-, Meta- and Para-Fluorofentanyl by Hepatocytes and High-Resolution Mass Spectrometry. *JOURNAL OF ANALYTICAL TOXICOLOGY*, *44*(2), 140-148. https://doi.org/10.1093/jat/bkz081

Heiskanen, T., Langel, K., Gunnar, T., Lillsunde, P., & Kalso, E. A. (2015). Opioid Concentrations in Oral Fluid and Plasma in Cancer Patients With Pain. *Journal of Pain and Symptom Management*, *50*(4), 524-532. https://doi.org/https://doi.org/10.1016/j.jpainsymman.2014.09.004

Hicks, D., Baehr, C., Silva-Ortiz, P., Khaimraj, A., Luengas, D., Hamid, F. A., & Pravetoni, M. (2022). Advancing humanized monoclonal antibody for counteracting fentanyl toxicity towards clinical development. *HUMAN VACCINES & IMMUNOTHERAPEUTICS*, *18*(6), 2122507.

Jannetto, P. J., Helander, A., Garg, U., Janis, G. C., Goldberger, B., & Ketha, H. (2019). The fentanyl epidemic and evolution of fentanyl analogs in the United States and the European Union. *Clin Chem*, *65*(2), 242-253.

Janssen, P. A., Jageneau, A. H., Demoen, P. J., Westeringh, C. v. D., Raeymaekers, A. H., Wouters, M. S., Sanczuk, S., Hermans, B. K., & Loomans, J. L. (1958). Compounds Related to Pethidine--I. Mannich Bases Derived from Norpethidine and Acetophenones. *Journal of Medicinal Chemistry*, *1*(1), 105-120.

Jordan, C. G., Kennalley, A. L., Roberts, A. L., Nemes, K. M., Dolma, T., & Piper, B. J. (2022). The Potential of Methocinnamox as a Future Treatment for Opioid Use Disorder: A Narrative Review. *Pharmacy*, *10*(3), 48.

Kahl, J. H., Gonyea, J., Humphrey, S. M., Hime, G. W., & Boland, D. M. (2018). Quantitative Analysis of Fentanyl and Six Fentanyl Analogs in Postmortem Specimens by UHPLC-MS-MS. *J Anal Toxicol*, *42*(8), 570-580. https://doi.org/10.1093/jat/bky054

Kalkman G. A., v. d. B. W., Pierce M., Atsma F., Vissers K. C. P.,, & Schers H. J., v. D. R. T. M., Kramers C. and Schellekens A. F. A. (2022). Monitoring Opioids in Europe: The Need for Shared Definitions and Measuring Drivers of Opioid Use and Related Harms. In.

Ketchum, J. (2006). Chemical Warfare Secrets Almost Forgotten. ChemBooks. *Inc, Santa Rosa, CA*.

Kranenburg, R., Verduin, J., de Ridder, R., Weesepoel, Y., Alewijn, M., Heerschop, M., Keizers, P., van Esch, A., & van Asten, A. (2021). Performance evaluation of handheld Raman spectroscopy for cocaine detection in forensic case samples [Article]. *DRUG TESTING AND ANALYSIS*, *13*(5), 1054-1067. https://doi.org/10.1002/dta.2993

Krieter, P., Gyaw, S., Crystal, R., & Skolnick, P. (2019). Fighting fire with fire: development of intranasal nalmefene to treat synthetic opioid overdose. *JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS*, *371*(2), 409-415.

Kronstrand, R., Åstrand, A., Watanabe, S., Gréen, H., & Vikingsson, S. (2021). Circumstances, postmortem findings, blood concentrations and metabolism in a series of methoxyacetylfentanyl-related deaths. *JOURNAL OF ANALYTICAL TOXICOLOGY*, *45*(8), 760-771.

Langston, J. L., Moffett, M. C., Makar, J. R., Burgan, B. M., & Myers, T. M. (2020). Carfentanil toxicity in the African green monkey: Therapeutic efficacy of naloxone. *TOXICOLOGY LETTERS*, *325*, 34-42. https://doi.org/10.1016/j.toxlet.2020.02.008

Lefrancois, E., Belackova, V., Silins, E., Latimer, J., Jauncey, M., Shimmon, R., Bordin, D., Augsburger, M., Esseiva, P., Roux, C., & Morelato, M. (2020). Substances injected at the Sydney supervised injecting facility: A chemical analysis of used injecting equipment and comparison with self-reported drug type [Article]. *DRUG AND ALCOHOL DEPENDENCE*, *209*, Article ARTN 107909. https://doi.org/10.1016/j.drugalcdep.2020.107909

Li, L., & Quintero, X. (2021). Rapid orthogonal screening of forensic drugs using a compact UHPLC-PDA/SQD; a complement to GC-MS [Article]. *FORENSIC SCIENCE INTERNATIONAL*, *318*, Article ARTN 110565. https://doi.org/10.1016/j.forsciint.2020.110565

Maguire, D. R., Gerak, L. R., Sanchez, J. J., Javors, M. A., Disney, A., Husbands, S. M., & France, C. P. (2020). Effects of acute and repeated treatment with methocinnamox, a mu opioid receptor antagonist, on fentanyl self-administration in rhesus monkeys. *Neuropsychopharmacology*, *45*(12), 1986-1993.

Mannocchi, G., Pirani, F., Gottardi, M., Sirignano, A., Busardo, F., & Ricci, G. (2021). Determination of nine new fentanyl analogues and metabolites in consumers' urine by ultra-high-performance liquid chromatography-tandem mass spectrometry. *European Review for Medical and Pharmacological Sciences*, *25*(12), 4394-4399.

Mathews, R. J. (2018). Central Nervous System-acting chemicals and the Chemical Weapons Convention: A former Scientific Adviser's perspective. *PURE AND APPLIED CHEMISTRY*, *90*(10), 1559-1575. https://doi.org/10.1515/pac-2018-0502

McCranor, B. J., Jennings, L., Tressler, J., Tuet, W. Y., Cox, V. E. D., Racine, M., Stone, S., Pierce, S., Pueblo, E., Dukes, A., Litvin, S. R., Leyden, M. R., Vignola, J. N., Pennington, M. R., & Wong, B. (2020). Assessment of naloxone as a therapeutic for inhaled carfentanil in the ferret. *TOXICOLOGY REPORTS*, *7*, 1112-1120. https://doi.org/10.1016/j.toxrep.2020.08.019

Misailidi, N., Papoutsis, I., Nikolaou, P., Katselou, M., Spiliopoulou, C., & Athanaselis, S. (2018). Furanylfentanyl: another fentanyl analogue, another hazard for public health. *FORENSIC TOXICOLOGY*, *36*(1), 1-11. https://doi.org/10.1007/s11419-017-0371-z

Mishra, R., Goud, K., Li, Z., Moonla, C., Mohamed, M., Tehrani, F., Teymourian, H., & Wang, J. (2020). Continuous Opioid Monitoring along with Nerve Agents on a Wearable Microneedle Sensor Array [Article]. *JOURNAL OF THE AMERICAN CHEMICAL SOCIETY*, *142*(13), 5991-5995. https://doi.org/10.1021/jacs.0c01883

Monje B., G.-M. A., Ortega-Navarro Ch., Herranz-Alonso A. and, & M., S.-S. (2018). Trends in hospital consumption of analgesics after the implementation of a pain performance improvement plan. In: Rev Bras Anestesiol.

Montesano, C., Vannutelli, G., Fanti, F., Vincenti, F., Gregori, A., Rita Togna, A., Canazza, I., Marti, M., & Sergi, M. (2017). Identification of MT-45 metabolites: in silico prediction, in vitro incubation with rat hepatocytes and in vivo confirmation. *JOURNAL OF ANALYTICAL TOXICOLOGY*, *41*(8), 688-697.

Montesano, C., Vincenti, F., Fanti, F., Marti, M., Bilel, S., Togna, A. R., Gregori, A., Di Rosa, F., & Sergi, M. (2021). Untargeted metabolic profiling of 4-fluoro-furanylfentanyl and isobutyrylfentanyl in mouse hepatocytes and urine by means of LC-HRMS. *METABOLITES*, *11*(2), 97.

Mörén, L., Qvarnström, J., Larsson, A., & Östin, A. (2021). Chemical profiling of dispersed fentanyl analogues sampled from indoor surfaces using multivariate data classification to determine synthesis methods. *FORENSIC CHEMISTRY*, *24*, 100328. https://doi.org/https://doi.org/10.1016/j.forc.2021.100328

Mueller, F., Bogdal, C., Pfeiffer, B., Andrello, L., Ceschi, A., Thomas, A., & Grata, E. (2021). Isotonitazene: Fatal intoxication in three cases involving this unreported novel psychoactive substance in Switzerland. *FORENSIC SCIENCE INTERNATIONAL*, *320*. https://doi.org/10.1016/j.forsciint.2021.110686

NATO. (AEP 66). NATO Handbook for Sampling and Identification of Biological. In *Chemical and Radiological Agents (SIBCRA), Edition A, Version* (Vol. 1).

Nedahl, M., Johansen, S. S., & Linnet, K. (2020). Postmortem Brain–Blood Ratios of Codeine, Fentanyl, Oxycodone and Tramadol. *JOURNAL OF ANALYTICAL TOXICOLOGY*, *45*(1), 53-59. https://doi.org/10.1093/jat/bkaa048

Negri, A., Townshend, H., McSweeney, T., Angelopoulou, O., Banayoti, H., Prilutskaya, M., Bowden-Jones, O., & Corazza, O. (2021). Carfentanil on the darknet: Potential scam or alarming public health threat? *Int J Drug Policy*, *91*, 103118. https://doi.org/10.1016/j.drugpo.2021.103118

NIOSH. (2011). Fentanyl: Incapacitating Agent. In: The National Institute for Occupational Safety and Health (NIOSH)

Noble, C., Weihe Dalsgaard, P., Stybe Johansen, S., & Linnet, K. (2018). Application of a screening method for fentanyl and its analogues using UHPLC-QTOF-MS with data-independent acquisition (DIA) in MSE mode and retrospective analysis of authentic forensic blood samples. *DRUG TESTING AND ANALYSIS*, *10*(4), 651-662.

Oldenhof, S., Ten Pierick, A., Bruinsma, J., Eustace, S., Hulshof, J., van den Berg, J., & Hoitink, M. (2019). Identification of a novel fentanyl analogue: p-Hydroxy-butyrylfentanyl. *DRUG TESTING AND ANALYSIS*.

Ordean, A., & Tubman-Broeren, M. (2023). Safety and Efficacy of Buprenorphine-Naloxone in Pregnancy: A Systematic Review of the Literature. *Pathophysiology*, *30*(1), 27-36. https://www.mdpi.com/1873-149X/30/1/4

Popławska, M., Bednarek, E., Naumczuk, B., Kozerski, L., & Błażewicz, A. (2021). Identification and structure characterization of five synthetic opioids: 3, 4-methylenedioxy-U-47700, o-methyl-acetylfentanyl, 2-thiophenefentanyl, benzoylfentanyl and benzoylbenzylfentanyl. *FORENSIC TOXICOLOGY*, *39*, 45-58.

Rab, E., Flanagan, R. J., & Hudson, S. (2019). Detection of fentanyl and fentanyl analogues in biological samples using liquid chromatography–high resolution mass spectrometry. *FORENSIC SCIENCE INTERNATIONAL*, *300*, 13-18. https://doi.org/https://doi.org/10.1016/j.forsciint.2019.04.008

Riches, J. R., Read, R. W., Black, R. M., Cooper, N. J., & Timperley, C. M. (2012). Analysis of clothing and urine from Moscow theatre siege casualties reveals carfentanil and remifentanil use. *J Anal Toxicol*, *36*(9), 647-656. https://doi.org/10.1093/jat/bks078

Rzasa Lynn, R., & Galinkin, J. (2018). Naloxone dosage for opioid reversal: current evidence and clinical implications. *Therapeutic Advances in Drug Safety*, *9*(1), 63-88. https://doi.org/10.1177/2042098617744161

Salomone, A., Palamar, J. J., Bigiarini, R., Gerace, E., Di Corcia, D., & Vincenti, M. (2019). Detection of Fentanyl Analogs and Synthetic Opioids in Real Hair Samples. *J Anal Toxicol*, *43*(4), 259-265. https://doi.org/10.1093/jat/bky093

SAMHSA. (2018). Substance Abuse and Mental Health Services Administration. In.

Schubert, I., Ihle, P., & Sabatowski, R. (2013). Increase in opiate prescription in Germany between 2000 and 2010: a study based on insurance data. *Deutsches Ärzteblatt International*, *110*(4), 45.

Sisco, E., Robinson, E., Burns, A., & Mead, R. (2019). What's in the bag? Analysis of exterior drug packaging by TD-DART-MS to predict the contents [Article]. *FORENSIC SCIENCE INTERNATIONAL*, *304*, Article ARTN 109939. https://doi.org/10.1016/j.forsciint.2019.109939

Stanley, T. H. (2014). The fentanyl story. *J Pain*, *15*(12), 1215-1226. https://doi.org/10.1016/j.jpain.2014.08.010

Stephanson, N., Signell, P., Helander, A., & Beck, O. (2017). Use of LC–HRMS in full scan-XIC mode for multi-analyte urine drug testing–a step towards a 'black-box'solution? *Journal of Mass Spectrometry*, *52*(8), 497-506.

Steuer, A. E., Williner, E., Staeheli, S. N., & Kraemer, T. (2017). Studies on the metabolism of the fentanyl-derived designer drug butyrfentanyl in human in vitro liver preparations and authentic human samples using liquid chromatography-high resolution mass spectrometry (LC-HRMS). *DRUG TESTING AND ANALYSIS*, *9*(7), 1085-1092.

Tabarra, I., Soares, S., Rosado, T., Goncalves, J., Luis, A., Malaca, S., Barroso, M., Keller, T., Restolho, J., & Gallardo, E. (2019). Novel synthetic opioids - toxicological aspects and analysis. *FORENSIC SCIENCES RESEARCH*, *4*(2), 111-140. https://doi.org/10.1080/20961790.2019.1588933

Ti, L., Tobias, S., Maghsoudi, N., Milloy, M., McDonald, K., Shapiro, A., Beriault, D., Stefan, C., Lysyshyn, M., & Werb, D. (2021). Detection of synthetic cannabinoid adulteration in the unregulated drug supply in three Canadian settings [Article]. *Drug and Alcohol Review*, *40*(4), 580-585. https://doi.org/10.1111/dar.13237

Timperley, C. M., Forman, J. E., Aas, P., Abdollahi, M., Benachour, D., Al-Amri, A. S., Baulig, A., Becker-Arnold, R., Borrett, V., Carino, F. A., Curty, C., Gonzalez, D., Geist, M., Kane, W., Kovarik, Z., Martinez-Alvarez, R., Mikulak, R., Mourao, N. M. F., Neffe, S., . . . Izzati, F. N. (2018). Advice from the Scientific Advisory Board of the Organisation for the Prohibition of Chemical Weapons on riot control agents in connection to the Chemical Weapons Convention. *RSC ADVANCES*, *8*(73), 41731-41739. https://doi.org/10.1039/c8ra08273a

Tobias, S., Shapiro, A., Grant, C., Patel, P., Lysyshyn, M., & Ti, L. (2021). Drug checking identifies counterfeit alprazolam tablets [Article]. *DRUG AND ALCOHOL DEPENDENCE*, *218*, Article ARTN 108300. https://doi.org/10.1016/j.drugalcdep.2020.108300

Townsend, E. A., Bremer, P. T., Jacob, N. T., Negus, S. S., Janda, K. D., & Banks, M. L. (2021). A synthetic opioid vaccine attenuates fentanyl-vs-food choice in male and female rhesus monkeys. *DRUG AND ALCOHOL DEPENDENCE*, *218*, 108348.

Tuet, W. Y., Pierce, S. A., Racine, M. C., Tressler, J., McCranor, B. J., Sciuto, A. M., & Wong, B. (2019). Changes in murine respiratory dynamics induced by aerosolized carfentanil inhalation: Efficacy of naloxone and naltrexone. *TOXICOLOGY LETTERS*, *316*, 127-135. https://doi.org/10.1016/j.toxlet.2019.09.012

UNODC. (2017). Global smart update: Fentanyl and its analogues – 50 years on. In: United Nations Office on Drugs and Crime

UNODC. (2022). *World Drug Report*. https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2022.html

Verkouteren, R., Heckert, N., Leigh, S., Sisco, E., Norris, J., Lawrence, J., & Burns, A. (2019). ASTM E2677: International Standard on Limit of Detection for Trace Detectors—Explosives, Opioids, and Ozone. In. American Society for Testing and Materials.

Vikingsson, S., Rautio, T., Wallgren, J., Åstrand, A., Watanabe, S., Dahlén, J., Wohlfarth, A., Konradsson, P., Wu, X., & Kronstrand, R. (2019). LC-QTOF-MS identification of major urinary cyclopropylfentanyl metabolites using synthesized standards. *JOURNAL OF ANALYTICAL TOXICOLOGY*, *43*(8), 607-614.

Vincenti, F., Pagano, F., Montesano, C., Sciubba, F., Di Cocco, M. E., Gregori, A., Di Rosa, F., Lombardi, L., Sergi, M., & Curini, R. (2020). Multi-analytical characterization of 4-fluoro-furanyl fentanyl in a drug seizure. *FORENSIC CHEMISTRY*, *21*. https://doi.org/10.1016/j.forc.2020.100283

Wallgren, J., Vikingsson, S., Rautio, T., Nasr, E., Åstrand, A., Watanabe, S., Kronstrand, R., Gréen, H., Dahlén, J., & Wu, X. (2020). Structure elucidation of urinary metabolites of fentanyl and five fentanyl analogs using LC-QTOF-MS, hepatocyte incubations and synthesized reference standards. *JOURNAL OF ANALYTICAL TOXICOLOGY*, *44*(9), 993-1003.

Watanabe, S., Vikingsson, S., Roman, M., Green, H., Kronstrand, R., & Wohlfarth, A. (2017). In vitro and in vivo metabolite identification studies for the new synthetic opioids acetylfentanyl, acrylfentanyl, furanylfentanyl, and 4-fluoro-isobutyrylfentanyl. *The AAPS Journal*, *19*, 1102-1122.

West, H., Fitzgerald, J., Hopkins, K., Li, E., Clark, N., Tzanetis, S., Greene, S., & Reid, G. (2021). Early Warning System for Illicit Drug Use at Large Public Events: Trace Residue Analysis of Discarded Drug Packaging Samples [Article]. *Journal of the American Society For Mass Spectrometry*, *32*(10), 2604-2614. https://doi.org/10.1021/jasms.1c00232

Wilde, M., Sommer, M. J., Auwärter, V., & Hermanns-Clausen, M. (2020). Acute severe intoxication with cyclopropylfentanyl, a novel synthetic opioid. *TOXICOLOGY LETTERS*, *320*, 109-112.

Yong, Z., Hao, W., Weifang, Y., Qiyuan, D., Xinjian, C., Wenqiao, J., & Youcheng, Z. (2003). Synthesis and analgesic activity of stereoisomers of cis-fluoro-ohmefentanyl. *Pharmazie*, *58*(5), 300-302.

Zawilska, J. B., Kuczyńska, K., Kosmal, W., Markiewicz, K., & Adamowicz, P. (2021). Carfentanil–from an animal anesthetic to a deadly illicit drug. *FORENSIC SCIENCE INTERNATIONAL*, *320*, 110715.