TERROR
Strengthened preparedness and response to biological and chemical terror attacks

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WP8 Novel Threats

D8.4: Synthetic Opioids- risk assessments and recommendations for future governance guidelines

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Key Findings

This report presents a series of recommendations aimed at improving the management and mitigation of risks associated with synthetic opioids. The recommendations are aimed at member state policy makers as well as the scientific research community to draw attention to research that could be considered to be dual use.

Our findings underline the urgent need for enhanced surveillance, improved detection methods, and comprehensive preparedness measures. The rapid pace at which new synthetic opioids are synthesised and modified poses a significant challenge, often outpacing existing legal and regulatory frameworks. Furthermore, the varied and potent nature of these substances exacerbates the risk of overdose and fatalities, complicating detection, and response efforts.

Leveraging technologies such as artificial intelligence (AI) and machine learning can play a critical role in anticipating the emergence of new synthetic opioids. These technologies can analyse vast datasets to predict trends and identify potential new substances before they infiltrate the market, thereby enabling proactive measures, including choosing right types of medical countermeasures to new substances.

The standardisation of detection methods across EU member states could facilitate better data collection and sharing across regions, improving the overall response to opioid incidents. This is of particular importance for on-site detection, where more robust and sensitive techniques and approaches should be implemented and further developed. Uniform detection protocols would enhance the ability of first responders and medical personnel to quickly and accurately identify synthetic opioids and ensure timely and appropriate medical interventions.

Preparedness activities, including drills and training scenarios that specifically involve synthetic opioids, are invaluable for preparing healthcare providers and emergency responders to recognize and manage mass casualty incidents involving these drugs, which are often not immediately recognized as what they are due to their prevalence in individual overdose cases rather than mass exposure. Here the first responder might think first of another group chemical weapon, the organophates which cause the cholinergic toxidrome that can confuse the first responder Therefore it is important to include the distinction between the two toxidromes into the drills for first responders.

Furthermore, there is a need to expand access to naloxone for individuals who are at occupational risk of exposure to synthetic opioids. This includes not only health professionals but also law enforcement officers and other first responders who might encounter these substances during their duties.

Additionally, we recommend the development of guidelines for publishers and funding bodies to help recognise and mitigate security risks associated with the publication of sensitive information on synthetic opioid production. This measure is intended to prevent the misuse of scientific research for the production of potent and dangerous substances.

Finally, tighter control of precursor substances used in the synthesis of synthetic opioids will help curb their illicit manufacture. Regulating these substances at the international level would reduce the availability of critical components needed for the production of synthetic opioids.

The EC plays a pivotal role in creating policies and regulatory frameworks that can harmonise approaches to complex challenges. By establishing clear standards for synthetic biology and chemistry, the EC is in a position to ensure consistency in safety, ethical considerations, and quality across member states. Further, the EC can negotiate international agreements, participate in global forums, and advocate for regulatory frameworks that reflect the EU's values and standards. This harmonisation is crucial for preventing a fragmented approach to biosecurity and biosafety.

Objectives

Relevant risk assessments will be written to inform Member States on the most pressing risks posed by synthetic opioids.

Recommendations made on the governance of synthetic opioids for the benefit of Member States.

Background

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".

Overview of Synthetic Opioids

Synthetic opioids are a class of potent man-made drugs, engineered to mimic the effects of naturally occurring opioids like morphine and codeine. Unlike their natural counterparts, synthetic opioids such as fentanyl and its various analogues, are produced entirely through chemical synthesis and may have a potency hundreds or even thousands of times greater than morphine (Armenian et al., 2018). In 2023, the EU Early Warning System on new psychoactive substances identified new synthetic opioids in at least 16 EU Member States, Norway, and Türkiye. Notably, there were outbreaks of poisonings and overdoses involving nitazene opioids reported in five countries. Additionally, there were instances of nitazene opioids being mis-sold as heroin (EMCDDA, 2024). The potency of synthetic opioids has contributed to their widespread illicit production and use, posing a higher risk of overdose and death and leading to a substantial increase in fatalities worldwide (Jannetto et al., 2019).

In addition to the immediate health risks of overdose and death, synthetic opioids pose significant public health challenges. They strain healthcare systems with increased demands for emergency response, addiction treatment, and long-term societal costs related to loss of productivity and law enforcement efforts. The problem is not confined within national borders; the global nature of

synthetic opioid trafficking necessitates robust international cooperation. Countries must work together to share intelligence, harmonise regulatory frameworks, and disrupt illicit supply chains to effectively combat this issue.

The regulatory challenges are considerable. The rapid pace of development of new synthetic opioids often outstrips existing legal frameworks and enforcement capabilities, as manufacturers frequently alter molecular structures to evade restrictions. Additionally, the detection and identification of these new compounds require advanced technology and specialised expertise. This technological and knowledge gap creates inconsistencies in response and mitigation strategies, affecting local, national, and international efforts to combat the spread of these dangerous substances.

Synthetic Opioids as a weapon

Synthetic opioids, particularly fentanyl and its analogues like carfentanil, have emerged as potential weapons of terror due to their extreme potency and relative ease of production. Very small amounts can be lethal, making them a serious concern for public safety and national security. If used as a weapon, their high toxicity and rapid onset of effects has the potential to cause mass casualties or widespread panic.

The threat is multifaceted. Firstly, these substances can be integrated into existing illicit drug markets, masked as other less potent drugs, which can lead to unintentional mass overdoses. This method of distribution could act as a covert operation to cause harm indirectly. More directly, synthetic opioids could be aerosolized and released in public spaces such as subways, airports, or event venues, where they could incapacitate or kill large numbers of people quickly. The ease with which these compounds can be synthesized from precursor chemicals that are not difficult to obtain adds to the potential for misuse by terrorist groups.

Addressing this threat requires a coordinated approach involving improved surveillance and intelligence gathering, stricter regulation of precursor chemicals, and enhanced public health preparedness. It also necessitates international cooperation, as the ingredients and knowledge to produce these drugs can traverse borders easily. Moreover, there is a need for public education on the dangers of synthetic opioids, which could help in early detection and prevention of their use in terror activities.

Identified risks / threats

The table below (Table 1) summarises risks identified while conducting a literature review focused on synthetic opioids on behalf of JA Terror. Each entry outlines a specific challenge and provides an overview of the associated risks.

Table 1: Risks identified from Synthetic Opioids Literature Review, produced as part of Joint Action TERROR

Risk #	Identified risk	Description of risk
1	The engineering of new substances	Engineering of new synthetic opioids poses significant risks due to unknown health effects, challenges in medical response due to unfamiliar toxic profiles, and gaps in regulatory coverage. Drugs might quickly enter illicit markets, evade detection in standard drug tests, and spread rapidly, complicating public health efforts and law enforcement. AI has the potential to exacerbate this risk. AI systems can analyse extensive databases of chemical structures and their pharmacological impacts to pinpoint potential opioid analogues.
2	Ease of production and distribution	Synthetic opioids can be synthesised using relatively simple chemical processes, and the precursor chemicals are often readily available. This ease of production makes it possible for non-state actors or terrorists to manufacture these drugs without specialised knowledge, increasing the risk of their use in criminal or terrorist activities. Newer and simpler delivery mechanisms such as NSO aerosol released by a drone over a large area are increasingly of concern.
3	High Potency	The extreme potency of synthetic opioids like the most potent fentanyl derivatives and nitazenes makes them particularly dangerous as weapons. Even small quantities can result in mass casualties.

4	Detection challenges	Detecting synthetic opioids presents several challenges, particularly due to the constant emergence of new substances and their varied chemical structures. Currently, field detection methods may not be sensitive enough to detect low yet toxic concentrations of synthetic opioids, nor specific enough to differentiate between closely related compounds, leading to potential false positives or negatives.
5	Protection and Response Challenges	The standard protective gear used by first responders may not be adequate against synthetic opioid exposure, particularly when these substances are aerosolized. Working dogs are particularly vulnerable when responding to an incident. The rapid onset of symptoms following exposure can also complicate emergency response efforts.
6	Complications in Medical Treatment	The effective treatment of mass exposure to synthetic opioids requires specific antidotes, such as naloxone, in large quantities. There may be logistical challenges in storing and distributing adequate amounts of these antidotes, especially in a mass casualty scenario. Opioid overdose may not be immediately recognised in situations of mass casualties as it is generally observed in smaller numbers of patients and the most expected scenario might be organophate poisoning with a toxidrome not unsimilar opioid toxidrome. Synthetic opioids might although requires higher and repeated doses of Naloxone to give a long lasting reversal effect.
7	Information sharing on advances in synthetic opioid production (e.g., scientific publications)	Information sharing can inadvertently facilitate the spread of knowledge on how to synthesise potent substances. Detailed publications or discussions can provide both legitimate researchers and illicit drug manufacturers with insights into new synthetic pathways or modifications to existing opioids, potentially leading to the production of more potent and dangerous substances.
8	Potential for public panic	The use of synthetic opioids as a weapon can cause significant public fear and panic. This fear can lead to widespread social disruption and strain on/overwhelming of emergency and medical services.
9	Evasion of legislation	The rapid development and modification of synthetic opioids outpace current regulatory frameworks, making it difficult to control and monitor these substances effectively. This lag in regulation can be exploited to acquire or distribute these drugs for malicious purposes.

Recommendations

The following recommendations are suggested to mitigate each of the risks outlined in table 1.

Recommendation 1: Legislation on illicit drugs and opioids should become more and more generic with prediction on future potential new synthetic opioids before they reach the market.

Legislation on illicit drugs and opioids should become more and more generic, regulating the basic structure of molecules. In this case all newly emerging synthetic opioids will be considered automatically as illicit, without the need of legislative adjustments, that often take a lot of time. Some countries within the EU and the UK already have this kind of legislation. In that case the legislation can follow the approach of in-field analysis focusing on the identification of the basic structure or the group of molecules, allowing immediately to take appropriate countermeasures, both from health protection and juridical perspective.

Prediction on new synthetic opioids

AI is likely to accelerate the engineering of new substances however it could also hold the key to recognizing them and mitigating this risk. At present AI's role in drug discovery and design involves using machine learning models to rapidly predict the molecular structures of compounds that could specifically target opioid receptors with high efficiency and specificity. These AI systems analyse extensive databases of chemical structures and their pharmacological impacts to pinpoint potential opioid analogues.

Additionally, AI enhances the ability to simulate and model interactions at the molecular level between new synthetic opioids and various receptors in the human body. This advanced simulation helps predict the effectiveness and strength of new compounds before actual synthesis in laboratories, which could accelerate the drug development process.

Furthermore, AI contributes to optimizing chemical synthesis pathways. It identifies the most efficient methods for manufacturing new drugs by determining optimal conditions such as catalysts, temperature, solvents, and other chemical reactions. This not only increases the purity and quantity of these compounds but also streamlines the production process, making it faster and more cost-

effective. This capability, while beneficial in a pharmaceutical context, also poses risks if misused for creating potent illicit drugs.

A thorough understanding of what is likely to emerge will assist preparedness activities, ensure detection methods are appropriate and provide an opportunity to review regulatory frameworks remain fit for purpose.

After potential new synthetic opioids are predicted and described by AI, AI can also be used to give recommendations regarding medical countermeasures to these substances. This includes that it can support the decisionmakers to decide if the existing and known medical countermeasures are sufficient of if known protocols must be optimized. AI can help to identify and invent new potential medical countermeasures if necessary.

Recommendation 2: Standardisation of detection methods

The standardisation of detection methods across the EU could bring significant benefits. By implementing uniform detection protocols, the EU can ensure consistency in identifying synthetic opioids, irrespective of where they are detected. This uniformity is essential for the reliability of data concerning drug prevalence and trends and allows for more accurate monitoring and response strategies.

Further, standardisation leads to better quality control and validation across laboratories. With established protocols, the likelihood of errors decreases, and the accuracy and reliability of test results is enhanced. This is crucial for maintaining regulatory compliance and ensuring that all laboratories adhere to the same high standards.

Additionally, standardised methods facilitate efficient resource allocation and training. Laboratories across the EU can share resources, training programs, and information, reducing costs and enhancing operational efficiency. This collaborative approach also supports quicker responses to public health emergencies, such as overdose outbreaks, enabling labs to swiftly confirm the presence of specific opioids and inform relevant public health and law enforcement agencies.

The European Union Drugs Agency (EUDA, www.euda.europa.eu) is a new agency for contributing to EU preparedness on drugs through four main actions: anticipate, alert, respond and learn. Previously the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the new agency was formed on 2nd July 2024. The new agency will help to ensure that the decisions of EU and national

policymakers, professionals and practitioners are based on objective and verified facts, not ideology or moral and value judgements. In addition, the agency will identify important drug-related threats, helping EU countries to be better prepared to handle them. The Agency gathers vital information on drugs through Reitox, the European information network on drugs and drug addiction. Reitox is composed of designated national institutions or agencies responsible for collecting and reporting data on drugs and addiction. By linking national drug information systems, Reitox serves as the primary channel through which the EUDA exchanges data and methodological insights on these issues across Europe. The data collected through Reitox play a key role in monitoring and evaluating the outcomes of the EU's drugs action plans within its broader drug strategy. Additionally, this data helps shape EU drug policies, offering guidance for national responses related to treatment, prevention, and harm reduction initiatives. The collaboration between the EU Early Warning System on new psychoactive substances and the Reitox network enables timely decisions to bring emerging substances under control within the EU.

Next to standardization of protocols and procedures in the (forensic) laboratories across Europe, more effort should be put into the development and implementation of robust, sensitive and accurate identification techniques for in-field analysis. This is to allow the rapid identification of the threat, ensure the protection of first responders and selection of the best countermeasures. Ideally, this technique/method should combine a separation technique and a sensitive and specific detector like mass spectrometry, allowing the analysis of both chemical (powders, swabs) and biological (e.g., urine, saliva) samples. Liquid chromatography combined with mass spectrometry seems to be a good candidate to this end. Additionally, portable devices well-suited for this purpose are emerging, especially when combined with up-to-date libraries. Moreover, even if a new emerging compound is detected, mass spectrometry could allow identification of the chemical structure or the group of products it belongs to, often specific enough to select the appropriate counter measures.

Recommendation 3: Preparedness activities should include scenarios involving synthetic opioids.

Including synthetic opioids in preparedness scenarios equips first responders and healthcare providers with crucial experience and knowledge to handle real-life situations. Synthetic opioids can have rapid

and severe effects; thus, preparedness drills are vital for improving the efficiency and safety of the emergency response.

In this regard, enhancing Early Warning Systems (EWS) by establishing or strengthening workstreams to foster voluntary cooperation among forensic laboratories, national stakeholders, communities, NGOs, health organizations, and researchers/academia, is vital for a cohesive response to opioid incidents, ensuring that all parties can work together effectively in the event of an actual emergency. Moreover, it is necessary to enhance the collection and sharing of non-personal data at national, regional, and sub-regional levels for real-time usage. This includes creating mechanisms to alert emergency rooms and clinicians about new substances identified through seizure data and international early warning alerts, in collaboration with emergency rooms and clinical treatment providers.

Preparedness activities help to identify gaps in current healthcare protocols and promotes the development of more effective medical interventions, such as ensuring adequate availability of naloxone. Moreover, preparedness activities can help health professionals to understand the signs of synthetic opioid overdose in mass casualty scenarios as opioid toxidrome, a situation they might not typically expect, given their experience is often with individual cases and 'user' dose incidents, compared with a potential terror scenario and organophate derivates causing a somewhat similar toxidrome, used as weapons in a terror attack might be more expected. This training can open their minds to the possibility of such attacks and train them to respond appropriately.

Preparedness scenarios should include risk communication strategies to ensure they are prepared to assuage public panic that could follow a mass casualty event.

Recommendation 4: Review who has an occupational risk of contact with synthetic opioids and expand access to naloxone

Synthetic opioids present a significant risk to individuals who may come into contact with them during their professional activities. Consideration should be given not only to occupations that face direct exposure through medical treatment or law enforcement activities, but also to those likely to face accidental exposure through airborne particles or contact with contaminated surfaces. Understanding the specific conditions and scenarios in which these risks occur will help in crafting targeted strategies to mitigate them.

Once identified, at-risk occupational groups can be offered access to naloxone as well as training programs on how to safely administer it. These training sessions should cover the identification of overdose symptoms, proper administration techniques, and the follow-up steps required after administration. Additionally, policies should be put in place to ensure that naloxone kits are readily accessible in areas where the risk of exposure to synthetic opioids is high.

Recommendation 5: Develop guidelines for publishers and funding bodies to assist in recognising (bio)security risks

Publishers and funding bodies should play a proactive role in ensuring that research outputs do not contribute to public health threats or criminal activities.

Guidelines for publishers should encourage a thorough review process that includes an assessment of the research's potential to be used in harmful ways, together with an author declaration as an additional safeguard. Similarly, funding bodies should require robust risk assessments from researchers seeking grants for studies related to synthetic opioids or their precursors. This process should ensure that the proposed research includes plans for secure handling, storage, and disposal of synthetic opioids, and measures to prevent unauthorized access to knowledge and materials that could be used for illicit production.

Guidelines should also recommend strategies for redacting sensitive data in publications, without diluting the scientific merit or utility of the research. This could involve omitting specific details about chemical synthesis pathways or the use of general terms when describing novel methodologies for creating potent opioids. Furthermore, there should be a mechanism in place for peer reviewers to flag high-risk research and for journals to consult with experts in both biological and chemical security, when necessary.

Recommendation 6: Control of substances

This recommendation focuses on enhancing the regulation of precursor chemicals and laboratory equipment that can be used to synthesize opioids. By controlling materials, authorities can help prevent illicit manufacture, thereby reducing their availability on the black market.

Effective control of precursor chemicals is required and lists should be regularly updated to include new substances as they are identified. Regulations should mandate strict licensing and monitoring of any business or entity that handles listed chemicals. Similarly, the sale and distribution of specialised laboratory equipment that could be used in the synthesis of opioids should be monitored and sold only to verified and licensed laboratories or institutions that have a legitimate need for such apparatus.

Recommendation 7: Strengthening co-operation

This recommendation aims to tackle the rapidly evolving challenges posed by regionally detected synthetic drugs by hosting or participating in regular, recurring meetings with regional partners, intelligence analysts, networks, and stakeholders. These meetings should aim to foster continuous dialogue to understand the scope and nature of synthetic drug issues across regions, to develop and implement effective policies to combat the production, distribution, and use of synthetic drugs, to coordinate actions among regional partners to ensure a unified and effective response, to enhance data-sharing practices to facilitate the real-time exchange of information on synthetic drug trends and incidents, and to implement targeted programs that address specific challenges identified through collaborative efforts.

Through regular communication and collaboration, these meetings will enable a comprehensive and dynamic approach to addressing synthetic drug challenges regionally.

Table 2: Summary of recommendation and the identified risks that they mitigate. See table 1 for corresponding risk numbers.

Recommendations	Risk (number correlates to risk identified in Table 1)
Recommendation 1: Utilise artificial intelligence and machine learning to analyse trends and predict potential new synthetic opioids, and also the effects of existing medical countermeasures before the new synthetic opioids reach the market.	1, 6
Recommendation 2: Standardisation of detection methods	4
Recommendation 3: Preparedness activities should include scenarios involving synthetic opioids.	5, 6, 8
Recommendation 4: Review who has an occupational risk of contact with synthetic opioids and expand access to naloxone	3, 5
Recommendation 5: Develop guidelines for publishers and funding bodies to assist in recognising biosecurity risks	7
Recommendation 6: Control of substances	2, 9

Recommendation 7: Strengthening cooperation	1, 4, 5, 6, 7, 9

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