EUDA
EUROPEAN UNION DRUGS AGENCY

THREAT ASSESSMENT REPORT

Assessing the threat posed by the increased availability, use and harms of highly potent synthetic opioids in the Baltic region

Contents

Executive summary

This threat assessment examines the evolving presence and impact of highly potent synthetic opioids, particularly the group of 2-benzylbenzimidazole opioids (the so-called ‘nitazenes’) and carfentanil, in Estonia, Latvia and Lithuania. Over the past decade, these substances have largely replaced fentanyl and heroin, leading to a high burden of drug-induced deaths and acute toxicity cases. The Baltic region is disproportionately affected by this phenomenon, with the majority of nitazenes and all carfentanil seizures in the EU taking place in these three countries. The continued adaptability of synthetic opioid markets, the challenges in implementing and scaling up harm reduction responses, and gaps in monitoring systems highlight the need for a more coordinated and sustainable approach at both the national and EU levels.

Main findings

The illicit opioid market in the Baltic region has undergone significant transformation. Nitazenes have largely replaced fentanyl and its derivatives in Estonia and Latvia, while carfentanil remains dominant in Lithuania, reflecting regional differences in supply and distribution. New synthetic opioids continue to emerge, demonstrating the market’s ability to adapt.

Trafficking routes vary: nitazenes are primarily sourced from China and transported via postal and courier services, while carfentanil is likely to originate from Russia and enters Lithuania through land routes. Criminal networks in Latvia play a key role in regional trafficking, with reported links to Russian organised crime groups. The growing role of digital platforms, including encrypted messaging apps, further complicates law enforcement efforts.

In 2023, Estonia and Latvia recorded a sharp increase in drug-induced deaths, largely driven by nitazenes, while carfentanil remained the main contributor to fatalities in Lithuania. The majority of opioid-induced deaths occurred in urban centres, particularly in capital regions, which have the highest levels of synthetic opioid-related mortality.

Polysubstance use is identified as a key driver of drug-related harms, with nitazenes and carfentanil frequently detected alongside benzodiazepines, methadone, stimulants (amphetamine, methamphetamine, cocaine) and other opioids. There is also a high risk of variability in synthetic opioid concentration due to inconsistent adulteration processes, increasing the likelihood of unintentional overdoses. Users are often unaware of exactly what substances they are taking, particularly when synthetic opioids are mis-sold as heroin or

fentanyl. The limited availability of drug-checking services further restricts opportunities for harm reduction.

Access to harm reduction services remains limited across the Baltic region, leaving certain populations underserved. The coverage of opioid agonist treatment (OAT) and needle and syringe programmes (NSPs) remains low, particularly in non-urban areas. Naloxone distribution is inconsistent, with Estonia the only country in the region operating a formal take-home naloxone programme. Legal, social and structural barriers further hinder treatment and harm reduction efforts, including stigma, administrative restrictions and poor adaptation of OAT to meet the needs of synthetic opioid users. These factors can contribute to poor treatment retention and continued overdose risks.

Strengthening responses and preparedness

The rapid adaptability of illicit markets to regulatory and enforcement measures and the consequences for public health highlight the need for a coordinated, multi-sectoral approach, integrating health, security, policy and monitoring strategies. Strengthening national early warning systems, improving detection and monitoring, expanding harm reduction services and reinforcing law enforcement efforts are key in preventing and mitigating further harm.

At the national level, it will be important to prioritise the following responses:

- Integrate evidence-based prevention and overdose response training into preparedness strategies, including first aid and naloxone use for bystanders, particularly in high-risk populations. Scale up treatment and harm reduction services, including OAT and the distribution of naloxone, in order to increase accessibility and widen geographical coverage.
- Enhance early warning capacities and analytical capabilities to improve the detection of emerging synthetic opioids in seized drug samples as well as in biological samples taken in forensic and clinical toxicology settings.
- Strengthen cross-sector collaboration, particularly between public health and law enforcement agencies, to improve information-sharing and rapid response capabilities.

At the European level, it will be important to prioritise the following responses in order to support Member States' readiness to respond to synthetic opioid threats:

- Improve the mapping of criminal networks and enhance precursor tracking to better understand synthetic opioid supply routes.
- Invest in innovative drug detection tools as well as supporting research on nitazenes and other highly potent synthetic opioids.
- Strengthen monitoring by including syringe residue analysis, hospital emergency data, ambulance service records, drug consumption rooms and drug checking service data collections, and naloxone use tracking.
- Expand test purchase programmes to anticipate new synthetic opioids available in the market.
- Foster cross-border collaboration, including intelligence-sharing, forensic cooperation and joint law enforcement actions, particularly through mechanisms such as EMPACT (the European Multidisciplinary Platform Against Criminal Threats) and in partnership with key source and transit countries.

Given the increasing availability of highly potent synthetic opioids, a timely and coordinated response could help prevent and mitigate risks and enhance preparedness. While the Baltic region has been the area most affected by this issue, reports of nitazenes-related overdoses in other EU countries highlight the need for vigilance. Improving detection will be key to strengthening national and European responses, supporting timely interventions, expanding harm reduction efforts and preventing the further spread of these substances.

Box 1: The first EUDA health and security threat assessment — a pilot exercise

This report represents the first EUDA health and security threat assessment (TA) conducted under the new mandate of the European Union Drugs Agency (EUDA), following its introduction in July 2024. It was approached as a pilot exercise to test new in-house processes, from appraisal of signals to output production, including the methods developed specifically for this new activity and the processes designed to promote engagement and collaboration with national stakeholders.

This TA was conducted at the initiative of the EUDA in response to numerous signals identified through the EUDA's monitoring activities, highlighting the impact of highly potent synthetic opioids, particularly nitazenes and carfentanil, in the Baltic countries.

The primary audience for this report includes the national authorities of Estonia, Latvia and Lithuania, including the Reitox national focal points, as well as European policymakers. It aims to provide them with insights into the emerging threat of highly potent synthetic opioids and guidance in formulating evidence-based policy and intervention strategies. The findings of this assessment also inform the work of the EUDA in monitoring developments in the region and across the EU, supporting early warning, risk assessment and response efforts.

Threat assessment: objectives and rationale

The opioid situation in the Baltic countries has for some years required close monitoring and assessment. Fifteen years ago, a shift in the availability of opioids in Estonia led to a large outbreak of fentanyl-related deaths, peaking in 2012. The current availability and use of nitazenes and carfentanil, their role in a growing proportion and number of drug-induced deaths and emergencies, and their potential for further spread highlight the need for in-depth assessment.

The aim of this threat assessment (TA) is to examine the risks posed by the emergence and impact of highly potent synthetic opioids, specifically the group of 2-benzylbenzimidazole opioids (the so-called 'nitazenes') and carfentanil (see Annex 4), in the Baltic countries, namely Estonia, Latvia and Lithuania. These substances contribute significantly to the burden of drug-induced deaths in these countries, raising concerns that their high potency and risk of overdose could lead to even greater harm if their availability and accessibility increase. This TA was launched in response to signals detected through the EUDA's monitoring systems, including the EU Early Warning System on new psychoactive substances, drug-induced deaths data, acute toxicity presentations to hospitals, ambulance emergency responses data, forensic analyses, law enforcement seizures and reports from national experts.

The objectives of this assessment are to evaluate the availability, use and associated risks of these highly potent synthetic opioids while identifying gaps in health and law enforcement responses, with a key goal being to propose evidence-based response options for Member States and European policymakers to mitigate the threat posed by these substances. By focusing on the Baltic region, where these substances have had the most significant impact so far, this assessment aims to support situational awareness and intervention measures, providing evidence to inform national and EU-level policy responses.

This TA, undertaken in collaboration with the Reitox national focal points from the three Baltic countries, takes a mid- to long-term perspective, aiming to inform preparedness and resilience strategies by identifying systemic vulnerabilities and structural weaknesses. Through an analysis of the broader patterns and drivers of synthetic opioid-related threats, it seeks to provide insights to support early warning capabilities, enhance response coordination and inform sustainable policy measures. By offering timely and structured insights, this assessment will:

- Identify key trends and possible drivers influencing the presence and impact of highly potent synthetic opioids in the Baltic region;
- Assess public health and security considerations, helping to contextualise the risks posed by these substances;
- Inform early warning and intervention measures, ensuring that monitoring and response systems are proactive rather than reactive.

The findings will also support national authorities and inform European policymakers in the development of proportionate and targeted responses, including enhanced monitoring, harm reduction measures and law enforcement strategies.

Regional context

Availability and impact of nitazenes and carfentanil in the Baltic countries

As of late 2024, the EU Early Warning System on new psychoactive substances (EU EWS) was actively monitoring 22 different nitazenes, while the presence of carfentanil has been noted since 2013. In the EU, countries in the Baltic region are disproportionately affected by highly potent synthetic opioids. In 2023, all carfentanil seizures and 86 % of nitazenes seizures reported to the EU EWS occurred in Estonia, Latvia and Lithuania, accounting for 96 % of the total amount of nitazenes seized across the EU. These figures highlight the scale of the issue in the region and the importance of ongoing monitoring and targeted responses.

Detections of highly potent synthetic opioids in the Baltic region indicate a noteworthy shift in local drug markets. Since 2019, when isotonitazene was identified for the first time in the EU, nitazenes have been increasingly identified in Estonia and Latvia, with forensic and toxicology reports connecting them to a growing number of drug-induced deaths. By 2023, nitazenes were linked to 52 % of such deaths in Estonia and 66 % in Latvia. Derivatives such as protonitazene and metonitazene have become more common in Estonia, while isotonitazene, protonitazene and metonitazene are most frequently detected in Latvia. Although nitazenes remain less commonly reported in Lithuania, a small number of detections in recent years indicate their presence in the market.

In Lithuania, carfentanil — a synthetic opioid significantly more potent than fentanyl — has replaced other opioids in the illicit market and was involved in 39 % of drug-induced deaths in 2023. Detections of carfentanil have also been reported in Estonia and Latvia, though at lower levels according to different indicators, such as syringe residue analysis.

Regulatory responses to new synthetic opioids

The control of nitazenes and carfentanil has evolved in response to their increasing detection in drug markets and associated harms. At the international level, between 2020 and 2025, 15 nitazenes were reviewed by the WHO Expert Committee on Drug Dependence (ECDD) and subsequently seven have been placed in Schedule I of the 1961 UN Convention due to their potential risks to public health — a step which must be transposed into national legislation. Carfentanil was placed in Schedule I and Schedule IV of the 1961 UN Convention following its review in 2017.

At the EU level, isotonitazene was the first of the nitazenes to undergo a risk assessment by the EUDA in 2020, leading to its inclusion in the list of substances under EU drug control legislation. National-level controls vary, with several EU Member States enacting independent national control measures to address emerging concerns. Since July 2024, China has controlled 10 nitazenes, a move that may influence supply chains and lead to shifts in the European drug market.

In response to its growing availability and the increase in harms linked to it in the EU, carfentanil was risk assessed by the EUDA in 2017 (EMCDDA, 2018). The risk assessment report examined the presence of carfentanil in multiple drug-induced deaths, particularly among heroin users. While these regulatory actions have shaped the availability of highly potent synthetic opioids in the EU, continued vigilance and adaptability remain important in addressing changes in the drug landscape.

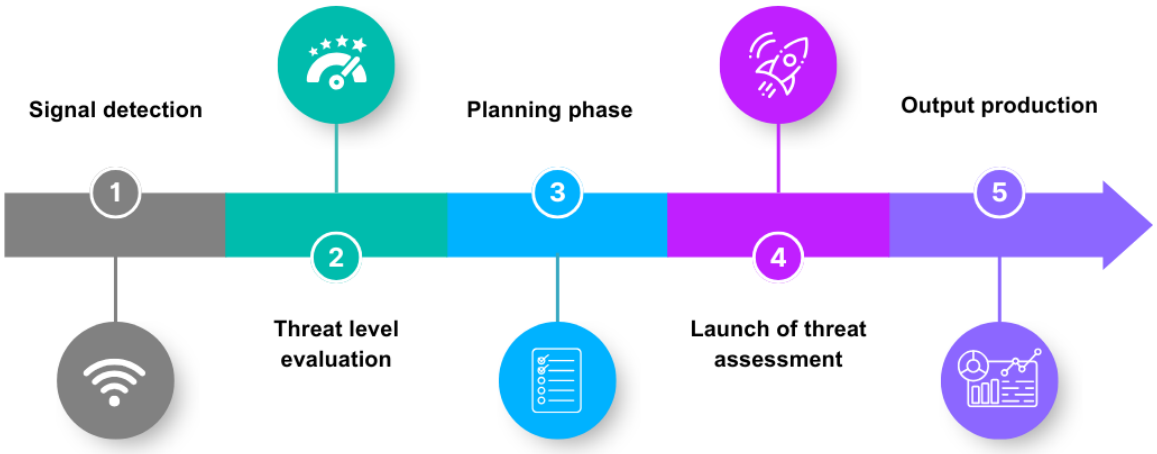
Overview of the threat assessment approach

This threat assessment (TA) was launched in response to signals detected through the EUDA's monitoring activities, linked to the emergence of nitazenes and carfentanil in the Baltic region. Data collection and analysis was conducted during a 10-week period, and was guided by key research questions, covering the crucial aspects of supply, demand, health impacts, security challenges and national responses (see Annex 2x for details).

A TA team was established for the purpose of undertaking this assessment, comprising a team coordinator, eight scientific and data analysts from the EUDA and an external facilitator. The team worked closely with Reitox focal point representatives from Lithuania, Latvia and Estonia.

The process from start to finish is visualised in Figure 1.

Figure 1. EUDA health and security threat assessment process



Data sources and analytical approach

The assessment combined multiple data sources, including:

- Primary data from national (NFPs) and European monitoring systems, including the EU Early Warning System on new psychoactive substances, covering drug seizures, drug-induced deaths, syringe residue analyses, ambulance calls, harm reduction services and hospital admissions;
- A structured literature review, examining epidemiological trends, market dynamics, health risks and public health responses;
- Expert consultations, involving three NFPs, with professionals from health, law enforcement and policy sectors (see Table A2.2 in Annex 2 for the full set of data sources).

TA findings were synthesised by triangulating the quantitative and qualitative data. Where data gaps were identified, additional input was sought directly from Reitox NFPs.

Focusing on a number of key areas — security and trafficking, harms and responses, monitoring and early warning, and policy — response options were developed through an iterative process, incorporating input from EUDA expert analysts, national focal points and available scientific evidence. The response options were then structured into three tiers based on priority, feasibility and potential impact:

- Tier 1: Actions that are immediately actionable and expected to have a high impact;
- Tier 2: Measures that require additional planning or resources but remain highly feasible;
- Tier 3: Longer-term strategies addressing systemic challenges to improve resilience and preparedness.

Finally, further considerations were drawn from the analysis, representing cross-cutting principles and strategic elements that support the successful implementation of the proposed response options. For full details on the methodology, data sources, analytical process and limitations, see Annex 2.

Threat assessment findings

This section presents the key findings of the threat assessment, providing an evidence-based analysis of the availability, use, harms and responses related to highly potent synthetic opioids in the Baltic region. The findings are structured around the main thematic areas (markets, use and harms, responses and monitoring). Each section begins with key messages, followed by a brief overview of the thematic data and analysis. Where relevant, implications are also summarised. Concrete options for response are outlined, in order to provide practical, evidence-based approaches to mitigating the threat posed by these substances and strengthening preparedness at both national and regional levels.

Markets assessment: nitazene and carfentanil availability and markets in the Baltic region

Key messages

- **Regional market transformation:** Nitazenes have replaced fentanyl and its derivatives in Estonia and Latvia, while carfentanil remains dominant in Lithuania, highlighting regional differences in synthetic opioid markets.
- **Baltic countries are disproportionately affected:** The majority of nitazenes and all carfentanil seizures in the EU occur within Estonia, Latvia and Lithuania, underlining the need to develop targeted responses in the region.
- **Decline in fentanyl availability:** It appears that law enforcement and regulatory efforts may have significantly reduced the presence of fentanyl across the Baltic region, with only sporadic detections remaining.
- **Market adaptability:** The emergence of new nitazenes such as ethyleneoxynitazene and new synthetic opioids such as orphines highlights the ongoing diversification of the illicit opioid market, as suppliers introduce new compounds to circumvent regulatory controls.
- **Urban concentration of use:** Highly potent synthetic opioids are primarily concentrated in more densely populated regions. However, limited data

collection in rural regions makes it difficult to assess their full geographic distribution.

Between 2009 and 2024, 88 new opioids were identified in the EU and reported to the EU Early Warning System on new psychoactive substances. Fentanyl derivatives first appeared in 2012, including carfentanil, which became one of the most potent synthetic opioids detected in the region. Regulatory measures, such as China's 2019 generic ban on all fentanils, led to a decline in fentanyl availability and related harms. However, this shift was followed by the emergence of nitazenes, first detected in 2019. By 2024, 22 nitazenes had been reported to the EU Early Warning System. Despite regulatory responses at the international, EU and national levels, the market continues to evolve, highlighting the adaptability of illicit suppliers and the challenges of exerting effective control over drug supply.

The opioid and stimulant markets in the Baltic region exhibit distinct but interconnected trends. While highly potent synthetic substances, such as nitazenes and carfentanil, now dominate the opioid market, it is important to recognise that stimulants remain the primary illicit substance used by high-risk drug users. In Tallinn, amphetamine and methamphetamine were the most frequently detected substances in syringe residue analyses, while in Riga, cocaine was the most frequently detected stimulant.

At the same time, major shifts have taken place in the opioid market. Nitazenes have replaced heroin and fentanyl and its derivates in Estonia and Latvia, driven by their high potency and presumed low production costs. By 2023, nitazenes were implicated in half of Estonia's drug-induced deaths, with 30 % of syringe residue samples testing positive for nitazenes. Preliminary 2024 data suggest a slight decrease in nitazenes detected in such deaths and in the percentage of syringes containing nitazenes. The most frequently detected nitazenes in Estonia were protonitazene and metonitazene, although forensic data from 2023-24 indicates that at least five additional nitazenes have been identified. Similarly, Latvia recorded a sharp increase in nitazenes detections, particularly isotonitazene and metonitazene, but seizure data suggests a broader presence, with six different nitazenes reported in 2023-24.

By contrast, carfentanil remains the dominant synthetic opioid in Lithuania, where in Vilnius and Klaipėda it was detected in over 90 % of analysed syringes in 2023 and 70 % in 2024. Nitazenes remain rare in Lithuania, with only four detections in 249 syringes analysed in 2024. While carfentanil was previously present in Estonia and Latvia, its presence has declined as nitazenes have become more established. The availability of fentanyl across the

Baltic region has significantly decreased, with only sporadic detections reported — a trend attributed to law enforcement efforts and regulatory measures. The detection of nitazenes through wastewater analysis has been consistently reported in Tallinn, while the capital cities of Latvia and Lithuania do not conduct municipal wastewater monitoring for synthetic opioids.

The emergence in 2024 of new nitazenes — such as ethyleneoxynitazene and N-desethyl-isotonitazene in Estonia and Latvia — suggests continued market adaptation. Additionally, first reported to the EWS in 2024, syringe residue analysis from Riga detected N-desethyletonitazene and protonitazepyne, alongside orphine opioids, a new group of new synthetic opioids that have started to appear on the market. The detection of these substances highlights the ongoing diversification of the illicit opioid market, as suppliers introduce new compounds to circumvent regulatory controls.

Focus group discussions confirmed the disappearance of heroin from the opioid market in all three countries, with carfentanil and nitazenes filling the void left by the decline of fentanyl and heroin.

In 2023, Member States reported 927 seizures of new opioids to the EU Early Warning System, amounting to 22 kg of material and representing 3 % of all new psychoactive substance seizures. The Baltic region played a central role in these developments.

- **Carfentanil seizures in 2023:** 225 (24 % of all new synthetic opioid seizures), totalling 7.04 kg, all from the Baltic countries — Estonia (0.44 kg), Latvia (0.42 kg) and Lithuania (6.18 kg)**.** Quantified seized samples in Lithuania showed carfentanil content ranging from 0.000003 grams to 0.7962 grams per sample. Preliminary data suggest that the quantity of carfentanil seized in Lithuania in 2024 and reported to the EWS decreased from 6.2 kg (2023) to 2 kg (2024).

- **Nitazenes seizures in 2023:** 497 (54% of all new synthetic opioid seizures), totalling 10 kg**,** with the Baltic region accounting for 86 % of seizures and 96 % of the material seized. Preliminary 2024 data suggests that nitazenes seizures in Estonia decreased by more than half, from 5.415 kg in 2023 to 2.294 kg in 2024.

These data highlight that the Baltic region has been disproportionately affected by the emergence of highly potent synthetic opioids in the EU**.**

Markets assessment: product potency and adulteration

Key messages

- **Extreme potency as a core risk factor:** Highly potent synthetic opioids such as carfentanil and nitazenes pose a serious risk of life-threatening respiratory depression, even in microgram doses. Their high receptor affinity and rapid onset of action mean that even a single exposure can result in severe poisoning or death, particularly among individuals with low opioid tolerance.
- **Supply-level adulteration of synthetic opioids**: Highly potent synthetic opioids might be mixed with other substances at the supply level, increasing the risk of overdose. Mixtures often include benzodiazepines, methadone, diphenhydramine and stimulants such as amphetamine, methamphetamine and cocaine.
- **Complicating overdose management:** Xylazine, an animal sedative, has been detected in nitazenes samples in Estonia and Latvia. While detections remain limited, its presence complicates overdose management and raises concerns about severe poisoning.
- **High variability in drug concentration:** There is a high risk of significant variability in synthetic opioid concentration due to inconsistent adulteration processes. Uneven distribution of active ingredients within the same batch increases the likelihood of unintentional overdose.
- **Unintentional use of potent substances:** Users may unknowingly use adulterated potent synthetic opioids, generally sold in powder form and sometimes misrepresented or mis-sold as heroin or fentanyl. This lack of awareness and the drugs' high potency increase the risks of severe poisoning.
- **Limited access to drug-checking services:** Inadequate availability of drug-checking services in the Baltic region reduces the opportunity to identify adulterants before use, limiting harm reduction interventions. The extreme potency of nitazenes and carfentanil presents a central and standalone health risk, independent of adulteration or mixing. Some of these substances are hundreds to thousands of times more potent than morphine (Ujváry et al., 2021), meaning that even microgram-level exposures can cause life-threatening respiratory depression. This high potency increases the likelihood of fatal

overdoses, especially among opioid-naive individuals or those who are unaware of what substance they have consumed.

Another critical concern in the Baltic drug market is the presence of adulterants in these highly potent synthetic opioids. Syringe residue and seizure data indicate that nitazenes and carfentanil might be mixed with benzodiazepines, methadone, diphenhydramine and/or stimulants, supposedly at the supply level. These mixtures, introduced either during production or distribution, increase overdose risks, particularly when consumed unknowingly.

One particularly concerning adulterant is xylazine, a veterinary sedative detected in nitazenes samples in Estonia and Latvia. Xylazine is not an opioid, meaning that naloxone is ineffective in reversing its effects. While detections of xylazine remain low, its presence in synthetic opioid mixtures adds complexity to overdose management and raises concerns about the unpredictability of street drug compositions. It is also unknown whether laboratories routinely screen for xylazine, meaning its presence may be underreported.

The diversity of synthetic opioid mixtures introduces further health risks due to the variability in potency. Limited knowledge about the cutting agents and dilution processes used in the illicit market means that users are often exposed to unpredictable dosages, increasing the likelihood of severe poisoning. Drug-checking services are not available in the region, making it difficult for consumers or harm reduction services to identify these substances before use. Furthermore, forensic laboratories do not routinely quantify the concentration of these potent synthetic opioids in seized materials, adding another layer of uncertainty regarding the potency of the substances in circulation.

The issue of adulteration in highly potent synthetic opioids involves a range of implications. The unpredictability of the composition of street drug samples increases the health risks for users, who may unintentionally consume highly potent mixtures of substances. Implementing drug-checking services could help detect dangerous adulterants before consumption. In addition, the presence of benzodiazepines, xylazine or other non-opioid sedatives in synthetic opioid mixtures complicates overdose reversal efforts, as benzodiazepine-opioid combinations can increase sedation and respiratory depression, requiring more intense emergency care interventions.

Markets assessment: trafficking routes and distribution networks

Key messages

- **China and Russia as primary sources:** Nitazenes originate mainly from China and carfentanil is sourced from Russia and China. Currently, there is limited evidence for the production of fentanyl in the Baltic region and no evidence for the production of nitazenes.
- **Latvia's role in regional trafficking:** Criminal groups based in Latvia appear to play an important role in the trafficking and distribution of synthetic opioids, with reported links to Russian organised crime groups (OCGs) and evidence of small-scale fentanyl production.
- **Diverse trafficking routes:** Postal and courier services play a major role in the supply of nitazenes, while carfentanil primarily enters the region via land routes. Both substances are also distributed through online platforms and encrypted messaging apps.
- **Growing role of digital platforms:** Encrypted apps like Telegram facilitate covert transactions, with products advertised through QR codes and sales completed via private chats and drop-off points. Encryption and decentralised online markets continue to challenge law enforcement efforts.

The production and trafficking of nitazenes and carfentanil in the Baltic region are linked to international supply chains, with China identified as the primary source of nitazenes and Russia and China as the main origins for carfentanil. While no domestic production has been confirmed, localised activities have been observed. In 2020, for example, a small-scale facility processing and packaging isotonitazene for sale in the domestic market was dismantled in Latvia. Seizures of fentanyl precursors in Latvia in 2023 and the dismantling of one illicit production laboratory in 2024, indicate that low-level fentanyl production takes place within the region. However, there is currently no evidence regarding the availability of nitazenes precursors in the Baltic countries.

Criminal gangs based in Latvia appear to play an important role in synthetic opioid distribution within the region, likely due to the country's geographic proximity to Russia and to

their connections with organised crime groups (OCGs). These OCGs, which often have Russian links, are reported to operate across multiple countries, facilitating the movement of highly potent synthetic opioids into and within the region. The discovery of a fentanyl production site in Latvia in May 2023 further indicates the country's role in trafficking and regional distribution.

Trafficking routes rely on multiple transportation methods, reflecting the diverse supply channels that sustain the market. Nitazenes are primarily imported from China as pure powders and are often transported via courier and postal services. Online marketplaces in the Netherlands, Germany, France, Poland, Finland, Norway and Spain have also been identified as sites for wholesale suppliers. Carfentanil, on the other hand, enters the region primarily via land routes, particularly from Russia and Ukraine, with smaller volumes reported to originate from China. While online platforms do play a role in the carfentanil supply chain, physical distribution networks remain the dominant trafficking mechanism.

The role of digital platforms in synthetic opioid trafficking is growing. While opioids do not dominate online drug markets, nitazenes and carfentanil appear to occupy a niche, low-volume segment of online sales. Encrypted messaging apps, particularly Telegram, facilitate covert transactions, with products advertised via QR codes and sales completed in private chats after background checks. Transactions are then finalised through postal services, physical exchanges or drop-off points, with surface web shops occasionally selling non-controlled nitazenes.

The focus groups provided additional insights into these trafficking dynamics. In Lithuania, law enforcement representatives described how carfentanil enters the country primarily through land routes from Latvia and the eastern EU, with smaller shipments arriving from China. In Latvia, participants reported that nitazenes are typically imported as pure powders from China or India and then diluted domestically for local distribution. The use of digital platforms, parcel lockers and encrypted messaging services was highlighted as a key shift in distribution methods. In Estonia, law enforcement respondents stressed the critical role of cross-border cooperation in tackling synthetic opioid trafficking, noting the challenges of disrupting production hubs outside the EU. They also emphasised the need for more flexible legal frameworks to address new substances as they emerge.

These findings illustrate how illicit supply chains are evolving, capitalising on presumed low production costs, logistical efficiency and digital tools, which leads to law enforcement responses becoming increasingly complex. The demand for any available opioid, regardless of origin or type, continues to sustain supply chains, highlighting the adaptability of illicit markets in response to regulatory measures and enforcement actions. While enforcement efforts remain essential, a comprehensive response to these potent opioids must also prioritise reducing demand through prevention, treatment and harm reduction initiatives to reduce opioid dependence and limit the market for these substances.

Markets assessment: options for response

The drug market response options focus on improving intelligence-sharing, enhancing operational responses and building capacity to detect and disrupt synthetic opioid trafficking. By strengthening collaboration across borders, advancing law enforcement training and leveraging existing EU mechanisms, such as EMPACT, these measures aim to target organised criminal networks and disrupt the flow of highly potent synthetic opioids. The options below reflect a balanced approach to enhancing security responses while fostering cooperation at regional and EU levels.

Countries are invited to explore the following options to improve security preparedness and address the evolving synthetic opioid threat effectively.

Tier 1

1. Enhance regional collaboration in the Baltic countries and across the EU by improving intelligence-sharing, integrating operational information on organised criminal networks and strengthening the exchange of data on seizures, concealment methods and modi operandi. This includes joint investigations at regional and European levels, notably through frameworks such as EMPACT, to prioritise high-value targets and address synthetic opioid trafficking networks.

Supporting evidence: Regional experience of joint collaboration between law enforcement agencies from the Baltic countries has shown success in reducing the availability of fentanyl in the region.

Tier 2

2. Enhance training, the sharing of best practices and the provision of specialist equipment for law enforcement to detect new psychoactive substances.

Supporting evidence: The emergence of NPS poses significant challenges to detection systems, with evidence highlighting the need for enhanced monitoring and surveillance capabilities.

3. Further invest in the research and development of screening tools (screening mail, parcels, etc.) and advanced technologies (e.g., machine learning and data modelling) to improve interdictions and investigations across ports, airports and online platforms.

Supporting evidence: Europol and national law enforcement agencies have demonstrated success in leveraging AI to process and analyse complex datasets, enhancing investigative efficiency. The EncroChat takedown illustrates how large-scale data analysis can uncover criminal networks, leading to arrests and asset seizures. AI-driven tools enable law enforcement to identify patterns and connections within vast datasets, improving interdictions and investigations.

Tier 3

4. Enhance awareness-raising activities and training for law enforcement professionals handling highly potent synthetic opioids to prevent and respond to occupational exposure risks, including in the following areas: risk assessing exposure scenarios, the use of personal protective equipment (PPE), the provision of first aid and naloxone administration.

Supporting evidence: Case investigations have documented health impacts resulting from unintentional occupational exposure among law enforcement officers, emphasising the need for preventive measures and training.

Implementation considerations

In addition to the response options outlined above, the key considerations listed below provide essential guiding principles and strategies to support policy and operational responses. They highlight important aspects for successful implementation, seek to strengthen long-term approaches by addressing structural challenges in law enforcement and security cooperation, and enhance the overall preparedness to mitigate the impact of synthetic opioids. Through fostering intelligence-sharing, improving detection capabilities and strengthening international collaboration, the following proposals aim to enhance coordination and effective responses to synthetic opioid trafficking.

- Expand awareness, training and operational capacity for law enforcement personnel with regard to trafficking indicators, precursor flows and financial networks linked to synthetic opioid markets. This includes strengthening financial investigations into money laundering networks, monitoring cryptocurrency transactions and tracking illicit financial flows associated with synthetic opioid trafficking.

- Strengthen intelligence-sharing and cooperation on precursor supply chains to detect vulnerabilities and disrupt illicit opioid production.

- Enhance partnerships through EMPACT and other European security instruments to support joint investigations, operational task forces and regional cooperation in tackling synthetic opioid trafficking.
- Improve the mapping and profiling of organised crime networks involved in heroin, synthetic opioid and precursor trafficking to prioritise enforcement actions against high-risk criminal groups.
- Expand efforts to systematically track and disrupt online sales of highly potent synthetic opioids across darknet marketplaces, social media platforms and e-commerce sites.

Situation and harms assessment: prevalence and patterns of the use of nitazenes and carfentanil in the Baltic region

Key messages

- Stimulants remain the most commonly used illicit drugs among high-risk drug users (HRDUs) in this region. While synthetic opioids contribute significantly to drug-related harms, their overall prevalence is lower and their use is largely confined to specific subpopulations.
- Synthetic opioid use remains highly concentrated among marginalised populations, particularly middle-aged men with long histories of opioid dependence and incarceration. The ageing PWID population in the Baltic region suggests that the use of these substances has not significantly expanded to younger users, but continues to impact an entrenched high-risk group.
- Polysubstance use is a defining feature of synthetic opioid use in the Baltic region, increasing the risk of overdose. Syringe residue and seizure data show combinations of nitazenes and carfentanil with benzodiazepines, stimulants, alcohol and opioids. While some users mix substances intentionally, others do so unknowingly, increasing the likelihood of severe poisoning.

Available estimates suggest that overall opioid use prevalence in Latvia and Lithuania is higher than the EU average of 3 per 1 000 people aged 15-64. In Latvia, estimates from 2016 and 2017, based on the Treatment Multiplier method, indicate a prevalence ranging between 4.1 and 7.0 per 1 000, with a central estimate of 5.7 per 1 000 in 2017. In Lithuania, estimates from 2016, derived using the Mortality Multiplier and Capture-Recapture methods, suggest a prevalence of between 2.2 and 6.5 per 1 000, depending on the methodology applied. Opioid use prevalence estimates for Estonia are not available. While these figures highlight a relatively high prevalence in the Baltic region, methodological differences and the lack of recent estimates should be taken into account when interpreting the data. Nevertheless, these prevalence rates may contribute to explaining the elevated drug-related death rates observed in the region.

While the overall prevalence of synthetic opioid use in the Baltic region appears low, these substances are associated with a high burden of harm, particularly among people who inject drugs (PWID). Current epidemiological drug use indicators lack sensitivity and timeliness in

detecting nitazenes and carfentanil, while self-reported use of these substances is often unreliable. Users are frequently unaware of the exact substances they are taking, particularly in cases where fentanyl, heroin or methadone are adulterated, misrepresented and mis-sold as other substances. For example, a recent study in Lithuania (Jakubauskiene et al., 2024) found that half of the respondents reported injecting fentanyl, despite fentanyl no longer being available on the market, suggesting that they were using something else, most likely carfentanil.

Synthetic opioid use is largely concentrated among marginalised populations, particularly middle-aged men with long histories of opioid dependence and incarceration. Many of these users belong to Russian-speaking communities in northern and eastern regions, which face substantial barriers to harm reduction and treatment services. The PWID population in the Baltic region is ageing, as reflected in bio-behavioural surveys and drug-related-death data, suggesting that the use of these substances has not significantly expanded to younger populations but rather continues to impact an entrenched cohort of ageing high-risk users.

Polysubstance use is a defining feature of synthetic opioid consumption in the Baltic region. Syringe residue data consistently indicate that nitazenes and carfentanil are rarely used in isolation, with frequent combinations detected featuring benzodiazepines, stimulants (e.g. amphetamine, methamphetamine, mephedrone, cocaine), alcohol or methadone and other opioids. In Latvia, mixtures with benzodiazepines — referred to as ‘benzo-dope’ — have been recorded, particularly with bromazolam, a type of benzodiazepine that is about 10 times more potent than traditional benzodiazepines. In Lithuania, carfentanil is often combined with methadone and/or diphenhydramine, an antihistamine that enhances sedation, while in Estonia and Latvia, syringe residues have revealed cocaine mixed with metonitazene, a finding also supported by seizure data. It should be noted that analyses of reused syringes may also contribute to the detection of multiple substances within the same syringe, potentially overestimating the extent of intentional polysubstance use.

The motivations behind polysubstance use vary. Some users intentionally mix substances, for example combining stimulants with carfentanil to counteract sedation and prolong euphoria. In Lithuania, users report consuming carfentanil every 3-4 hours, including at night, contributing to intense patterns of repeated dosing and rapid dependency. However, other polysubstance use patterns appear unintentional, stemming from limited awareness of substance content, as highly potent synthetic opioids are often adulterated, mis-sold or unknowingly consumed. This increases the risk of severe poisoning and overdose, as users may be unprepared for the potency and effects of the substances they are consuming.

Women remain a minority among synthetic opioid users, but face particular risks, including higher rates of drug poisoning at younger ages and exposure through polysubstance use. Although minors account for a small proportion of opioid users, there are increasing reports of non-fatal poisonings linked to nitazenes, raising concerns about early exposure and future

substance use disorders. Given their potency, even a single exposure to highly potent synthetic opioids can be fatal. This highlights the urgent need to expand prevention strategies to reduce first-time use, particularly among vulnerable groups.

Despite the established presence in the region of highly potent synthetic opioids, significant data gaps remain, particularly regarding non-injecting opioid users and non-fatal overdoses. For example, there is currently no standardised mechanism to record the use of nitazenes or carfentanil among those seeking treatment for opioid dependence, either in the Baltic region or elsewhere in the EU. This lack of data limits the ability of the relevant agencies to assess treatment needs, monitor trends and develop effective harm reduction and treatment strategies.

Situation and harms assessment: highly potent synthetic opioids and drug-related mortality

Key messages

- **Rising drug-induced deaths**: In 2023, Estonia and Latvia recorded a sharp increase in drug-related deaths (DRDs), largely driven by nitazenes. In Lithuania, carfentanil remains a key factor in drug-induced deaths.
- **Acute toxicity and emergency medical service (EMS) response:** Overdose-related ambulance call-outs and hospitalisations have increased significantly, reflecting the high potency of these synthetic opioids and the risks they pose for users.
- **Urban concentration of harms:** Most opioid-related deaths occur in capital regions, with urban areas acting as hotspots for synthetic-opioid-related mortality.
- **Polysubstance use as a common factor:** The majority of deaths involve polysubstance use, with highly potent synthetic opioids frequently combined with stimulants such as amphetamine, methamphetamine and cocaine.

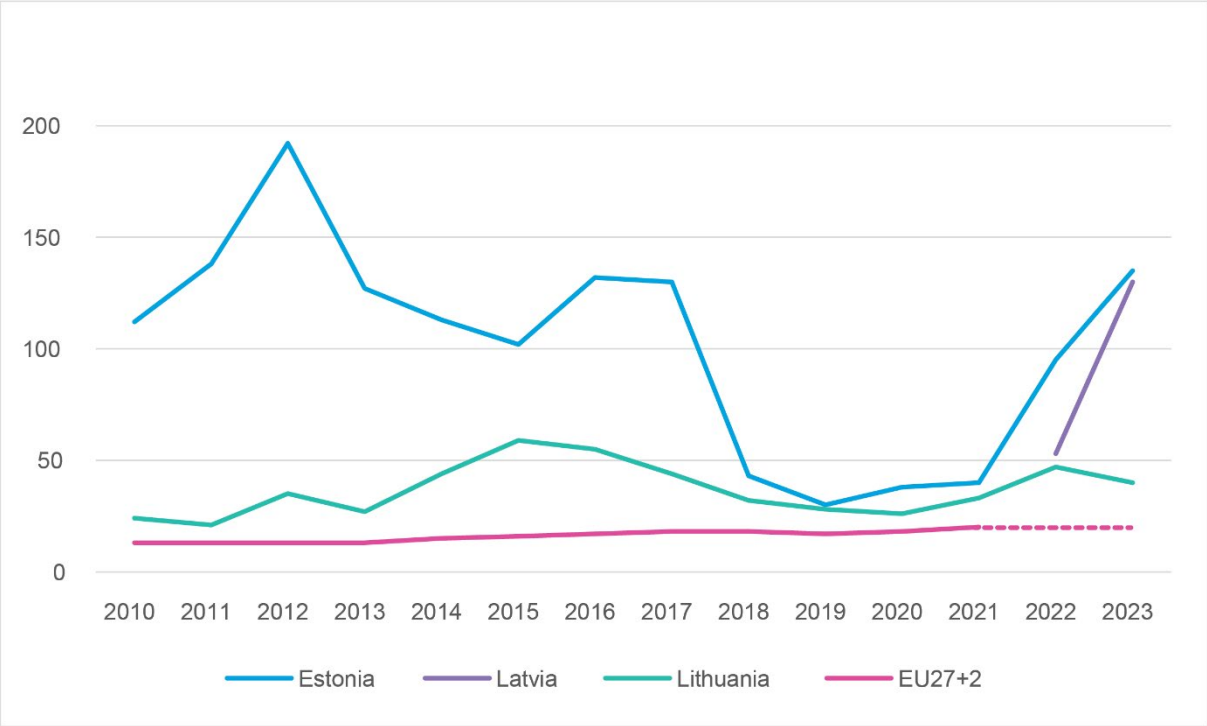
The availability of nitazenes and carfentanil in the Baltic region has led to an overall rise in drug-related deaths (DRDs), acute toxicity cases and associated health risks. Estonia and Latvia have experienced particularly sharp increases in mortality, with drug-related death

rates significantly exceeding the EU average. In 2023, nitazenes were linked to at least 150 deaths across five EU countries, with 132 (88 %) occurring in Estonia and Latvia alone.

Estonia recorded 119 DRDs in 2023, up from 82 in 2022, representing 135 deaths per million people aged 15-64 — six times the estimated EU average (see Figure 2). Nitazenes were implicated in 52 % (62/119) of cases, often in combination with stimulants such as amphetamine or methamphetamine. Preliminary 2024 data indicate a decrease in the overall number of deaths in Estonia (92) as well as in the percentage where nitazenes were detected (44 %). These preliminary data should be interpreted with caution as consolidated data for 2024 will only be available later in 2025. Latvia recorded 154 DRDs in 2023 (130 deaths per million people aged 15-64), with nitazenes — particularly isotonitazene — contributing to 66 % (101/154) of deaths. It should be noted that comparisons with previous years should be made with caution, as forensic detection of nitazenes in Latvia only became possible in December 2022 following the introduction of new toxicology screening methods. Preliminary 2024 data suggest that nitazenes continue to be involved in the majority of opioid-related fatalities.

In contrast, Lithuania reported a slight decline in DRDs, from 87 in 2022 to 74 in 2023 (40 deaths per million people aged 15-64, about twice the estimated EU average). However, carfentanil remained a key driver of opioid-related fatalities, and was detected in nearly half of all cases. Across all three countries, most deaths were linked to polysubstance use, particularly combinations of highly potent synthetic opioids with amphetamine, methamphetamine and cocaine. Mortality rates were highest among males aged 25-44, with urban areas acting as hotspots for opioid-related harms. In 2023, 67 % of Estonia’s DRDs occurred in Tallinn, 74 % in Riga (Latvia) and 57 % in Vilnius (Lithuania).

Figure 2. Trends in drug-induced mortality rates per million among adults (15-64) in Latvia, Lithuania and Estonia



Notes: The trend in the mortality rate for the EU27 plus Türkiye and Norway is computed as the weighted average of the available mortality rates (from 21 countries in 2023), using the population aged 15-64 in the corresponding year as weights. In Latvia, from May to June 2022, better detection of all drugs resulted in some cases who might have been missed before being reported as drug-induced deaths. The detection of nitazenes substances in biological materials from deceased persons in Latvia only began in December 2022, following the introduction of new detection equipment (with two cases identified that month). As a result, numbers in 2022 might be underestimated and comparisons of the overall number of drug-induced deaths and of the number of cases associated with nitazenes between 2022 and 2023 should be interpreted with caution (see Annex 1).

Acute toxicity and emergency medical responses

The potency of nitazenes and carfentanil has possibly led to a surge in emergency medical service (EMS) interventions in Estonia and Latvia. While making precise attributions to specific substances is challenging, trends in overdose incidents and naloxone administration suggest that highly potent synthetic opioids might be responsible for a substantial portion of opioid-related medical emergencies.

In Tallinn (Estonia), ambulance call-outs for overdoses increased by 40 % between 2022 and 2023, rising from 605 to 845 cases, with naloxone administered in 59 % of incidents. In Latvia, the emergency services responded to over 4 000 overdose incidents in 2023, a 9 % increase from the previous year, with naloxone administered in approximately 2 400 cases

(around 60%). Lithuania also recorded a 31 % increase in hospitalisations due to drug poisoning in 2023, although data gaps prevent precise identification of the substances involved.

Despite the high visibility of EMS cases, these figures probably underestimate the true burden of synthetic-opioid-related harm, as many overdoses go unreported or do not result in emergency care-seeking behaviour. The availability and potency of nitazenes and carfentanil continue to present significant challenges for frontline responders.

From January 2023 to November 2024, the Euro-DEN sentinel hospital in Riga (Latvia) reported 100 acute drug toxicity presentations (provisional data). Of these, analytical screening detected 18 cases involving nitazenes and one case where etonitazene was present. Six different nitazenes were detected in these presentations: etodesnitazene, etonitazene, isotonitazene, metodesnitazene, metonitazene and protonitazene. Available data for 2024 showed no nitazenes-related presentations reported by the other sentinel centres in the Baltic region (i.e., Pärnu and Tallinn in Estonia, and Vilnius in Lithuania). However, most presentations with opioids were self-reported and the opioid was recorded as ‘opioid unknown’. No analytical confirmation was available and it is possible that some presentations involving nitazenes may have been missed.

Impact on drug-related infectious diseases

The Baltic region has long reported some of the highest rates of HIV and HCV among PWID in the EU, exacerbated by limited harm reduction access and frequent injection behaviours. In Estonia, the latest seroprevalence studies (RDS), conducted in Tallinn (2022) and Narva (2023), reported HIV prevalence of 50 % among PWID. The prevalence of viraemic HCV infection measured by HCV-RNA tests carried out within the same study in Tallinn showed that 56 % of PWID were infected with HCV. In Latvia, a cohort study in Riga, conducted in 2022, estimated that 29 % of recruited PWID were HIV+, while a national study among PWID in Lithuania (RDS) reported a HIV prevalence of 19 % in 2023.

While the direct impact of highly potent synthetic opioids on HIV and HCV transmission is difficult to quantify, the elevated frequency of injections associated with fentanyl and nitazenes poses additional risks. In Lithuania, a recent study found that half of respondents who reported injecting fentanyl (most likely carfentanil) did so three times a day, often in combination with alcohol. Historical outbreaks, such as the 2016-17 HIV outbreak in Lithuanian prisons, highlight the persistent vulnerability of populations at high risk.

The infectious disease burden in the region is shaped more by long-standing structural barriers than the emergence of nitazenes and carfentanil alone. Despite the availability of

harm reduction programmes, coverage remains insufficient, particularly in non-urban areas. Expanding needle and syringe programmes (NSPs) and opioid agonist treatment (OAT) remains critical to mitigating drug-related health harms.

Public health responses assessment: treatment and harm reduction response

Key messages

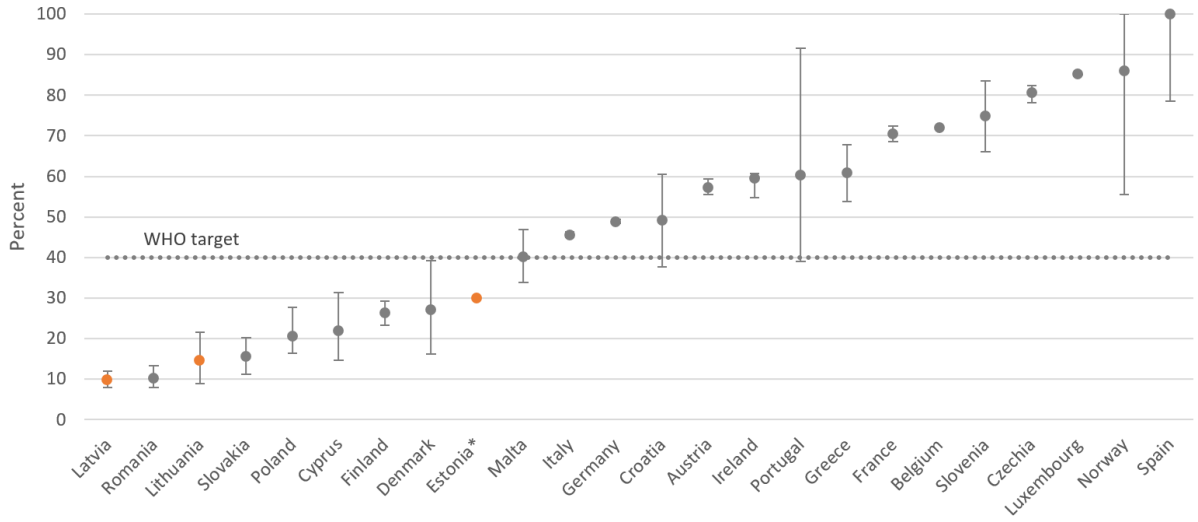
- **Limited access to harm reduction services:** OAT and NSP coverage remains low across the Baltic region, leaving populations at increased risk of harm underserved.
- **Naloxone distribution remains inconsistent**: Only Estonia has a formal take-home naloxone programme, while Latvia and Lithuania rely primarily on EMS interventions.
- **Need for bystander overdose response training:** The response to opioid overdoses by bystanders necessitates first aid training, in line with current emergency medical recommendations — particularly CPR and the titrated administration of naloxone (see Box 2).
- **Structural and legal barriers hinder responses:** Administrative restrictions, stigma and limited adaptation of OAT contribute to poor treatment retention and high overdose risks. In addition, many rural and non-urban areas have limited access to harm reduction services, creating treatment gaps.

Opioid agonist treatment (OAT) is a critical intervention in reducing illicit opioid use, opioid-related overdose mortality and injection-related health risks. However, coverage in the Baltic region remains low, with estimates suggesting that only 10 % of high-risk populations in Latvia, 15 % in Lithuania and around 30 % in Estonia receive OAT (see Figure 3). Access barriers include geographical disparities, stigma, restrictive prescribing regulations and service-entry thresholds. In Estonia, OAT initiation is permitted in custodial settings, while in Latvia, the mobile methadone bus in Riga represents a step towards improving access.

Needle and syringe programmes (NSPs) are also fragmented across the region. Estonia operates the most extensive NSP network, including pharmacy-based distribution, whereas

Latvia relies on a limited number of mobile units. Lithuania operates only nine fixed NSP sites, and has no pharmacy or prison-based initiatives. These gaps in harm reduction services exacerbate health risks for people who inject drugs (PWID) and contribute to the high burden of infectious diseases in the region.

Figure 3. Estimated coverage of opioid agonist treatment in 2023 or the most recent year in the EU and Norway



Note: * Estonia does not currently provide an updated national estimate of the high-risk opioid-using population. However, a 2019 study estimated 8 600 PWID in 2015 (Raag et al., 2019), with little evidence of major change since then. Applying available data on opioid injection patterns (Des Jarlais et al., 2023; Uusküla et al., 2018) suggests a crude estimate of around 3 400 opioid users, of whom approximately 30 % are in opioid agonist treatment. This estimate aligns with earlier findings and should be interpreted with caution due to methodological limitations.

The uneven distribution of naloxone remains a major challenge in preventing opioid-related fatalities. Estonia's take-home naloxone programme, launched in 2013, has demonstrated promising results, distributing 8 452 kits and training 7 040 individuals by 2023. However, the potency of nitazenes has led to a near tripling of drug-induced deaths since 2021, highlighting the urgent need to reinforce and expand naloxone programmes. Estonian police now carry a kit of two doses of inter-nasal naloxone as part of their overdose response efforts, further expanding naloxone availability among first responders.

In contrast, Latvia does not have a take-home naloxone programme, meaning that emergency medical services remain the primary overdose responders. This reliance on pre-hospital care places a significant burden on such services, particularly as nitazenes were implicated in most drug-induced deaths in 2023. Lithuania has made limited progress, issuing 1 700 naloxone kits in 2023, but coverage remains insufficient given the risks posed by highly potent synthetic opioids like carfentanil.

Focus groups conducted in Estonia, Latvia and Lithuania identified several systemic challenges to responding to the harms associated with these substances. They raised the fact that the accessibility of treatment remains a key challenge. In Lithuania, OAT is available in only five treatment centres, leaving many outside the capital region without access. Estonia has gaps in mental health services, particularly for dual-diagnosis patients with substance use and psychiatric disorders. Many high-risk drug users who take nitazenes lack health insurance, preventing them from accessing public healthcare services.

It was further highlighted that adapting OAT to nitazenes and carfentanil use remains complex. Health professionals in Latvia and Lithuania reported difficulties in treating users of nitazenes, who often require higher methadone doses or alternative formulations such as injectable prolonged-release buprenorphine to improve treatment attractiveness, acceptability and retention. Social and legal barriers continue to limit naloxone access. In Lithuania, administrative restrictions prevent distribution through low-threshold services, while in Estonia, stigma remains a major obstacle, discouraging many users from seeking help.

In addition, the rise of highly potent synthetic opioids has increased interest in drug-checking services. Participants from low-threshold services in the focus groups called for rapid detection capabilities to inform users and health professionals about the presence of highly potent synthetic opioids in users' drug samples. However, discussions highlighted the issues of costs, political acceptance and legal challenges as barriers to implementing such measures.

Anecdotal evidence indicates that overdose responses increasingly require larger doses of naloxone. Health professionals across all three countries reported cases where multiple doses were necessary to reverse nitazenes overdoses, highlighting the importance of providing evidence-based training in first aid and naloxone administration with regard to these substances (see Box 2 and Annex 3). Police and emergency responders were frequently identified as key naloxone carriers, underscoring their frontline role in overdose prevention.

Finally, overdose prevention has been a central component of previous responses in the region and must remain a priority. However, the core challenge extends beyond the presence of specific substances like nitazenes or fentanyl analogues. Insufficient coverage of comprehensive public health services leaves people who use drugs vulnerable to a range of harms, regardless of which substances are in circulation. To address current and future threats, countries will need to adopt forward-looking strategies that build long-term resilience to synthetic opioid surges. This requires a holistic public health approach that integrates efforts to raise awareness, improve OAT uptake and accessibility, enhance overdose prevention, strengthen infectious disease control, and expand broader health and social responses.

Box 2. Managing acute opioid toxicity — key considerations for emergency response

Acute opioid toxicity is a leading cause of emergency medical presentations, with respiratory depression being the primary life-threatening complication. The increasing presence of high-potency synthetic opioids, such as nitazenes and fentanils described in this assessment, poses significant challenges for emergency responders, requiring enhanced clinical awareness and close patient monitoring (Blundell et al., 2024; Lavonas et al., 2023). Many of these opioids are more potent and/or have a longer half-life than heroin, and so patients may potentially require a higher overall dose of naloxone and/or more prolonged treatment. However, it is important, even in the era of potent new synthetic opioids, to maintain the approach of giving titrated doses of naloxone to patients with acute opioid toxicity (UK Government, 2017; CDC, n.d.).

Recognition and initial management

Acute opioid toxicity typically presents with drowsiness, respiratory depression and pin-point pupils. However, polysubstance use — particularly with benzodiazepines, alcohol or stimulants — can obscure or complicate diagnosis (Heier et al., 2022). Given the potency of new synthetic opioids, prompt intervention is critical. Basic and advanced life support (BLS/ALS) principles remain central, with delivering airway and breathing support (including rescue breaths) as the first priority for those with respiratory arrest or severe respiratory depression (Hewett Brumberg et al., 2024).

Naloxone administration

Naloxone is the primary treatment for acute opioid toxicity. The titration of naloxone, meaning the stepwise administration of doses based on the patient's respiratory status, is recommended to reverse respiratory depression while minimising the risk of precipitated withdrawal, particularly in opioid-dependent individuals (Blundell et al., 2024; Lavonas et al., 2023). In the pre-hospital environment, this involves giving an initial intramuscular dose (e.g., 400 micrograms), waiting 2-3 minutes, and administering additional doses as needed, up to a recommended maximum of 2 mg in the case of bystander use (UK Government, 2017; CDC, n.d.). For intranasal naloxone, the same stepwise approach should be followed, with repeat doses administered if respiratory depression persists. Professional emergency responders and clinicians in a hospital environment may use titrated intravenous naloxone and for those requiring

repeated doses of naloxone a continuous naloxone infusion may be required, depending on the circumstances.

Post-naloxone monitoring and observation

Because naloxone has a shorter half-life than many opioids, individuals require prolonged monitoring (at least 4-6 hours, or up to 12 hours for long-acting opioids) (CDC, n.d.). Patients managed with naloxone should be assessed for ongoing respiratory depression and provided with harm reduction support, including take-home naloxone and a referral to drug treatment services.

Emergency response systems must adapt to the increasing risks posed by highly potent synthetic opioids, ensuring that first responders, healthcare providers and affected communities are equipped with the knowledge, tools and protocols necessary to reduce fatalities and improve patient outcomes (EUDA, n.d.).

See Annex 3 for a detailed clinical discussion on acute opioid toxicity management.

Public health responses assessment: options for response

The public health response options and key considerations recommended by the EUDA aim to improve access to life-saving harm reduction measures, enhance OAT coverage and ensure continuity of care for people with opioid use disorders. By addressing systemic barriers, promoting health services in diverse settings and empowering civil society, the suggested options support equitable healthcare access and can reduce opioid-related harms. The suggested intervention options are designed to prioritise underserved populations while reinforcing sustainable and evidence-based interventions.

Countries are encouraged to consider the following options to enhance their public health systems and improve preparedness for emerging synthetic opioid threats.

Tier 1

1. Develop and commit to national tangible drug treatment and harm reduction targets by 2030, as part of comprehensive national preparedness plans, to drive measurable progress, including opioid agonist treatment, naloxone distribution, and needle and syringe exchange coverage targets.

Supporting evidence: Recent research emphasises the importance of resilience-based public health approaches and comprehensive response strategies. However, specific evidence for the effectiveness of target-setting remains limited and requires further research.

2. Improve naloxone provision, expanding training opportunities and geographical coverage and targeting a broader range of non-professional first responders (e.g., users, family members, law enforcement officers, peers and prison staff).

Supporting evidence: Multiple studies demonstrate the effectiveness of naloxone training programmes and distribution. A 2016 study (McDonald and Strang, 2016) showed significant improvements in knowledge and attitudes following naloxone training interventions. Research indicates high acceptability among service users and effectiveness in emergency response scenarios.

Tier 2

3. Improve the availability and accessibility of OAT by addressing legal and systemic barriers and enlisting the support of medical professionals and public health centres.

This includes ensuring the availability of methadone and buprenorphine — listed on the WHO Model List of Essential Medicines — as critical components of equitable healthcare access. Any actions pursued should draw on lessons learnt from other EU countries, mitigate the risk of diversion and prioritise under-served regions to reduce opioid-related harms. Regular quality and satisfaction evaluations should be used to monitor effectiveness and improve service delivery.

Supporting evidence: Multiple high-quality population-based studies, systematic reviews and real-world implementation studies provide strong evidence for the effectiveness of OAT interventions. The evidence supports the use of flexible take-home dosing strategies, which show consistently improved patient outcomes' patient outcomes. Moreover, person-centred approaches, which focus on patient autonomy, individualised care and flexible treatment options, have been shown to yield positive outcomes in terms of treatment retention and satisfaction. In addition, significant cost implications are associated with different dispensing models, and the potential exists for more efficient resource allocation. For example, weekly or biweekly dispensing could lead to cost savings while maintaining treatment effectiveness.

Implementation considerations

In addition to the options grounded in science, the key considerations listed below provide essential guiding principles and strategies to inform policy and programme design by highlighting critical aspects for successful implementation. They support long-term strategies by framing the broader public health environment needed to maximise the impact of suggested interventions and enhance the overall preparedness to mitigate the threat posed by highly potent synthetic opioids.

- Ensure gender-sensitive and inclusive harm reduction programmes that address the specific needs of women, young people, incarcerated individuals and marginalised communities, including Russian-speaking populations.
- Guarantee continuity of care between community and custodial settings by expanding OAT in prisons, aligning prison health services with community standards and introducing naloxone distribution in correctional facilities.
- Strengthen integrated care models based on WHO best practices, ensuring comprehensive service provision in the areas of substance use, mental health, infectious diseases and social care.
- Support the role of civil society organisations in delivering harm reduction services and strengthening community engagement, with a focus on capacity-building.

- Leverage European funding mechanisms to scale up naloxone provision and improve OAT accessibility, particularly in underserved areas and for those at higher risk of harm.
- Facilitate rapid access to emerging clinical research and best practices for frontline professionals — including alternatives to methadone treatment and overdose reversal strategies — by fast-tracking updates to prescribing guidelines and OAT protocols.
- Support the implementation of additional overdose prevention and harm reduction measures, including drug checking, overdose warning networks and drug consumption rooms, to reduce the health risks associated with highly potent synthetic opioids.

Box 3: Responding to the emergence of nitazenes — prioritising life-saving interventions

Given the high potency and rapid onset of nitazenes, immediate life-saving measures must be prioritised as the first line of response. While long-term strategies remain essential, countries facing the emergence of these substances need to ensure that first responders, including emergency medical personnel, law enforcement officers, harm reduction workers, people who use drugs and their contacts/families, are trained to recognise and respond effectively to nitazenes overdoses.

Naloxone distribution should be quickly scaled up, ensuring broad availability across key populations and strategic locations, such as harm reduction services, shelters, police units and outreach programmes. Given the higher doses of naloxone that may be required to reverse nitazenes overdoses in pre-hospital and emergency settings, national frameworks should anticipate and address any potential barriers to increasing overall dosage recommendations.

At the same time, national authorities should conduct rapid assessments to identify gaps in overdose response capacity and develop immediate contingency plans. This includes ensuring that there are adequate stockpiles of naloxone and that clinical protocols for opioid toxicity management are evidence-based (see Annex 3), as well as streamlining any legal and regulatory frameworks that could delay emergency interventions.

Although systemic and long-term strategies are necessary, an immediate and coordinated response is critical to prevent loss of life. A balanced approach — one that combines urgent action with sustained investment in harm reduction, treatment and

structural interventions — will be essential in effectively mitigating the impact of nitazenes.

Monitoring assessment: robustness of national early warning systems and monitoring capacities for responding to the threat of synthetic opioids

Key messages

- **Progress in detection and identification:** Latvia and Estonia have strengthened their forensic capabilities, improving early identification of highly potent synthetic opioids.
- **Urban bias in monitoring systems:** Current national frameworks focus primarily on high-risk urban populations, leaving gaps in the data concerning drug use in rural areas and among people who use but do not inject drugs.
- **Challenges in translating data into action:** While national focal points in the Baltic countries generate detailed intelligence, resource constraints can limit their ability to implement fully coordinated policy or operational responses.
- **Enhanced inter-agency coordination:** Ongoing efforts are needed to strengthen inter-agency coordination, ensuring that data-sharing and cooperation between ministries effectively support early warning responses.
- **Need for sustainable funding and improved infrastructure:** Sustainable funding and infrastructure improvements are needed to advance real-time detection and response systems, ensuring rapid identification of emerging synthetic opioids.

The monitoring capacities in the Baltic region have made progress in detecting highly potent synthetic opioids, allowing for earlier identification of emerging threats. Latvia has enhanced its forensic capabilities, introducing more sensitive analytical equipment to perform toxicology analysis in mid-2022, which enabled the detection of nitazenes in 110 post-mortem cases by 2023. Estonia has been quick to notify the EU Early Warning System (EWS) of new compounds, such as ethyleneoxynitazene and N-desethyl-isotonitazene, in accordance with the mandatory reporting requirements for Member States. These detections contribute to regional preparedness by improving the early identification of emerging new synthetic opioids. Systematic drug-induced-death reporting has also advanced, with Latvia's State Centre for Forensic Medical Examination expanding its analytical scope, while Lithuania has

begun integrating toxicological findings into its General Mortality Register, thus strengthening national data collection on opioid-related fatalities. Moreover, syringe residue analysis has emerged as a valuable tool in the region for identifying the presence of highly potent synthetic opioids in circulation, complementing forensic toxicology and seizure data in monitoring emerging drug trends.

Despite these developments, several challenges remain in strengthening early warning and monitoring capacities. Existing frameworks are often concentrated in urban areas, with more limited coverage extending to rural regions, creating potential gaps in the detection of emerging drug-related threats such as potent synthetic opioids. Beyond high-risk injecting drug users, monitoring frameworks in the Baltic region are also limited in their ability to capture other populations, such as recreational or non-injecting opioid users. This results in gaps in understanding the full extent of synthetic opioid use, meaning that the broader impact of these substances could be underestimated.

Regional collaboration efforts continue to evolve but remain constrained by data-sharing limitations, inconsistencies in timely alert integration, and the availability of resources. While investments in forensic capacity and monitoring technologies are increasing, variations in funding and infrastructure present challenges to achieving a fully harmonised and effective EWS at both national and regional levels. It is important to note that these challenges are not unique to the Baltic region but are also experienced to different degrees by other EU Member States, where disparities in forensic capacity, timely data-sharing and cross-sector collaboration continue to affect national and regional preparedness efforts.

Although national systems collect a wide range of data, the capacity to translate this information into operational and policy measures remains limited. National focal points in the region reported often being overburdened during crises, juggling local, national and EU-level responsibilities without additional resources. Enhancing mechanisms for coordination, information exchange and sustained funding will be essential to strengthening early detection, monitoring and response capabilities in the region.

Monitoring assessment: options for response

The monitoring and early warning response options aim to strengthen national and regional capacities to detect, assess and respond to the emergence of highly potent synthetic opioids. Enhancing national early warning systems and forensic and toxicology capabilities is essential to improving situational awareness and ensuring timely intervention. These measures include expanding laboratory detection capabilities and improving data-sharing mechanisms. By integrating multi-source data, including forensic analysis, wastewater epidemiology and hospital emergency surveillance, the proposed options seek to enhance

preparedness and mitigate the health and security risks associated with highly potent synthetic opioids.

Countries are encouraged to consider the following options to improve their monitoring and early warning systems, ensuring a proactive and coordinated response to emerging drug threats.

Tier 1

1. Support and strengthen national and sub-national early warning systems to improve preparedness and ensure clear procedures for reporting, assessing and responding to the identification of emerging highly potent synthetic opioids. Improving collaboration and information exchange between national stakeholders is key to achieving this goal.

Supporting evidence: EWS systems have demonstrated value in tracking NPS-related overdoses including deaths, although with noted limitations in terms of comprehensive reporting.

Tier 2

2. Increase the ability of forensic, toxicology and other testing laboratories to rapidly detect new opioids, their precursors and metabolites through training, data-sharing and improved analytical tools.

Supporting evidence: Recent advances in analytical techniques demonstrate improved detection capabilities for broad-spectrum drug screening, particularly in the case of emerging substances. Studies also show the successful identification of highly potent synthetic opioids including nitazenes in post-mortem samples. Research indicates the importance of sensitive analytical instrumentation for detecting low concentrations of potent substances.

3. Increase the availability of reference standards and analytical data libraries to improve the detection of emerging new psychoactive substances, ensuring also that this information is shared effectively among relevant stakeholders at both national and regional levels.

Supporting evidence: Research indicates the importance of maintaining up-to-date libraries for new psychoactive substances.

Implementation considerations

In addition to the response options outlined above, the key considerations listed below provide guiding principles and strategies to strengthen national and regional monitoring capacities. These considerations support long-term approaches by improving data collection and analysis, and enhance overall preparedness. By expanding forensic and toxicological capabilities, integrating multi-source data and improving early warning mechanisms, these measures aim to ensure a timely and coordinated response to emerging synthetic opioid threats.

- Enhance forensic and toxicology laboratory capacity to detect highly potent synthetic opioids, adulterants and precursor chemicals by improving training, resources and data-sharing mechanisms.
- Expand wastewater epidemiology, syringe residue analysis and forensic drug analysis to improve the timely detection of emerging synthetic opioid use trends and support early warning systems.
- Strengthen the monitoring of seized materials' price, purity and composition to track market trends and detect sudden shifts in synthetic opioid availability.
- Improve naloxone surveillance by gathering data on barriers, user knowledge and administration patterns through targeted field surveys and first responder interviews.
- Increase sustainable and long-term funding for surveillance indicators and data collection tools, ensuring continuity beyond temporary research initiatives.
- Expand pre-hospital and hospital emergency surveillance, including with data collected from ambulance services, to improve the detection of acute drug toxicity trends and strengthen preparedness.

Conclusions: strengthening preparedness at the national and EU level

The findings of this threat assessment highlight the growing availability and harms of highly potent synthetic opioids, specifically nitazenes and carfentanil, in Estonia, Latvia and Lithuania. The emergence of these substances signals a worrying shift in regional drug markets, with serious implications for public health and security. While currently concentrated in the Baltic countries, increasing reports of overdose outbreaks and fatalities in other EU countries indicate a need for vigilance and proactive responses to prevent the further spread of this threat.

This analysis highlights the interplay between supply-side adaptability and demand-side vulnerabilities as key drivers of the current synthetic opioid threat. The important role played by law enforcement agencies as well as the unintended consequences of actions are raised here. On the security front, the trafficking of nitazenes and carfentanil involves both physical and digital supply chains, with illicit markets leveraging online platforms, encrypted communications and postal networks to facilitate distribution. Organised crime networks have exploited market conditions to introduce highly potent synthetic opioids, adapting swiftly to regulatory controls and law enforcement efforts. At the same time, disruptions in the availability of traditional opioids, such as heroin and fentanyl, have left opioid-dependent populations with limited alternatives, increasing their exposure to often more potent and unpredictable substances.

The public health consequences are evident, with Estonia and Latvia in particular experiencing a significant burden of drug-induced deaths. The crisis is exacerbated by polysubstance use patterns, unpredictable adulteration of substances and systemic gaps in the availability of harm reduction and treatment programmes.

There is a particular need for coordinated policy responses that strengthen national preparedness, improve early warning systems and enhance cross-sector collaboration in the Baltic region. While technical and operational measures are essential, policy frameworks play a crucial role in shaping long-term resilience against synthetic opioid threats. To address the challenges identified in this assessment, the following policy response options should be considered at the national level:

- **Develop, implement, and maintain comprehensive national preparedness and response plans:** Establish national preparedness and response plans backed by political commitment and sustainable funding. These should include both immediate response measures for outbreak management and longer-term strategies to prevent and mitigate synthetic opioid threats. Plans should cover harm reduction scale-up, naloxone access, strengthening monitoring, including early warning and alerting, and inter-agency coordination. Across Europe, several countries are already developing national overdose prevention networks, user-focussed alert/warning systems and digital tools to support rapid response. The EUDA is actively supporting national focal points in strengthening national drug early warning and alert systems, including targeted risk communication.

- **Establish multi-stakeholder coordination mechanisms:** Formalise national and regional coordination mechanisms involving policymakers, health professionals, law enforcement bodies, civil society and people who use drugs. These platforms should facilitate early warning, information-sharing and evidence-based responses, and be closely linked to national preparedness efforts. Ensure robust and sustainable funding — sustainable funding mechanisms are essential to maintain effective opioid-related public health and security responses. Moving beyond short-term project-based funding towards the establishment of stable financing structures will help ensure the continuity of critical interventions such as forensic testing, harm reduction and law enforcement efforts.

- **Enhance rapid response to market shifts:** Given the volatility of opioid markets, national and regional authorities should formulate contingency planning to anticipate and respond to disruptions in heroin or fentanyl availability. This includes ensuring stable access to OAT and harm reduction services to prevent increased reliance on more potent synthetic opioids.

- **Strengthen national and regional policy frameworks:** Integrate foresight studies and scenario planning into national drug policy strategies to better anticipate and mitigate emerging synthetic opioid threats. This approach will improve long-term resilience and assist Member States' readiness to respond proactively to evolving drug market trends.

EU-level policy considerations

The lessons learned from the Baltic experience provide a roadmap for EU Member States seeking to enhance preparedness against the threat of highly potent synthetic opioids. A proactive, data-driven and collaborative approach — integrating health, security and policy responses — is essential to mitigating future harms and ensuring that the EU is equipped to

respond effectively to the threat of potent synthetic opioids. At the EU level, strategic gaps in intelligence, monitoring and law enforcement coordination can be addressed through collective action. The following measures should be considered:

- **Supporting the evaluation of Member States' preparedness:** Assess national capacities to respond to synthetic opioid threats, identifying gaps in harm reduction, treatment, forensic and toxicology capabilities, monitoring systems and cross-sector coordination. This should be accompanied by EU-level support for the development of national preparedness plans to strengthen readiness and response capacity.
- **Strengthening monitoring systems:** Support Member States in improving their capacity to collect and integrate key data sources for early warning and situational awareness. This includes expanding the use of syringe residue analysis, hospital emergency data, ambulance service records, naloxone use tracking, drug consumption room data, and information from drug-checking services. Strengthening these systems will help identify emerging threats, guide interventions and inform broader EU-level support.
- **Research into the pharmacology and toxicology of highly potent synthetic opioids:** Expand EU-supported research efforts to improve the understanding of these substances' potency and metabolism and their associated health risks for users. It is important to adopt an 'all hazards and risks approach', recognising that drug-related threats stem from multiple sources and require a multisectoral response.
- **Investment in innovative detection tools:** Support research into more effective rapid testing methods, including synthetic opioid test strips, while addressing current limitations in accuracy and reliability.
- **Monitoring online and darknet marketplaces:** Strengthen partnerships with industry to restrict illicit opioid sales via encrypted messaging platforms and surface web e-commerce channels.
- **Strengthened mapping of criminal networks and precursor monitoring:** Intensify efforts to track precursor flows and profile organised criminal groups involved in synthetic opioid trafficking, particularly as networks adapt to regulatory changes. EU-level mechanisms such as EMPACT should support these efforts through joint operations and intelligence-sharing.
- **Test purchase programmes:** Develop and expand test purchase initiatives to gather intelligence on emerging substances and strengthen early warning systems.
- **International cooperation with Member States and third countries:** Further enhancing cross-border collaboration in intelligence-sharing, forensic research and

joint law enforcement actions, particularly with key source and transit countries, is essential. As part of these efforts, the EU has established a dialogue on drug policy with China, exemplified by the third dialogue held in April 2024. Similar cooperation mechanisms with Russia are not in place.

Glossary

Carfentanil: A highly potent synthetic opioid derived from fentanyl, approximately 10 000 times more potent than morphine, primarily used as a tranquilizer for large animals and not approved for human use. It is associated with a high risk of fatal overdose in humans.

Darknet market: Online forum where goods and services, including the sale of drugs, are exchanged between parties who use digital encryption to conceal their identities.

Drug adulteration: The practice of adding active or inactive substances to a drug to increase its volume or alter its effects, often without the user being aware, potentially leading to unexpected and harmful consequences.

Drug-induced deaths: Death occurring shortly after consumption of one or more psychoactive drugs and directly related to, or associated with, this consumption. This does not include deaths indirectly linked to drugs (e.g., those caused by an accident while under the effect of the drug or by an infection acquired by drug injection), which are not covered in this report.

Early warning system on new psychoactive substances (EWS): The EU Early Warning System, operated by the EUDA in close cooperation with Europol, is the first step in a three-step legal framework designed to allow the European Union (EU) to rapidly detect, assess and respond to health and social threats caused by new psychoactive substances.

EMPACT (European Multidisciplinary Platform Against Criminal Threats): A permanent EU security initiative under the EU Policy Cycle for serious and organized crime, designed to promote intelligence-led, multidisciplinary, and multiagency cooperation among EU Member States, EU institutions, and third countries to combat key criminal threats through joint operational actions and strategic coordination.

Forensic laboratory: A facility equipped to perform scientific analyses on evidence collected during criminal investigations, including the examination of drugs, toxic substances and other physical evidence.

Forensic toxicology: The application of toxicology to legal investigations, focusing on the detection and interpretation of drugs and poisons in biological samples to establish their role in causing harm or death.

Highly potent synthetic opioids: In this report, the term highly potent synthetic opioids is used to reflect the key concern: the high potency of these substances (compared to heroin) and their associated health risks. This terminology includes both newly emerging opioids and those already established in illicit markets but with exceptionally high potency.

Naloxone: Semi-synthetic competitive opioid antagonist medication used to rapidly reverse opioid overdose.

Needle and syringe programmes (NSPs): The provision of sterile syringes, hypodermic needles and other injecting paraphernalia to people who inject drugs.

New synthetic opioids: A diverse group of new psychoactive substances, of synthetic origin, that act as agonists at opioid receptors. These have emerged as replacements for controlled opioids on the drug market. Many are characterised by high potency and associated with significant health risks, including fatal overdoses.

Nitazenes: Synthetic opioids with a 2-benzylbenzimidazole structure, known for their high potency dependence potential (e.g. isonitazene, metonitazene) and not approved as medicines. They emerged on the market following the imposition of control measures on fentanyl derivatives

Opioid agonist treatment (OAT): A medical treatment for opioid dependence that involves the use of opioid agonists, such as methadone or buprenorphine, to reduce withdrawal symptoms and cravings, thereby facilitating recovery and reducing the risk of overdose.

Organised crime groups (OCGs): Group of three or more persons acting together over a period of time with the aim of undertaking criminal activities for financial or material gain.

People who inject drugs (PWID): Those who use a drug (e.g. heroin, cocaine) that is administered with a needle and syringe.

Polysubstance use: The concurrent or sequential use of multiple psychoactive substances, including illicit drugs, new psychoactive substances, alcohol and prescription drugs, which can lead to increased health risks due to potential drug interactions and compounded effects.

Reitox national focal points (NFPs): Designated national institutions or agencies responsible for collecting and reporting data on the current drugs situation to the EUDA. These focal points are integral to the Reitox network, linking national drug information systems and facilitating the exchange of data and methodologies with the EUDA to ensure consistent and harmonised monitoring of the drug market across Europe.

Toxicological laboratory: A laboratory specialising in the analysis of biological samples to identify the presence and concentration of toxins, drugs or other hazardous chemicals, aiding in clinical diagnosis and forensic investigations.

Xylazine: A veterinary sedative not approved for human use that emerged as an adulterant in the illicit opioid supply, posing additional health risks to users, including severe skin ulcers and increased risk of overdose.

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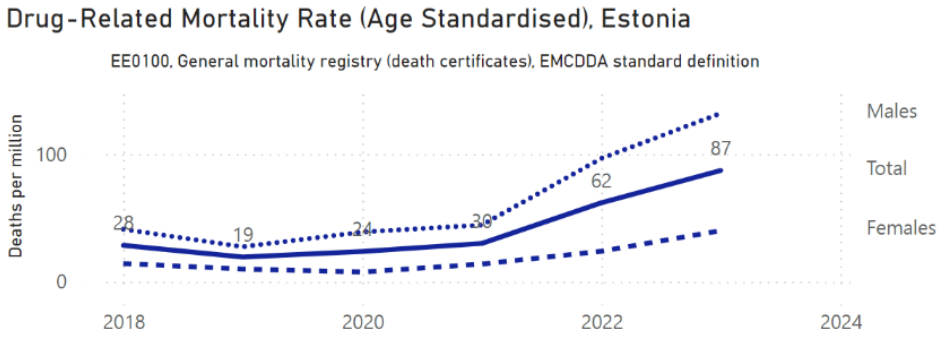
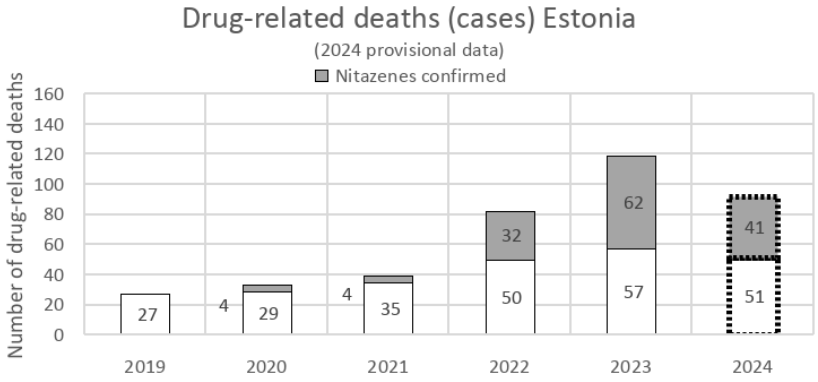
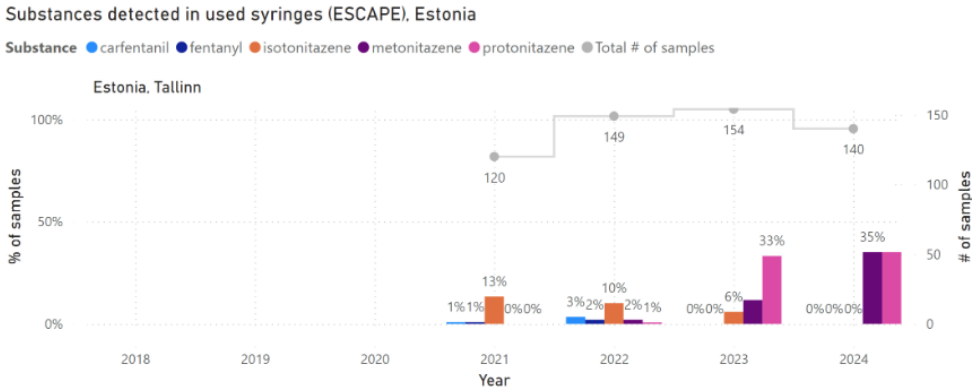
Annexes

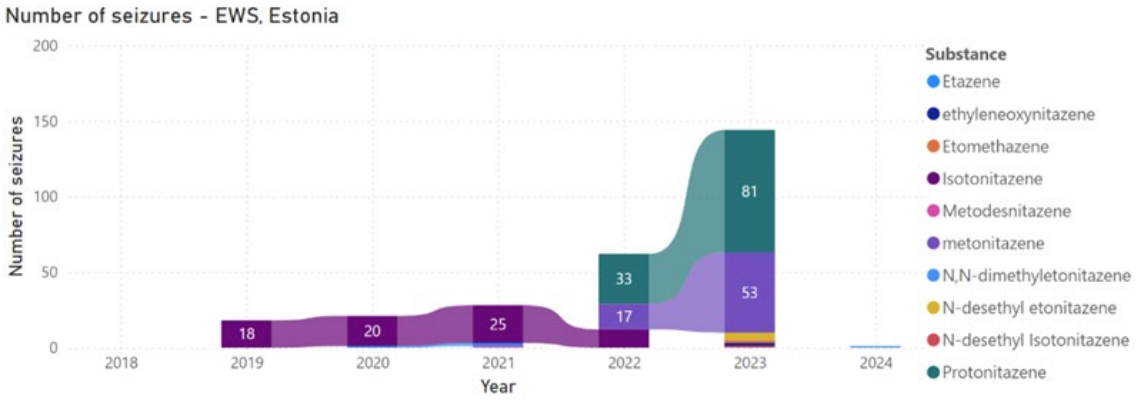
Annex 1 National key data on nitazenes and carfentanil in the Baltic region

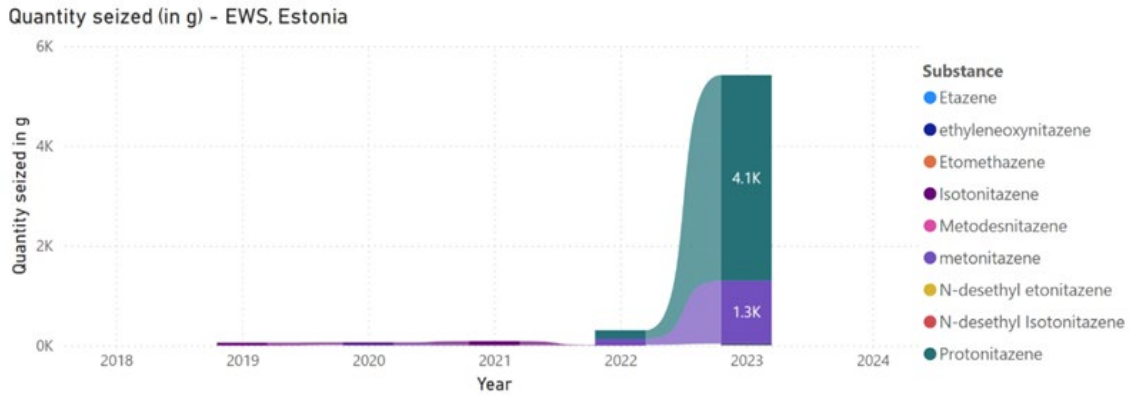
Key data — Estonia:

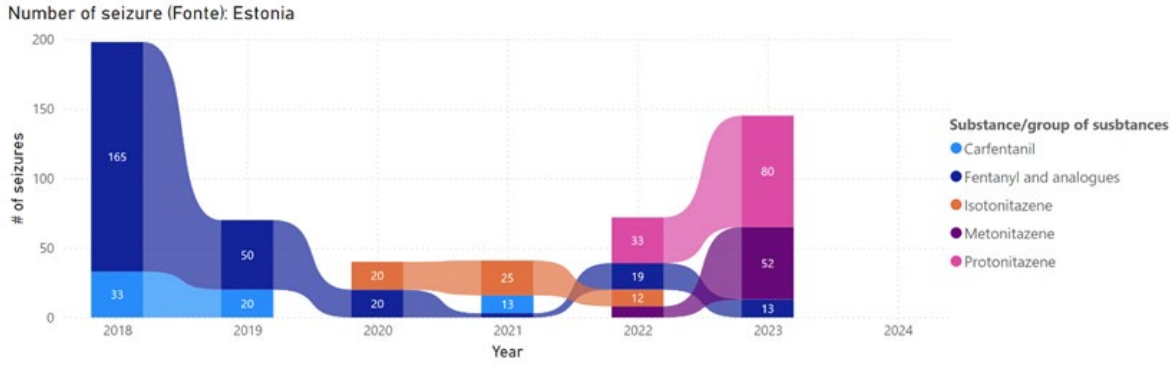


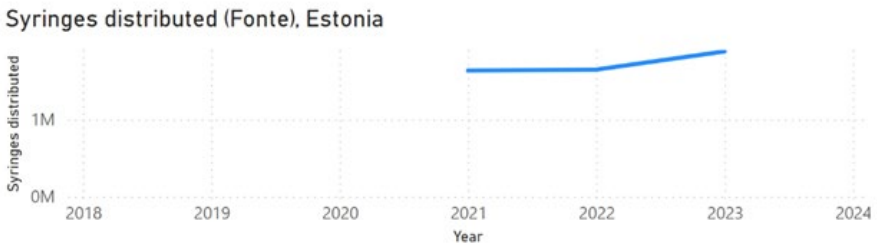




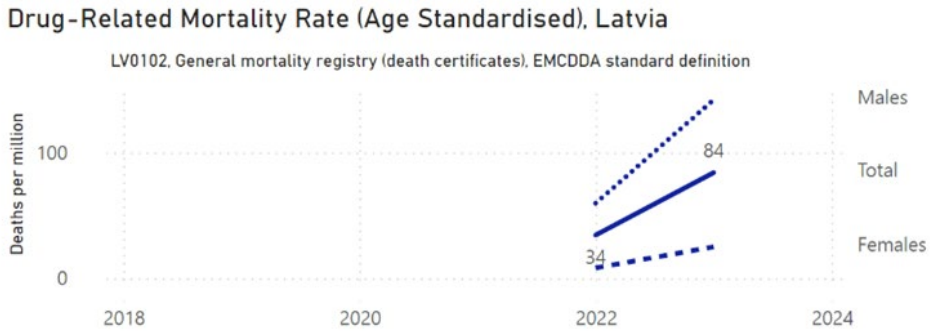

Number of seizures - EWS, Estonia
Number of seizures
200
150
100
50
0
2018
2019
2020
2021
2022
2023
2024
Year
18
20
25
33
17
81
53
Substance
Etazene
ethyleneoxynitazene
Etomethazene
Isotonitazene
Metodesnitazene
metonitazene
N,N-dimethyletonitazene
N-desethyl etonitazene
N-desethyl Isotonitazene
Protonitazene

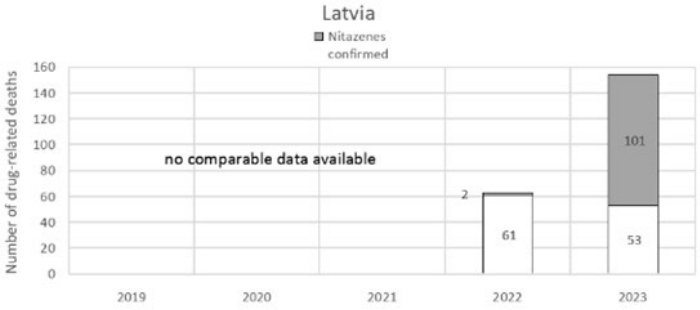

Quantity seized (in g) - EWS, Estonia
Quantity seized in g
6K
4K
2K
0K
2018
2019
2020
2021
2022
2023
2024
Year
4.1K
1.3K
Substance
Etazene
ethyleneoxynitazene
Etomethazene
Isotonitazene
Metodesnitazene
metonitazene
N-desethyl etonitazene
N-desethyl Isotonitazene
Protonitazene

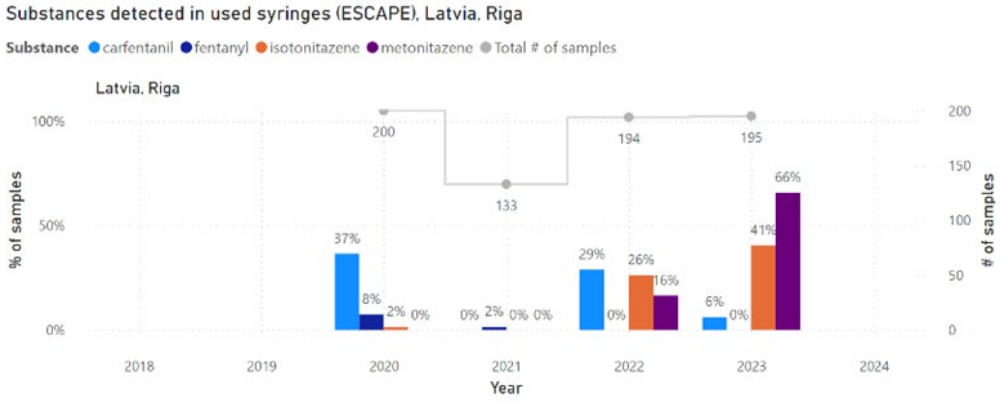

Number of seizure (Fonte): Estonia
# of seizures
200
150
100
50
0
2018
2019
2020
2021
2022
2023
2024
Year
165
33
50
20
20
20
25
13
33
19
12
80
52
13
Substance/group of susbtances
Carfentanil
Fentanyl and analogues
Isotonitazene
Metonitazene
Protonitazene

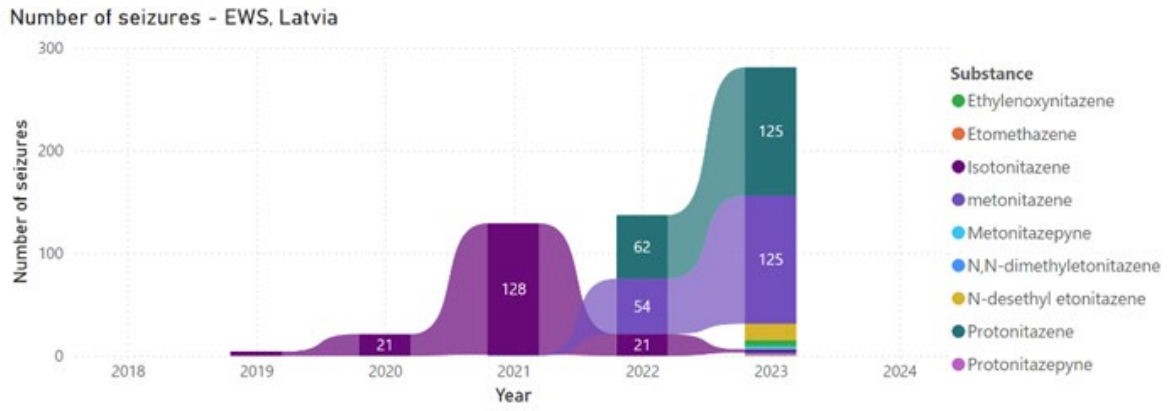

Syringes distributed (Fonte), Estonia
Syringes distributed
1M
0M
2018
2019
2020
2021
2022
2023
2024
Year

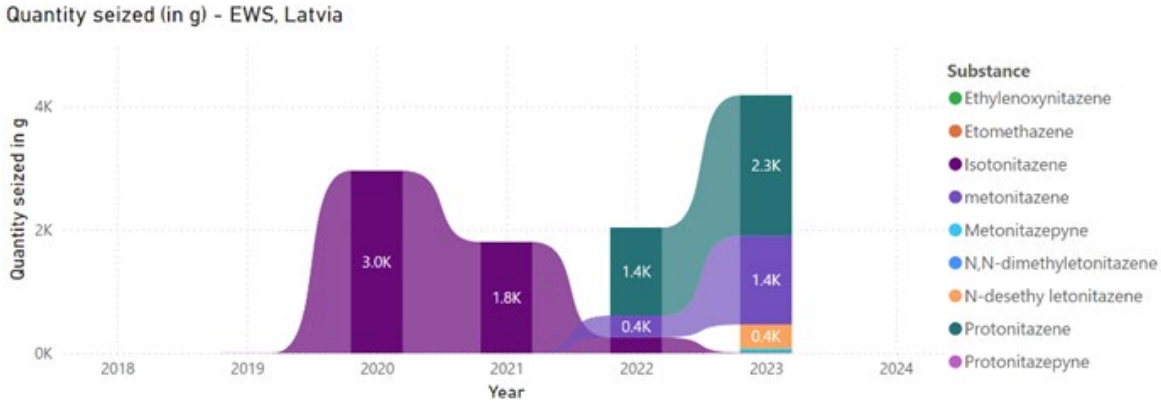
Key data — Latvia:



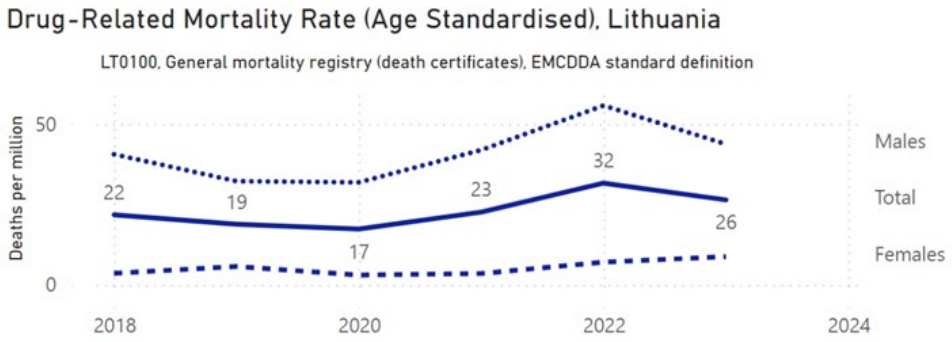


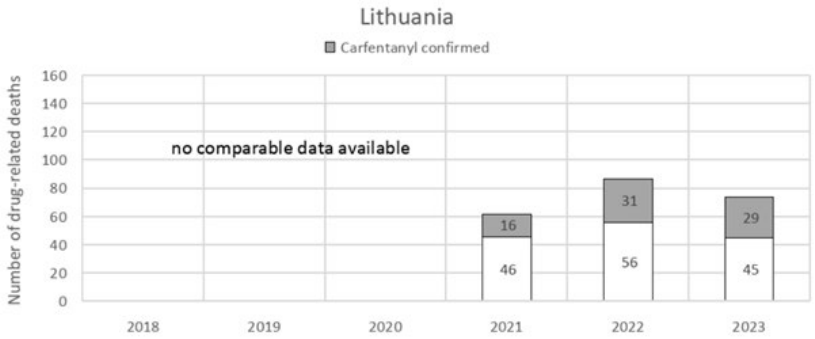


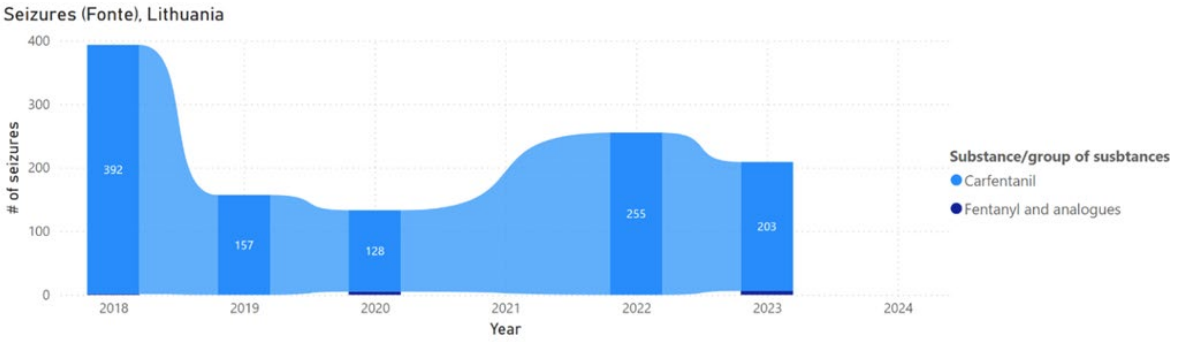

Number of seizures - EWS, Latvia
Number of seizures
300
200
100
0
2018
2019
2020
2021
2022
2023
2024
Year
21
128
62
54
21
125
125
Substance
Ethylenoxynitazene
Etomethazene
Isotonitazene
metonitazene
Metonitazepyne
N,N-dimethyletonitazene
N-desethyl etonitazene
Protonitazene
Protonitazepyne

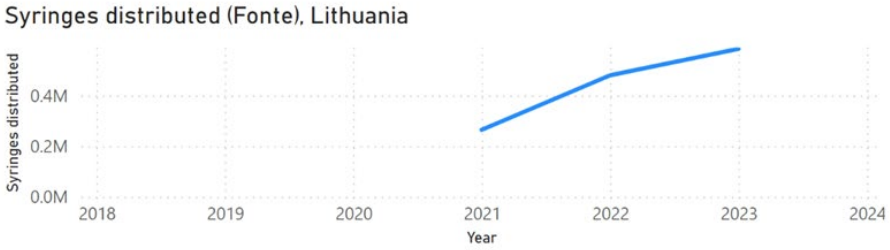

Quantity seized (in g) - EWS, Latvia
Quantity seized in g
4K
2K
0K
2018
2019
2020
2021
2022
2023
2024
Year
3.0K
1.8K
1.4K
0.4K
2.3K
1.4K
0.4K
Substance
Ethylenoxynitazene
Etomethazene
Isotonitazene
metonitazene
Metonitazepyne
N,N-dimethyletonitazene
N-desethy letonitazene
Protonitazene
Protonitazepyne

Key data — Lithuania:









Annex 2: Methods of the EUDA health and security threat assessment

Process overview

This health and security threat assessment was conducted over a 10-week period, following a multi-stage process designed to integrate quantitative and qualitative data sources. The assessment was launched in response to signals detected through the EUDA's monitoring activities, focusing on the emergence of nitazenes and carfentanil in the Baltic region.

At the outset, 10 research questions were identified to guide the analysis. These questions covered key aspects of the availability, use, harms and responses related to highly potent synthetic opioids, specifically nitazenes and carfentanil, in Estonia, Latvia and Lithuania. The findings presented in this report reflect the structured analysis conducted in relation to these research areas.

The assessment process included:

4. The collation and review of primary data from national monitoring frameworks, law enforcement agencies, forensic sources and public health indicators.
5. A structured, non-systematic literature and data review to contextualise findings and identify knowledge gaps.
6. Expert consultations, including three national focus groups, to gather insights from frontline professionals across health, security and policy sectors.
7. Data synthesis and interpretation, in the course of which EUDA analysts triangulated findings, identified key trends and developed response options.
8. Report drafting and review, with input from EUDA experts and Reitox national focal points to ensure alignment with the current understanding of the subject matter in the region.

An iterative approach of the process allowed for refinements as new information became available, ensuring that the assessment remained evidence-based and contextually relevant.

Methods

Primary data collection focused on information available from established national and European monitoring systems. Specifically, data from the three countries was gathered on the following areas (see Table A2.2 for the full set of data sources):

- The number and quantity of drugs seized by national law enforcement;
- Drug-related deaths and toxicology reports;
- Needle and syringe distribution and naloxone provision;
- Opioid agonist treatment (OAT) provision;
- Syringe residue analyses collected through the ESCAPE network;
- Hospital admissions linked to drug poisoning, reported by the Euro-DEN Plus network;
- Forensic drug analyses and seized sample quantities reported by the Reitox national focal points to the EUDA Early Warning System (EWS).

To ensure coverage of recent developments, the assessment incorporated national reports produced by the Reitox national focal points from Estonia, Latvia and Lithuania, covering the data collection years 2021-2023 and complemented by preliminary 2024 data on drug-induced deaths and law enforcement seizures provided by the NFPs.

In parallel, a structured, non-systematic literature review was conducted, focusing on:

- The pharmacological and regulatory context of nitazenes and carfentanil;
- Trends in detection, market dynamics and trafficking routes;
- Health risks, including polysubstance use and drug adulteration;
- Drug-related and emergency medical service responses and barriers to effective intervention;
- The strength of monitoring frameworks and early warning systems.

Where relevant, peer-reviewed and grey literature was used to supplement primary data sources, ensuring a comprehensive overview of the evolving situation.

Additionally, three online focus groups were conducted in the national language, one in each Baltic State, coordinated by the respective Reitox national focal points. Simultaneous machine translations allowed for real-time engagement by the EUDA assessment team. Participants included health professionals, harm reduction service providers, emergency medical staff, policymakers and law enforcement officials. Discussions focused on:

- The drivers behind the emergence of nitazenes and carfentanil;
- Current health and security challenges;
- Potential strategies to mitigate the risks associated with these substances.

Data synthesis and interpretation

Data synthesis and analysis took place during the Team analysis period, involving EUDA subject-matter experts in highly potent synthetic opioids, drug-related harms, public health responses, market monitoring and law enforcement. Analysts triangulated quantitative and qualitative data, identified key findings, and assessed knowledge gaps to inform response options.

The analysis was structured around 10 research questions, ensuring a focused examination of use, availability, harms and responses. These questions shaped the outline of the findings section, enabling a systematic assessment of the synthetic opioid situation in the Baltic region.

Where data gaps or inconsistencies arose, additional input was sought from Reitox national focal points, leveraging their expertise on local conditions. This iterative approach ensured that response options were evidence-based, feasible and aligned with national realities.

Development of response options

Options for response are presented in each of the main areas of the findings section (security and trafficking, harms and responses, monitoring and early warning, and policy). These have been developed to provide evidence-based, practical and tailored options for national and regional authorities in the Baltic region to enhance their preparedness and response to the threat of highly potent synthetic opioids. These options do not seek to prescribe actions but rather serve as a supportive framework to help countries address the challenges posed by highly potent synthetic opioids.

By focusing on policy, health, security and monitoring, the options for response aim to foster collaboration, strengthen systems and promote targeted interventions that align with national preparedness plans and regional priorities. The options were prioritised based on feasibility, impact and evidence, ensuring they are realistic, effective and supported by best practices.

The options are organised into three tiers that reflect their relative priority and urgency:

- Tier 1 options are generally rapidly actionable with higher impact;
- Tier 2 options require additional resources or planning but remain highly feasible;
- Tier 3 options address longer-term needs or systemic challenges essential for strengthening preparedness and ensuring sustainable responses to the threat of highly potent synthetic opioids.

In addition to the tiered response options, further considerations are provided in each section. These represent cross-cutting principles and strategic elements that support the successful implementation of the proposed response options. While the tiered actions focus on specific interventions, the further considerations highlight broader systemic factors — such as governance, funding, multi-agency coordination and service accessibility — that are essential for ensuring long-term preparedness and effective response efforts.

Report writing and review

The findings from the Team analysis, non-systematic literature review and focus groups formed the foundation of this threat assessment report. To ensure accuracy and alignment with current intelligence, the draft findings were subjected to:

- Internal review by EUDA experts; and
- External validation by the Reitox national focal points in Estonia, Latvia and Lithuania.

This health and security threat assessment will be updated as new information becomes available, reflecting the evolving nature of the supply and use of nitazenes and carfentanil in the region.

Table A2.1: EUDA threat assessment process

Phase	Description	Participants	Outputs	Duration
Signal detection	Signal identification through routine monitoring (DRD, EWS, SZR, ESCAPE)	EUDA	Signal evaluated and identified as potential threat	Week 1
Threat level evaluation	Threat level assessed, threat assessment launch signed off	Lead Scientific Sector, Head of Unit	Sign-off completed	Week 2
Planning phase	Methods development, resource allocation, EE, LV and LT national focal points informed	TA team coordinators	Research questions, timeline, data mapping produced, ad-hoc data collections planned	Week 3 and 4
Launch of threat assessment	Non-systematic literature and data review, ad-hoc data collection initiated	TA team coordinators	Data and literature summaries in annexes	Week 4
Team analysis period	In-depth data analysis and interpretation, national focus groups	EUDA subject-matter experts, TA team coordinators, EUDA reviewers, NFPs	Production of key findings, messages and options for response. Ad-hoc data collections and focus group input integrated.	Week 5 and 6
Output production	Threat assessment report produced and reviewed.	Internal and external review teams	Final report produced and disseminated	Week 7 to 10

Limitations

A range of methodological approaches were brought together in this threat assessment. Data source and methodological triangulation was employed to enhance the validity of the results, through both confirmatory and complementary analyses. The limitations of these analyses mainly relate to problems regarding the collection, quality and accuracy of data, as well as the temporal and spatial limitations of the data used. In the following sections, the key

limitations that might affect the interpretation and generalisability of this report are presented, and, where applicable, methods to mitigate these risks are described.

Temporal limitations/timeliness

The main limitation of the data sources available for this assessment is timeliness. Data reported through Reitox national focal points (for instance drug-induced deaths, OAT coverage and drug seizures) are typically submitted to the EUDA on an annual basis and have a lag of about 6-18 months. More recent, preliminary data for some of these sources can be obtained on an ad-hoc basis (as for this report), but interpretation of this data can be difficult due to uncertainty regarding its completeness. Whenever preliminary data are used in this report, they are interpreted cautiously and assessed as to whether they seem to confirm or contradict patterns detected in the validated key data sources.

Spatial limitations/representativeness

Data collected through sentinel networks, such as substances found in used syringes (ESCAPE project) and drug-related emergency room visits (EuroDEN), rely on a few sites in comparably large cities and are not necessarily nationally representative. Other data, such as drug seizures or number of syringes distributed, are available to the EUDA only at the national level, without a regional breakdown. These limitations could potentially mask geographic differences in the availability and use of highly potent synthetic opioids in the Baltic countries, and additional sources were used when available to mitigate this risk.

Data quality and accuracy

With regard to harms such as drug-induced deaths and drug-related hospital emergency room visits, it is often difficult to tell from the data available to the EUDA what exact role highly potent synthetic opioids played in these events, for instance whether such one of these particular substances was a leading cause of death in a drug-related death. Substances reported in drug-related emergency room visits are clinician and patient reported, and not always analytically confirmed, making these sources subject to reporting biases, particularly given that there are indications that at least some of the potent synthetic opioids users are not certain about what substance they are using. Therefore, more weight was given to data sources with analytical/forensic confirmation of the substances involved and whenever other or undefined opioids were reported in harms data, the possibility that potent synthetic opioids were involved was not excluded.

Additionally, detections by law enforcement reported through the EWS are not comparable with seizure data reported annually using key market indicators. Detections reported to the EWS are analytically confirmed by forensic laboratories. The EWS prioritises real-time detection and timely reporting of newly emerging substances, making it particularly effective for identifying new synthetic opioids and new psychoactive substances (NPS), while seizure data, provides a broader but less timely overview of drug markets. Annual data on markets reported through seizures focuses on controlled drugs, reflecting long-term trends.

Differences in reporting obligations also create discrepancies. EWS data submission is legally mandated at the EU level, ensuring greater consistency, while NFP data collection depends on national systems, leading to variations in how seizures are recorded and categorised. As a result, the two datasets are not directly comparable, although overlaps exist where both capture aspects of the availability of highly potent synthetic opioids and NPS.

Sentinel hospital emergency departments

There are a number of caveats and limitations regarding the data from sentinel hospital emergency departments: the findings of a sentinel hospital cannot be generalised to other hospitals, and it was not possible to compare the drugs analytically confirmed and the drugs reported (i.e., self-reported or reported based on the attending physician). The findings in the presentations for which analytical confirmation was available may be biased as they reflect instances where laboratory confirmation was requested by the physician, thus missing cases where this was not requested. The hospital emergency rooms ‘capture’ only those individuals whose condition prompts a call to emergency services, missing those alone or unattended, those who had milder symptoms which were resolved with ambulance/first aid intervention and those who died before reaching the hospital.

Analytical limitations

When multiple data sources exist for the same indicator but use different methods — such as in the recording of drug seizures or drug-induced deaths — reconciling discrepancies can be challenging. If conflicting data are identified, both sources are presented in this report, with the differences explicitly discussed. Interpreting longitudinal trends requires caution, as unobserved confounders can bias analysis. For instance, drug seizure data may not only reflect market availability but also law enforcement activity. Therefore, this report focuses on the presence of specific substances on local markets rather than year-to-year variations in seizure numbers. Similarly, drug-related death trends can be influenced by improvements in forensic capabilities, detection and reporting, meaning that increases in recorded cases may

not directly indicate rising harms. To maintain consistency, only data series confirmed to have been collected using stable methodologies and detection capacities are included.

Challenges in detecting nitazenes

The presence of nitazenes, particularly recently emerged analogues, and their role in serious adverse events (e.g., acute poisonings in hospital emergency rooms and medico-legal death investigations) may remain undetected in some cases. Routine screening for nitazenes is not conducted in all forensic and toxicology laboratories across Europe, meaning their presence in drug markets and toxicological samples can go unreported in certain areas. Additionally, analytical sensitivity poses a challenge. Nitazenes and their metabolites can be present at sub-nanogram concentrations, similar to carfentanil, making detection more difficult. Enhanced analytical scrutiny is necessary when testing for these substances to ensure accurate identification.

Further compounding the issue is the fact that not all forensic laboratories are integrated into national early warning systems. As a result, detections of nitazenes in certain areas may not be reported to Reitox national focal points and, consequently, may be missing from EUDA datasets. These gaps highlight the need for more comprehensive monitoring, improved laboratory coordination and expanded toxicological screening for synthetic opioids.

Qualitative data

Expert opinion provides valuable insights into, for example, current patterns of use, the drugs available on the market or the harms experienced by communities from drug trafficking. However, these insights are limited to their immediate professional environment and are not representative of the situation in a country. This threat assessment utilises and systematises expert opinions as a complement to, and to shed light on, the quantitative data, where these exist.

Table A2.2. Overview of indicators and data sources used in the TA, with main strengths and limitations

Indicator	Method/ data sources	Measuring	Source population	Sensitivity	Specificity	Timeliness	Stratification (age and gender)	Lab confirmation	Coverage	Trends available	Lithuania	Latvia	Estonia	Link to documents
Substances found in used syringes	ESCAPE	Use	PWID	Poor	Strong	Strong	Poor	Yes	Poor	Yes				https://euda.europa.eu/system/files/media/publications/documents/13572/ESCAPE-generic-protocol.pdf
Substances reported by Drug consumption rooms	ENDCR network – registry data	Use	HRDU, including PWID	Poor	Poor	Strong	Strong	No	Poor					
Substances found in wastewater	Wastewater sampling by the SCORE network	Use	Population from catchments areas	Strong	Strong	Strong	Poor	Yes	Strong	No				https://www.euda.europa.eu/publications/html/pods/waste-water-analysis_en#section4
Substances found in samples brought to drug checking services	TEDI - analysis of drug samples submitted by service users	Use	Recreational users	Poor	Strong	Strong	Poor	Yes	Poor					https://www.euda.europa.eu/data/stats2024/methods/drug-checking_en
Prevalence of self-reported use — key populations	Surveys, RDS, Web survey	Use	HRDU and recreational users	Poor	Poor	Poor	Strong	No	Poor					https://www.euda.europa.eu/activities/european-web-survey-on-drugs_en
Prevalence of self-reported use — general population	General population survey	Use	General population	Poor	Poor	Poor	Strong	No	Strong					https://www.euda.europa.eu/data/stats2024/gps_en

Prevalence of high-risk drug use	Indirect statistical methods	Use	Drug users experiencing harmful effects	Poor	Poor	Poor	Poor	No	Strong		https://www.euda.europa.eu/data/stats2024/methods/pdu_en
Drug-induced deaths	Registries	Harms	General population	Strong	Strong	Poor	Strong	Sometimes	Strong		https://www.euda.europa.eu/data/stats2024/methods/drd_en
Drug-related emergency room visits	Hospital admissions	Harms	Population from catchments areas	Strong	Poor	Strong	Strong	Sometimes	Poor		https://www.euda.europa.eu/publications/data-factsheet/european-drug-emergencies-network-euro-den-plus-data-and-analysis_en
Drug-related ambulance interventions	Pre-hospital registries	Harms	Population from catchments areas	Strong	Poor	Strong	Strong	Poor	Poor		
New drug treatment entries	Treatment demand indicator	Harms	HRDU	Strong	Poor	Poor	Strong	No	Strong		https://www.euda.europa.eu/data/stats2024/methods/tdi_en
OAT coverage	OAT registries + denominators	Interventions	HRDU	Poor	Strong	Poor	Poor	Poor	Strong		https://www.euda.europa.eu/data/stats2024/methods/hsr_en
First aid training and naloxone provision	Programmatic	Interventions	HRDU	Poor	Strong	Poor	NA	NA	Strong		https://www.euda.europa.eu/data/stats2024/methods/hsr_en
NSP availability and coverage	Programmatic	Interventions	HRDU	Poor	Strong	Poor	NA	NA	Strong		https://www.euda.europa.eu/data/stats2024/methods/hsr_en
Seizures — quantities	Law enforcement	Availability	NA	Poor	Strong	Poor	NA	Yes	Poor		https://www.euda.europa.eu/data/stats2024/methods/szr_en

Seizures — numbers	Law enforcement	Availability	NA	Poor	Strong	Poor	NA	Yes	Poor		https://www.euda.europa.eu/data/stats2024/methods/szr_en
Price and purity	Law enforcement	Availability	NA	Poor	Poor	Poor	NA	Yes	Poor		https://www.euda.europa.eu/data/stats2024/ppp_en
Darknet activity	Law enforcement	Availability	NA	Poor	Poor	Strong	NA	No	Poor		
Dismantled production laboratories in EU — numbers	Law enforcement	Availability	NA	Poor	Strong	Poor	NA	Yes	Poor		
Trafficking routes and production outside EU	Law enforcement	Availability	NA	Poor	Poor	Poor	NA	Sometimes	Poor		
EWS-NPS detection	EWS	Harms, Availability	NA	Strong	Strong	Strong	Strong	Yes	Strong		https://www.euda.europa.eu/activities/eu-early-warning-system-on-nps_en
Other event-based surveillance	Media monitoring	Use, Harms, Availability	Unknown	Strong	Strong	Strong	Strong	Sometimes	Unknown		
Qualitative information from key informants (users and practitioners)	Qualitative research including focus groups	Use, Harms, Availability	All	Strong	Poor	Strong	Strong	Poor	Poor		

Colour codes: Purple means ‘available’, light blue means ‘not available’. Greyed out text means that this indicator was not used in this TA.

Annex 3: Management of acute opioid toxicity in pre-hospital and hospital settings

Authors: Paul Dargan and David Wood, December 2024

Acute opioid toxicity is a common reason for presentation to the Emergency Department, with episodes of acute opioid toxicity frequently encountered by ambulance personnel and commonly managed by bystanders and peers using take-home naloxone. Educating opioid users and their contacts is important in order to improve awareness of acute opioid toxicity and increase the willingness to administer naloxone and call emergency medical services.

Acute opioid toxicity can result in significant morbidity and mortality, with death due to respiratory depression. Acute opioid toxicity typically causes the triad of (i) drowsiness progressing to coma, (ii) respiratory depression progressing to respiratory arrest, and (iii) pin-point pupils. Opioids are commonly used together with other substances (e.g. alcohol, benzodiazepines, pregabalin) that can exacerbate respiratory depression. Opioid use with stimulants such as cocaine/methamphetamine or synthetic cannabinoid receptor agonists is also common, and this can result in additional adverse effects and mask features of the typical opioid toxidrome, making it difficult to accurately identify opioid-related respiratory depression/arrest.

The mainstay of managing acute opioid toxicity is the antidote naloxone, which acts to reverse the respiratory depressant effects of opioids. The main adverse effect of naloxone is precipitating opioid withdrawal — this is more likely in individuals with opioid dependency, particularly if excess doses of naloxone are used. There have been numerous outbreaks of severe acute opioid toxicity/deaths due to potent new psychoactive substance opioids. Many of these opioids are more potent and/or have a longer half-life than heroin, and so patients may potentially require a higher overall dose of naloxone and/or more prolonged treatment. However, it is important to note that users and those treating individuals with acute opioid toxicity will not be aware of the opioid(s) that have been used. The initial approach to the management of acute opioid toxicity does not differ between opioid toxicity relating to acute heroin/prescription opioid toxicity and NPS opioid toxicity — **it remains important, even in the era of potent NPS opioids, to maintain the approach of giving titrated doses of naloxone to patients with acute opioid toxicity**.

This text provides a brief summary of the management of acute opioid toxicity — further details are available in recently published national guidelines from the UK and USA, both of

these provide flowcharts to provide practical guidance for management of acute opioid toxicity.

The management of patients in respiratory arrest or severe respiratory depression

The initial management of patients in respiratory arrest or with severe respiratory depression (a respiratory rate of less than five breaths per minute and/or oxygen saturations less than 85 % on air) both in the hospital and pre-hospital setting should focus on support of the airway and breathing using the standard Basic/Advanced Life Support (BLS/ALS) approach, including the use of rescue breaths ideally with a bag valve mask. This can be supplemented by the use of naloxone as described in more detail in the 'red' pathway in the UK guideline flowchart (Uk Government, 2017), and in the following sections.

Pre-hospital and bystander management of acute opioid toxicity

The approach to patient management can be summarised using the acronym ABCN:

- **A**mbulance: An ambulance should be called.
- **B**reathing and Re**C**overy Position: If the individual is not breathing or has severe respiratory depression give rescue breaths and put them in the recovery position.
- **N**aloxone: Administer naloxone. Naloxone should be given via the intramuscular or intranasal route depending on local/national protocols. We summarise here the use of intramuscular naloxone, the same step-wise/titrated approach should be used for intranasal naloxone:
  - If the individual has a low respiratory rate (less than 10 breaths per minute or, if the information is available, oxygen saturations less than 92 % on air) give a dose (usually 400 micrograms) of intramuscular naloxone.
  - Wait 2-3 minutes and if there is no response give another dose (usually 400 micrograms) of intramuscular naloxone.
  - Repeat as necessary every 2-3 minutes whilst waiting for the ambulance to arrive.
  - Generally, the maximum dose recommended for bystander naloxone administration is 2 mg. Ambulance/emergency medical service professionals may be able to give higher doses depending on local/national protocols. However, it is

important that the stepwise approach of doses of 400 micrograms of intramuscular naloxone is followed.

- If the patient refuses transport to hospital after an episode of severe acute opioid toxicity requiring naloxone administration, ambulance/emergency medical service staff should follow local protocols for determination of patient capacity to refuse care.
- Further titrated doses (usually 400 micrograms) of intramuscular naloxone may need to be administered by ambulance/emergency medical service staff if the patient has ongoing respiratory depression, using the thresholds noted above.

Emergency department/in-hospital management of acute opioid toxicity

The aim of managing patients with acute opioid toxicity in the Emergency Department is the reversal of opioid-related respiratory depression and the maintenance or airway protective reflexes rather than full reversal of unconsciousness. Naloxone should be given in titrated intravenous doses in those who have significant respiratory depression (respiratory rate less than 10 breaths per minute, oxygen saturations less than 92 % on room air, end-tidal CO_2 >7.0kPa) related to suspected acute opioid toxicity.

In those with respiratory arrest or severe respiratory depression (respiratory rate less than five breaths per minute or oxygen saturations less than 85 % on room air) the priority is ALS with bag-valve mask ventilation supplemented by naloxone administration: an initial dose of 400 micrograms delivered intravenously, followed by 800 micrograms intravenously if no response after 60 seconds, with further dosing following the ‘red’ pathway in the UK guideline flowchart.

Patients with moderate respiratory depression (respiratory rate 6-10 breaths per minute, oxygen saturations 86-92 % on room air or end-tidal CO_2 >7kPa), should be given supplemental oxygen and intravenous naloxone in titrated intravenous 100-200microgram boluses every 60 seconds to a maximum of 2 000 micrograms, aiming for a respiratory rate >10 breaths per-minute.

Because the duration of the action of naloxone may be shorter than the respiratory depressant effect of the opioid(s) used, repeat doses of naloxone or a naloxone infusion may be required. Patients who have been given naloxone should have observations (respiratory rate, oxygen saturations, level of consciousness and (if available) end-tidal CO_2) every 15

minutes for the first hour and then every 30 minutes for the next three hours. If there is deterioration (respiratory rate <10 breaths per minute) further titrated doses of intravenous naloxone should be given: 100-200 microgram boluses every 60 seconds to a maximum of 2 000 micrograms, aiming for a respiratory rate of >10 breaths per minute. Patients who require further doses of naloxone will need to be managed with a naloxone infusion.

All patients who require naloxone should be observed for at least four hours after the last dose of naloxone and for at least six hours after the suspected time of opioid use. Longer periods of observation of up to 12 hours may be required for those who have taken a longer-acting opioid (e.g. methadone or an NPS opioid). Prior to discharge from hospital, clinicians should take the opportunity to provide brief interventions regarding the risks of acute opioid toxicity, signpost patients to drug treatment services and (if available) prescribe take-home naloxone.

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Annex 4: Nitazenes monitored by the EWS as of December 2024. A brief overview of the chemistry, pharmacology and toxicology of carfentanil and nitazenes

Nitazenes

Table A4.1. Nitazenes monitored by the EU EWS

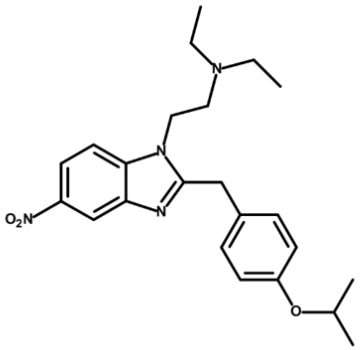
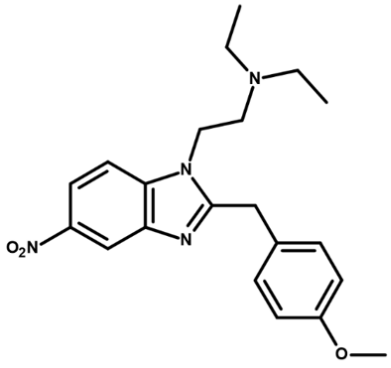
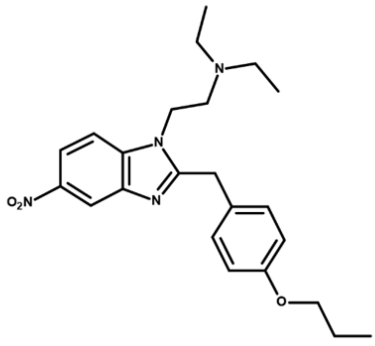
Common name	IUPAC name	Year of formal notification to the EU EWS
Isotonitazene	N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine	2019
Metonitazene	N,N-diethyl-2-[2-[(4-methoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]ethanamine	2020
Etazene	2-[(4-ethoxyphenyl)methyl]-N,N-diethyl-1H-benzimidazole-1-ethanamine	2020
Metodesnitazene	N,N-diethyl-2-[2-[(4-methoxyphenyl)methyl]benzimidazol-1-yl]ethanamine	2020
Fluonitazene	N,N-diethyl-2-{2-[(4-fluorophenyl)methyl]-5-nitro-1H-benzimidazol-1-yl}ethan-1-amine	2020
Etonitazepyne	2-(4-ethoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole	2021
Protonitazene	N,N-diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1H-benzimidazole-1-ethanamine	2021
Butonitazene	2-[(4-butoxyphenyl)methyl]-N,N-diethyl-5-nitro-1H-benzimidazole-1-ethanamine	2021
Etonitazepipne	2-(4-Ethoxybenzyl)-5-nitro-1-(2-(piperidin-1-yl)ethyl)-1H-benzo[d]imidazole	2022
Etomethazene	2-[(4-ethoxyphenyl)methyl]-N,N-diethyl-5-methyl-1H-benzimidazole-1-ethanamine	2023
Ethyleneoxynitazene	2-{2-[(2,3-dihydro-1-benzofuran-5-yl)methyl]-5-nitro-1H-benzimidazol-1-yl}-N,N-diethylethan-1-amine	2023
Protonitazepyne	5-nitro-2-[(4-propoxyphenyl)methyl]-1-(2-pyrrolidin-1-ylethyl)benzimidazole	2023
Metonitazepyne	2-(4-methoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazole	2023
N-desethyl etonitazene	2-[2-[(4-ethoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]-N-ethyl-ethanamine	2023
N-desethyl isotonitazene	N-ethyl-2-[2-[(4-isopropoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]ethanamine	2023
6-Methyl desnitroetonitazene	2-[(4-Ethoxyphenyl)methyl]-N,N-diethyl-6-methyl-1H-benzimidazole-1-ethanamine	2024
Fluetonitazene	N,N-diethyl-2-[2-[[4-(2-fluoroethoxy)phenyl]methyl]-5-nitro-benzimidazol-1-yl]ethanamine	2024

N,N-dimethyl etonitazene	2-[2-[(4-Ethoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]-N,N-dimethyl-ethanamine	2024
N-desethyl protonitazene	N-ethyl-2-{5-nitro-2-[(4-propoxyphenyl)methyl]-1H-1,3-benzimidazol-1-yl}ethan-1-amine	2024
Fluetonitazepyne	2-{[4-(2- 32.fluoroethoxy)phenyl]methyl}-5-nitro-1-[2-(pyrrolidin-1-yl)ethyl]-1H-1,3-benzimidazole	2024
Isobutonitazene	N,N-diethyl-2-(2-{[4-(2-methylpropoxy)phenyl]methyl}-5-nitro-1H-1,3-benzimidazol-1-yl)ethan-1-amine	2024
Desnitroclonitazene	2-{2-[(4-chlorophenyl)methyl]-1H-1,3-benzimidazol-1-yl}-N,N-diethylethan-1-amine	2024

Chemical structure

Nitazenes are a class of synthetic opioids structurally classified as 2-benzylbenzimidazoles. They were first synthesised in the 1950s as potential analgesics but were not marketed due to their high potency and associated risks. The core structure comprises a benzimidazole ring system with various substitutions that influence their pharmacological activity. For instance, etonitazene features a nitro group at the 5-position and an ethoxy group at the 4-position of the benzimidazole ring, contributing to its high affinity for opioid receptors (Ujváry et al., 2021).

Table A4.2. Chemical structure and IUPAC name of isotonitazene, metonitazene and protonitazene

Isotonitazene	Metonitazene	Protonitazene
N,N-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine	N,N-diethyl-2-[2-[(4-methoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]ethanamine	N,N-diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1H-benzimidazole-1-ethanamine
		

Pharmacology

Nitazenes act as potent agonists at the μ-opioid receptor, leading to pronounced analgesic effects. Their potency varies among analogues; some are reported to be up to 500 times more potent than morphine. This high potency significantly increases the risk of respiratory depression, a primary cause of fatal overdose in opioid misuse. The pharmacokinetic profiles of nitazenes, including absorption, distribution, metabolism and excretion, are not extensively documented, necessitating further research to inform clinical and forensic practices (Ujváry et al., 2021).

Health risks

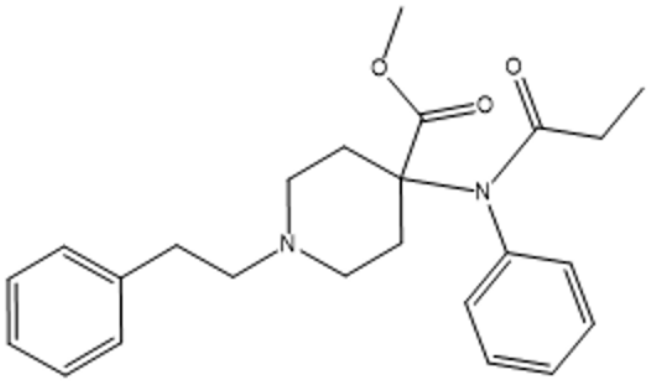
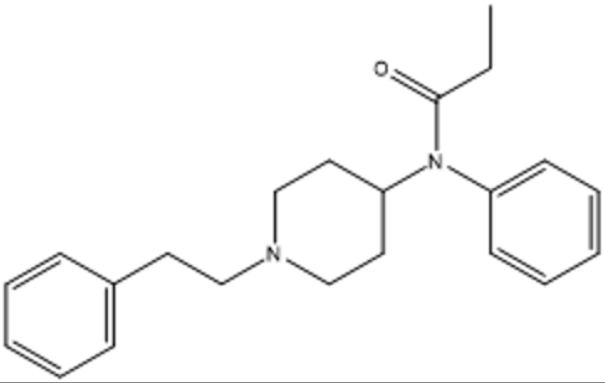
Similar to other types of opioid analgesics, such as morphine and fentanyl, the acute effects of nitazenes opioids include euphoria, relaxation, analgesia (a reduced ability to feel pain), sedation (inducing a state of calm or sleep), bradycardia (slowing of the heart), hypothermia (dangerously low body temperature) and respiratory depression (slowing down of breathing). It is this last effect that poses the greatest danger to users, as, owing to the apparently high potency of some of these compounds, sub-milligram doses may cause life-threatening poisoning from respiratory depression. Left untreated, this can lead to respiratory arrest (cessation of breathing) and death. This risk is greater in people with no or reduced tolerance to opioids and will be exacerbated by the use of other central nervous system depressants. The chronic health risks associated with nitazenes are likely to mirror those of other opioids, including the potential for dependence. Anecdotal reports from first responders and a small study of patients with confirmed poisoning from nitazenes have noted that, in some cases, larger and additional doses of naloxone have been required to reverse the respiratory depression caused by nitazenes compared to other opioids, including fentanyl. This finding requires further study.

Carfentanil

Chemical structure

Carfentanil is a synthetic opioid belonging to the phenylpiperidine class, structurally related to fentanyl. It is characterised by a piperidine ring with a phenethyl group at the nitrogen atom and a carboxymethyl ester at the 4-position.

Table A4.3. Molecular structure and IUPAC name of carfentanil (fentanyl is provided for comparison)

Carfentanil	Fentanyl
	
methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate	N-(1-(2-phenethyl)-4-piperidinyl-N-phenyl-propanamide

Molecular structure and IUPAC name of carfentanil (fentanyl is provided for comparison)

Pharmacology

Carfentanil functions as a highly selective agonist at the μ-opioid receptor, resulting in profound analgesia and sedation. When the agonist activity of the carfentanil is compared with that of morphine, its potency is much higher in tests in vivo (e.g., analgesia) than in tests in vitro (e.g., binding affinity for μ receptors). For example, the analgesic potency of carfentanil has been reported to be up to 10 000 times that of morphine, while its affinity for μ receptors is only 14 to 135 times higher. Due to its lipophilicity, it rapidly crosses the blood-brain barrier, leading to a swift onset of action. Its high receptor affinity and potency make it effective in veterinary medicine for immobilising large animals. However, in humans, even minimal exposure can cause severe respiratory depression and death.

Acute health risks

Carfentanil, a highly potent fentanyl analogue, poses significant acute health risks, primarily due to its capacity to induce rapid and severe respiratory depression. Overdose can result in apnoea, respiratory arrest and death. Several factors exacerbate these risks (EMCDDA and Europol, 2017):

- The difficulty in properly diluting carfentanil, which can lead to unintentional toxic dosing;
- Administration methods such as injection, insufflation and inhalation that increase bioavailability, heightening overdose risk;
- Lack of familiarity with carfentanil's effects and appropriate dosing, leading to misuse;
- Concurrent use of other central nervous system depressants (e.g., other opioids, benzodiazepines, gabapentinoids, alcohol), which amplifies respiratory depression, with individuals who have little or no opioid tolerance being particularly vulnerable;
- Solitary use, especially in private settings, reducing the likelihood of timely assistance during overdose.

Compounding these dangers, carfentanil might be misrepresented as or mixed with heroin and other illicit opioids, leaving users unaware of its presence. In cases of acute poisoning, naloxone can reverse respiratory depression caused by carfentanil; however, clinical experiences indicate that higher or multiple doses, including continuous infusions, may be necessary for effective reversal. Chronic health risks associated with carfentanil are likely to mirror those of other opioids, including the potential for dependence.

References

EMCDDA and Europol (2017), *EMCDDA–Europol joint report on a new psychoactive substance: methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil)*, Publications Office of the European Union, Luxembourg (https://www.euda.europa.eu/publications/joint-reports/carfentanil_en).

Ujváry, I., Jorge, R., Christie, R., Le Ruez, T., Danielsson, H. V., Kronstrand, R., Elliott, S., & Gallegos, A. (2021). *Dark net, telephones, and tablets: A review of the emerging class of highly potent benzimidazole opioids*. Drug Testing and Analysis, 13(3), 422–440. https://doi.org/10.1002/dta.2987