EUDA
EUROPEAN UNION DRUGS AGENCY

THREAT ASSESSMENT REPORT

Assessment of the threat posed by highly potent synthetic opioids in Europe

A scenario-based analysis to inform options for response

Contents

Executive summary

This threat assessment examines how highly potent synthetic opioids (HPSOs) could affect Europe over a near-term two-year period and what this could mean for preparedness. The two-year time frame is used for near-term preparedness because changes related to HPSOs can occur quickly but the assessment still allows for plausible development. The assessment uses structured expert input and scenario development to examine two ways in which HPSO-related risks could evolve over this period. The assessment is based on available signals and targeted evidence, including laboratory findings, clinical and forensic post-mortem information, and data on drug checking and law enforcement seizures. This assessment should be read as a structured summary of the available evidence rather than as a quantified estimate of prevalence and harms.

The findings should be interpreted against the background of Europe's wider opioid problem. Heroin remains Europe's most commonly used illicit opioid and continues to account for a large share of opioid-related harms in many EU Member States. Opioids, including heroin and its metabolites, are estimated to be present in around 7 out of 10 fatal overdoses in the European Union, often in combination with other substances. New HPSOs currently represent a smaller part of Europe's overall opioid market, but they are of high concern because very small quantities can cause severe poisoning, harms can emerge rapidly in specific local markets and misrepresented products may expose people who did not intend to use opioids.

Signals from recent years indicate a heterogeneous situation across Europe, with the strongest signals initially dominated by nitazenes and fentanyl analogues. More recent developments also include the emergence of orphine opioids, particularly cychlorphine and spirochlorphine, which increased in parts of Europe during 2025 and were associated with seizures (medical events), non-fatal poisonings and deaths. The strongest signals remain in the Baltic region, while episodic detections and misrepresented products have also been reported elsewhere in Europe. A particular concern is the trafficking and sale of products as medicines or as other drugs when they contain HPSOs, including falsified medicine tablets, because this can expose people with no intention to use opioids. The overall picture remains incomplete, particularly where testing capacity is limited, turnaround times are longer, or information and signals are not shared consistently between relevant actors.

Looking ahead, the main uncertainties concern how the situation may develop over the next two years, including whether exposure remains largely within established illicit opioid markets or whether it increasingly involves products sold as non-opioids or as medicines, extending exposure beyond established opioid-using populations. Recent international experience, particularly from North America, shows that patterns of harm linked to HPSOs can change

within a short time frame. This does not imply that Europe is on the same pathway, but it underlines the importance of maintaining preparedness arrangements that support earlier recognition, timely laboratory confirmation, clear situational understanding and effective response when local clusters of non-fatal poisonings and drug-induced deaths emerge or when misrepresented products are detected.

The report therefore sets out a list of priority actions for Member States and competent authorities to strengthen timely confirmation and coordination during suspected HPSO-related harm events and to enable rapid scaling-up of protective measures when harms increase. These actions include naloxone access, facilitated access to opioid agonist treatment and practical overdose guidance. Preparedness should continue to account for new nitazenes as well as other HPSOs, including orphines, particularly when wider changes in market and service conditions create opportunities for further emergence.

Box 1: Methods in brief

This report applies the European Union Drugs Agency (EUDA) scenario-based health and security threat assessment approach (see Annex 1 for a detailed description of the methods, data constraints and interpretive limitations). It combines a structured synthesis of European HPSO signals with internal and external expert input to identify key drivers, uncertainties, plausible future scenarios and priority options for response. Signals were drawn from available early warning system, forensic, toxicological, clinical, sentinel-monitoring, drug-checking and law enforcement information. A short national focal point pulse survey provided additional indicative input on national exposure and readiness. Key uncertainties were prioritised through structured expert judgement and used to develop contrasting scenarios. The scenarios are not predictions. They are preparedness tools used to examine how HPSO-related risks could evolve over a near-term two-year period and what this would mean for early detection, cross-sector coordination and the capacity to scale up relevant health and operational responses. Their likelihood and potential impact will depend on national and local conditions, including existing opioid markets, current HPSO exposure, digital and postal supply pathways, service coverage, detection capacity and coordination arrangements. The assessment is constrained by uneven testing, reporting and monitoring capacity across Member States and should not be interpreted as a quantified estimate of prevalence, exposure or burden.

Key points for decision-makers

- Over the near-term two-year time frame, two central preparedness questions are how quickly new HPSOs and variants will emerge and change, and whether they will remain mainly within illicit opioid markets or increasingly appear in products sold as medicines or as other drugs, potentially extending exposure beyond established opioid-using populations.
- Preparedness priorities at the national level should include timely laboratory confirmation, clear national coordination arrangements, timely reporting through competent national authorities and national focal points to the EU early warning system where relevant, rapid assessment and risk communication during suspected events, and the capacity to scale overdose prevention and response quickly during spikes in the number of localised harm events.
- Security and operational preparedness at the national level should include vigilance regarding online retail, encrypted communication channels, and postal or courier micro-shipments used for the distribution of HPSOs, as these facilitate low-visibility supply and repeated attempts to introduce HPSOs into different markets and populations. It should also include rapid identification and tracing of falsified medicines and other misrepresented products containing HPSOs, supported by timely sharing of HPSO-related forensic findings to support operational action, public health warnings and frontline response.
- The options for response presented in this report provide a general priority set to strengthen preparedness and reduce avoidable delay during suspected HPSO-related harm events. Additional measures will be required depending on the national context and the nature of incidents.

Highly potent synthetic opioids in Europe

Section 1 summarises the current situation in Europe, drawing on available highly potent synthetic opioid (HPSO) signals and highlighting the main limitations of the available evidence. It then describes the regional pattern of signals and the main factors that could shape how the situation develops over a near-term two-year period. Section 2 uses this analysis to set out two plausible scenarios and a short set of priority options for response.

Definition

The designation ‘highly potent synthetic opioids’ (HPSOs) is used in this threat assessment as a risk category and refers to very-high-potency synthetic opioids with high overdose risk, including nitazenes and other high-potency novel opioids, whether found alone, in mixtures or in misrepresented products. It is not used as a definitive substance list.

Data sources and limitations

Detection of HPSOs is reported through multiple sources, including law enforcement seizures, drug-checking and syringe residue analysis, and clinical or post-mortem toxicology. A recurring feature is misrepresentation, including falsified oxycodone-type tablets and other products that contain HPSOs but are sold or perceived as other opioids, medicines or non-opioid drugs, which can result in unintentional opioid exposure.

The current evidence is constrained by differences in detection, surveillance and reporting capacity for HPSOs across the EU Member States. In some contexts, convergence of multiple data sources increases confidence that exposure to HPSOs is established and harms are being detected. Elsewhere, signals remain sporadic and may not be captured in routine indicators, particularly where confirmatory testing for illicit substances, including HPSOs, is not systematic, turnaround times are longer or reporting pathways are fragmented. These limitations are most consequential for non-fatal poisonings and for emerging compounds and mixtures not consistently captured through routine laboratory screening. The following regional analysis summarises where signals of HPSOs are most consistent, where they remain episodic and where uncertainty remains.

Regional signal patterns

Signals on HPSO detection from 2024 to 2026, alongside earlier indications, point to a widening but heterogeneous presence of HPSOs across Europe. Severe harms linked to use of HPSOs remain concentrated in a limited number of countries and drug market environments, as described in the regional analysis below, but additional signals suggest broader geographic dispersion, evolving product formats, and mixtures that can increase toxicity and complicate clinical management.

The current HPSO situation needs to be placed within the broader European opioid market. Across most Member States, heroin and other established opioids remain the main source of opioid-related health burden, while HPSOs currently account for a more limited and uneven share of signals and harms. However, their public health significance is disproportionate to their market size because of their high potency, the small quantities required to produce retail-level doses and their potential to appear in products sold as other opioids, medicines or non-opioid drugs. The Baltic region remains the clearest European example of how HPSOs can become embedded in local opioid markets following heroin market disruption, while signals elsewhere currently remain more episodic and unevenly detected.

Established exposure in the Baltic region

The most consistent and severe signals of HPSO use and harms continue to originate in the Baltic region, notably Estonia, Latvia and Lithuania. These Member States have experienced long-standing disruption to heroin markets beginning in the first decade of the 21st century, which led to the emergence of fentanyl and subsequent waves of potent synthetic opioid use, including nitazenes in Estonia and Latvia and carfentanil in Lithuania (e.g. Abel-Ollo et al., 2025). In these contexts, nitazenes and, in some settings, fentanyl or fentanyl analogues have been repeatedly related to drug-induced deaths and have been detected in syringe residue and clinical or post-mortem toxicology. The persistence and severity of these signals point to established local markets for HPSOs rather than isolated or short-lived incursions. Evidence from multiple sources leads to comparatively high confidence in the presence and negative public health impact of HPSOs in these settings. At the same time, the appearance of new HPSO variants, including orphines, and sedative admixtures in some of these markets highlights how quickly products can change once HPSOs become embedded in the markets and communities. Recent reports of cychlorphine and spirochlorphine in Estonia and Latvia reinforce this picture (EUDA, 2026). In these two Member States, both cychlorphine and spirochlorphine have been used by people who inject opioids and appear to have at least partly replaced nitazenes in those settings, and they accounted for most reported orphine seizures from 2024 to 2025. In Latvia, this shift was also reflected in syringe residue findings; detection of cychlorphine in syringes increased from 10 in 181 syringes in late 2024 to 111 in 200 syringes in late 2025.

Ireland and the United Kingdom: connectivity and shared risk dynamics

Developments in Ireland and the United Kingdom are relevant for preparedness because they show how HPSOs can produce sudden outbreaks in nearby and partly connected drug environments, including through products sold as heroin, as medicines or as other drugs. The examples from the United Kingdom are included here as contextual background to interpret these risks and should not be read as an indicator of EU prevalence.

In Ireland, nitazenes were linked to a series of outbreaks on the heroin market from November 2023 onwards, including 57 overdoses in Dublin over five days and a further 20 overdoses in Cork over six days (Killeen et al., 2024; O'Donnell et al., 2024). Additional alerts were issued in 2024 following the seizure of protonitazene powder in Dublin and the identification of *N*-pyrrolidino protonitazene in a Dublin prison setting associated with a small number of overdoses (HSE, 2023). These events show that nitazenes can emerge suddenly, produce localised outbreaks and require urgent analytical review, targeted harm reduction interventions and risk communication tailored to different stakeholders.

In the United Kingdom, in early 2024 nitazenes were reported to have been detected in substances sold as other opioids and as benzodiazepines and cannabis products, meaning that some people were exposed without intending to use opioids; over the preceding six months, 54 deaths had been reported in which nitazenes were detected in post-mortem toxicology (Holland et al., 2024). In Scotland, Public Health Scotland updated its 'rapid action drug alerts and response' nitazene alert on 12 August 2025 after increasing instances of drugs sold as heroin and benzodiazepines (Public Health Scotland, 2025), and later, in its January 2026 rapid action reporting, noted medetomidine, a strong non-opioid veterinary sedative, in the drug supply (Public Health Scotland, 2026). Read together, the examples from Ireland and the United Kingdom illustrate how harms can increase quickly in nearby markets when HPSOs are mis-sold, appear in medicines or other drug products, or are combined with sedatives.

Northern, western and central Europe

HPSO-related signals have been reported across a growing number of northern and central European countries, but in most cases they remain episodic. These include seizures of falsified oxycodone-type tablets in several countries and detections through drug-checking services, alongside occasional clinical or toxicology alerts. In some countries, episodic signals have also been accompanied by an impact on public health, including localised clusters of poisonings or short-term increases in drug-induced deaths, indicating that harms may appear in bursts even when sustained national trends in the use of HPSOs are not established. The appearance of falsified medicine tablets containing nitazenes across

multiple countries is important because tablet products can circulate through user networks not typically associated with heroin or injecting drug use, which can widen exposure to opioid-naïve populations. Beyond the Baltic states, orphines have now also been identified through drug seizures, collected samples or biological samples in a growing number of countries, including Austria, Denmark, Finland, France, Germany, the Netherlands, Norway and Sweden. A probable cychlorphine exposure linked to a benzodiazepine tablet sold online was also reported in Germany in September 2025.

Southern and south-eastern Europe

Parts of southern and south-eastern Europe remain under-represented in current datasets, with limited routine visibility compared with other regions. For example, in Bulgaria and Greece, available signals point to fentanyl or related substances in specific contexts, including post-mortem toxicology, while comprehensive data on nitazenes and other emerging HPSOs are sparse. Bulgaria illustrates delayed recognition rather than comprehensive routine coverage, because the pattern became apparent primarily through post-mortem toxicology and subsequent aggregation of hospital and coroner reporting rather than real-time routine monitoring. Available information indicates a geographically diffusing pattern, with early fentanyl-involved deaths reported in Sofia in January 2024 and in Varna in February 2024, followed by early hospitalisations in Plovdiv in February 2024 and later in Sofia and Varna in March 2024, with a spread to additional regions and peaks in mid 2024 and again in August 2025. Isolated or sporadic orphine signals have also been reported in southern Europe, including cychlorphine in Italy and Spain, and one acute non-fatal poisoning involving cychlorphine in Italy.

Interpreting current signals

The current signals need to be interpreted with caution. In several countries, law enforcement seizures and drug-checking detection of HPSOs have occurred without corresponding increases in routine national indicators such as drug-induced deaths or treatment data. This does not necessarily mean that HPSOs are not causing harm. Detection in biological samples can be delayed where substances are present at low concentrations, where highly sensitive methods are not available, where reference standards are not yet available for newly emerging compounds or where the relevant substances are not included in routine screening. Differences in post-mortem toxicology practices, forensic reporting and the use of retrospective analysis can further affect recognition. These limitations mean that increases in availability may become visible earlier than increases in detected harm. Timely national and EU-level reporting, including through national focal points and the EU early warning system where relevant, is also important for shared situational understanding. Taken together, the available information indicates a heterogeneous situation across Europe, with high levels of harm due to the use of HPSOs concentrated in a limited number of Member

States and market environments, alongside wider but uneven signals of its presence and use elsewhere. Differences in detection capability, reporting, prevention, treatment and harm reduction service coverage mean that current signals related to HPSOs do not point to a single, uniform trajectory over a near-term two-year period.

The next section sets out two plausible scenarios to support preparedness planning under these uncertainties.

Looking ahead: possible highly potent synthetic opioid developments within a two-year period

Key factors shaping highly potent synthetic opioid developments over a two-year period

The trajectory of HPSO-related risks over a two-year period is shaped by a number of interacting factors that influence what HPSOs are available, who is exposed, how quickly harms become visible and how effectively systems can detect and respond (see Annexes 2 and 3). These factors do not operate in isolation and their relative importance varies across Member States and drug market environments. The seven factors below summarise the main sources of uncertainty that could change the scale, diffusion and severity of harms related to HPSOs over this period.

1. **Stability of established illicit opioid markets.** The first key uncertainty is whether established illicit opioid markets remain stable over the near term or whether changes in the availability, price or composition of heroin and other dominant opioids in specific national contexts create openings for HPSOs. In some parts of Europe, reduced heroin availability, falling purity, price changes or disruption to trafficking routes could increase replacement pressure and a shift towards synthetic opioids, as observed historically in the Baltic region. Geopolitical events, including conflict affecting established trafficking routes, may add further uncertainty to heroin supply and distribution. HPSOs may also emerge through contamination, misrepresentation or the replacement of locally available opioids. The availability of other opioids, including diverted opioid agonist treatment (OAT) medicines and some pharmaceutical opioids, can shape how people respond to market changes and may either buffer or redirect demand for HPSOs.

2. **Continuity and coverage of protective prevention, treatment and harm reduction measures.** The reach and continuity of OAT, take-home naloxone and low-threshold harm reduction services, and practical clinical guidance for overdose management, strongly influence whether changes in HPSO availability translate into severe harm and how quickly local clusters of non-fatal poisonings and drug-induced deaths can be mitigated. Disruptions to OAT continuity, including shortages, discontinuations or rapid switching of buprenorphine-based medicines, could increase vulnerability if they lead to treatment gaps, disengagement from care or movement towards diverted medicines or illicit opioids. Differences across Member States in the coverage, accessibility and resilience of these protective measures can therefore produce markedly different

outcomes under similar exposure to HPSOs. Where such measures are constrained, the potential for severe impact can be high even when early signals of HPSO presence are weak.

3. **The pace at which HPSOs and related variants change.** Rapid turnover and the emergence of new HPSOs and related variants increase uncertainty for detection, clinical interpretation and scheduling, and they can create periods in which substances are present in supply and markets but are not routinely identified. This uncertainty is shaped by how quickly producers and supply networks adapt to controls and disruptions by switching to closely related analogues and is also shaped by the speed at which laboratory methods, reference information and legal controls are updated in response. Slower turnover in newly emerging HPSOs allows methods and practices to adapt more steadily. The recent increase in orphine detections in several Member States may partly be related to China's generic control of nitazene opioids introduced in July 2025 (China Ministry of Public Security et al., 2025), which appears to have reduced nitazene availability and may have encouraged replacement by substances such as cychlorphine.

4. **How HPSOs are presented and distributed.** Tablets and other pharmaceutical lookalike products can be easier to handle, share and sell, and they can reach networks not typically linked to heroin use or injecting. Low-volume economics and micro-shipments via postal or courier routes can facilitate repeated attempts to introduce products into different markets, while digitally enabled retailing can increase the speed of diffusion and complicate targeting by law enforcement. For example, in multiple Member States, orphines have been encountered in powders, liquids and blotters, and they are often sold online, including on the surface web, under their own names. In addition, in Estonia and Latvia, orphines have also been linked to street-level opioid supply.

5. **The presence of additional substances alongside HPSOs, including sedatives** (e.g. alpha-2 sedatives, benzodiazepines and z-drugs such as zolpidem and zopiclone). When opioids are combined with sedatives, alcohol or benzodiazepines, toxicity can increase and overdose presentations can be more difficult to manage clinically. This has been noted in guidance and investigations describing sedatives such as xylazine and medetomidine detected alongside opioids (CDC, 2024; Kariisa et al., 2023; Nham et al., 2025). Whether such combinations remain occasional or become more embedded in some supply chains affects the severity and presentation of harms.

6. **The extent to which HPSOs appear outside opioid products.** If HPSOs remain mainly within opioid products, exposure is more likely to remain concentrated among people with established opioid use patterns. If they appear more often in products sold as stimulants or benzodiazepines, or in misrepresented or falsified medicines, exposure broadens to opioid-naïve populations, and harms can become visible more quickly and across more settings.

7. **Operational readiness.** The speed with which signals are triangulated and translated into action depends on national arrangements for decision-making, information sharing and timely laboratory confirmation. Where laboratory capacity and reporting processes are limited, surveillance systems are not functioning and coordination pathways are unclear, laboratory confirmation may come only after harms have already become visible, reducing the timeliness and effectiveness of targeted alerts and responses.

Taken together, the seven factors outlined above can evolve in different ways and to different degrees across Member States. The next section uses them to set out two plausible scenarios for how the HPSO situation could develop over a near-term two-year period. To keep the scenarios focused and decision-relevant, they are structured around two uncertainties that most directly shape who is exposed and how quickly harms due to HPSOs can escalate.

These two uncertainties are the pace at which HPSOs change and the extent to which they remain mainly within illicit opioid markets or appear more often in products sold as non-opioids and in falsified medicines. The remaining factors influence how each scenario plays out by shaping vulnerability, including changes in heroin supply stability, and the coverage of harm reduction and treatment interventions. In this next section, ‘new HPSOs’ refers to high-potency synthetic opioids and variants newly detected in Europe or in a given Member State, including new variants within known opioid families and high-potency opioids that were previously rarely detected or not detected in Europe.

Scenario A: rapid emergence of new highly potent synthetic opioids with exposure largely confined to illicit opioid markets

In scenario A, new HPSOs and high-potency variants appear frequently and are detected intermittently across Member States. The defining feature is that exposure remains mainly within established opioid supply and use contexts and does not become widely embedded in non-opioid drug supplies. Recent experience with orphines, particularly cychlorphine and spirochlorphine, reinforces this pattern, as these substances have been detected in established opioid-using settings, including injecting use in Estonia and Latvia. In addition, law enforcement seizures in Estonia and Latvia have identified cychlorphine and spirochlorphine in mixtures with each other and with nitazenes.

Who is exposed and how exposure occurs

Exposure is concentrated among people with established illicit opioid use. Risk increases where illicit opioid product content and strength are uncertain and where individuals have

high levels of comorbidity that raise the risk of a drug-induced death. HPSOs appear through several routes within opioid markets, including contamination of heroin or other opioids, mis-selling as heroin or other opioids (including products sold as ‘strong’ heroin or other opioids that mask the true content), falsified opioid medicines and low-volume supply through postal routes or online vendors into opioid-seeking settings. Patterns are uneven across Member States. Where heroin scarcity, fragmented markets, illicit opioid supply volatility or systemic OAT disruptions are present, HPSOs are more likely to become a recurrent feature of drug use. Elsewhere, detections of HPSOs in drug markets remain episodic. HPSOs may circulate alongside heroin and other opioids rather than fully replacing them, but their presence can make the market less predictable and increase the risk of severe harm.

Harm pattern and time to detect harms

In this scenario, harms remain serious but largely concentrated. Severe poisonings and drug-induced deaths from use of HPSOs occur mainly among established opioid-using populations, particularly when potency varies between batches and when mixtures include sedatives such as alpha-2 adrenergic sedatives (e.g. xylazine, medetomidine). These harms may first appear as repeated local clusters of non-fatal poisonings and drug-induced deaths rather than as a clear national trend in routine indicators such as overdose mortality or treatment data. Where monitoring systems and the availability of low-threshold harm reduction services, OAT, take-home naloxone and emergency clinical response are stronger and more diversified, such clusters are more likely to be detected and mitigated early. Where routine toxicological and forensic testing does not keep pace with emerging compounds and mixtures, detection and attribution can lag even when HPSOs remain confined to parts of the illicit opioid market.

Detection and confirmation

The pressure in this scenario is sustained rather than acute. Toxicology and forensic laboratory systems must continue to identify newly emerging compounds, update methods and reference information, and communicate emerging risks to practitioners and frontline workers. There is a risk that harms are not fully detected or correctly attributed where testing is limited or inconsistent. Law enforcement faces repeated low-volume trafficking and distribution challenges involving falsified medicines and other misrepresented products that require rapid product identification and timely feedback from laboratories.

Pressure on services and coordination

The main burden in this scenario is sustained strain on early warning systems and toxicology and forensic capacity, together with a recurrent need to update, disseminate and implement

targeted clinical and operational guidance for frontline staff. Local clusters of non-fatal poisonings and drug-induced deaths linked to use of HPSOs can generate short periods of increased demand on ambulance services, emergency departments, hospitals, and low-threshold treatment and harm reduction services, including OAT. The coordination challenge is to maintain steady readiness and prioritisation over time when harms remain concentrated and do not visibly spread to broader non-opioid contexts. Key risks include staff fatigue, under-resourcing, and delays in strengthening laboratory testing capacity, reporting pathways, information exchange and escalation arrangements.

Protective factors

Established prevention, treatment and harm reduction interventions for opioid use disorder remain broadly protective where access and uptake are sufficient. This includes low-threshold services, take-home naloxone, OAT, and targeted alerts and risk communication for people using opioids and the services in contact with them. Where available, drug checking and supervised consumption services can reduce harm by identifying misrepresented products and supporting rapid outreach during local clusters of harms related to use of HPSOs. Over time, differences between Member States become more pronounced as preparedness and coverage vary.

Systemic risks

Systemic risks arise when surveillance systems, including toxicology and forensic systems, healthcare providers and law enforcement actors at the national level do not have clear arrangements for information exchange and for escalating suspected HPSO-related harm events to a coordinated national cross-sector response. Established arrangements for timely reporting and information sharing with the EU early warning system remain critical. In this scenario, the main risks include delayed confirmation of newly emerging compounds and delayed attribution of emergency presentations and opioid-related deaths where routine toxicological and forensic testing is limited. Sustained strain on toxicology, forensics and early warning functions can lengthen turnaround times and slow the translation of signals into actionable communication. Repeated local clusters can also create continued stress on frontline response systems, including ambulance services, emergency care and low-threshold services. A further risk is that, if harms remain intermittent and geographically concentrated, prioritisation and resourcing may decline over time, leaving gaps in testing coverage, turnaround times and coordination arrangements.

Scenario B: rapid emergence of new highly potent synthetic opioids in products sold as non-opioids and in misrepresented medicines

In scenario B, new HPSOs and high-potency variants appear frequently and are increasingly found in products sold as non-opioids, particularly stimulants and benzodiazepines, and in misrepresented or falsified medicines, including pharmaceutical lookalike tablets. The defining feature is that exposure extends beyond established opioid markets and reaches people with little or no opioid tolerance. Current EU evidence for orphines in products sold as non-opioid drugs or in falsified medicines remains limited. However, the case of probable cychlorphine exposure linked to a benzodiazepine tablet sold online in Germany shows that this pathway is plausible.

Who is exposed and how exposure occurs

Risk extends to opioid-naïve populations, including recreational and intermittent users, people using non-prescribed benzodiazepines, and people obtaining medicines through informal sources or online channels without anticipating opioid content. Exposure can occur through contaminated stimulant powders, benzodiazepine products and misrepresented tablets. Contamination may be geographically uneven when it occurs at specific points in the supply chain, but it can still spread quickly when contaminated products move quickly through local retail distribution, online sales and social-media-based supply. However, these distribution channels are not exclusive to this scenario and may also operate within established opioid markets. Importantly, misrepresented products can move through channels that are harder to identify and may reach people not normally connected to opioid health services, making detection, outreach and response more difficult. In some settings, distribution may rely on informal retail networks that are harder to map in real time than traditional opioid supply chains.

Harm pattern and time to detect harms

Harms can escalate abruptly rather than gradually. Multisite clusters of non-fatal overdoses and increases in drug-induced deaths may occur across multiple cities within short time frames, and presentations may be heterogeneous when mixtures vary, including when HPSOs are mixed with sedatives such as benzodiazepines or alpha-2 adrenergic sedatives (e.g. xylazine and medetomidine) and when opioid exposure is not anticipated. Initial signals may come from clusters of emergency presentations and deaths, before laboratory testing confirms the specific opioids and the contaminated products in circulation. This reduces the

time available for targeted prevention and increases the importance of rapid risk communication and operational coordination, even when full confirmation is not yet available.

Detection and confirmation

Laboratories and medico-legal systems may be under acute pressure due to the volume and complexity of testing required during suspected contamination events. Where routine toxicological and forensic testing is limited, contaminated products can continue to circulate before they are identified and linked to harm patterns. Differences in what types of samples are analysed, whether relevant substances are included in routine screening, the sensitivity of methods used where compounds are present at low concentrations, the availability of reference standards for newly emerging substances, the use of retrospective analysis, and how toxicology findings are reported and communicated can delay laboratory confirmation and reduce shared understanding of the situation, particularly when multiple substances and mixtures appear simultaneously. The challenge is timely and reliable laboratory confirmation that enables targeted alerts and response.

Pressure on services and coordination

This scenario can generate a surge in demand for ambulance services, emergency departments and hospitals, and it can put pressure on toxicology and forensic capacity. Coordination challenges include aligning actions and messaging across health, toxicology or forensic services and law enforcement during evolving events and ensuring that time-critical information can be exchanged quickly within national legal and policy frameworks. Risk communication is more difficult because exposure extends into populations and settings not routinely associated with opioid use and due to uncertainties around the HPSOs and mixtures involved.

Protective factors

In this scenario, protective measures must be scalable and reach beyond services and environments linked to established opioid use. Low-threshold naloxone availability, rapid dissemination of practical overdose management guidance to frontline services, targeted alerts, and tailored prevention messages for populations and settings where tablets, stimulants or non-prescribed medicines are used become more important. The likelihood of wider exposure to HPSOs and higher mortality increases in instances where laboratory testing capacity is constrained; where coordination between health services, toxicology and forensic services, poison centres (where relevant) and law enforcement actors is unclear; or where access to effective treatment for opioid use disorder and harm reduction is limited.

Differences in the coverage, accessibility and surge capacity of these measures can translate into uneven impacts within and between Member States.

Systemic risks

Systemic risks arise when surveillance systems, including toxicology and forensic systems, healthcare providers and law enforcement actors do not have clear arrangements for information exchange and for escalating suspected HPSO-related harm events to a coordinated cross-sector response. In this scenario, the main risks include rapid, geographically dispersed spikes in the number of harm events affecting opioid-naïve populations, local overload of emergency care and laboratory services, and delays in confirming which HPSOs are driving harm when laboratory testing and reporting are under pressure. Fragmented understanding of the situation and inconsistent messaging can reduce the effectiveness of alerts and delay behaviour change, particularly when opioid exposure is not anticipated. A further risk is that repeated high-intensity events draw resources into short-term crisis response, which can leave less capacity for consolidating learning, strengthening protocols and improving readiness for subsequent incidents.

Scenarios A and B at a glance

	Scenario A: Emergence confined to opioid market	**Scenario B: Emergence extends beyond opioid market**
Who is mainly exposed	Mainly people with established illicit opioid use.	Broader populations, including opioid-naïve people exposed through products sold as non-opioids or as medicines.
How exposure occurs	Mainly within illicit opioid markets, including markets for heroin and other opioid products, and through falsified opioid medicines and mis-selling within opioid markets.	Through products sold as non-opioids and in misrepresented or falsified medicines, including stimulants and benzodiazepines.

How harms present	Serious but mainly concentrated, often as repeated local clusters.	More abrupt and geographically dispersed, with multisite clusters linked to products sold as non-opioids or as medicines.
Main pressure on response systems	Sustained strain on toxicology, forensic services, harm reduction and treatment services.	Acute pressure on emergency care, laboratories and multistakeholder coordination during suspected events.
Preparedness priorities	Maintaining readiness, detection capacity, targeted opioid alerts and core opioid response measures, including naloxone access, OAT coverage and low-threshold harm reduction.	Rapid recognition, faster coordination, broader prevention messaging, and the ability to extend protective measures beyond established opioid settings.

Options for response

The options below summarise priority preparedness actions for the near-term two-year period. They complement core protective measures that remain central to preparedness, in particular adequate access to OAT, take-home naloxone and low-threshold services. Higher coverage and continuity of OAT, broad naloxone access and low-threshold harm reduction services, including supervised consumption and drug checking where available and appropriate, remain key protective conditions for reducing the likelihood and severity of HPSO-related harms. These options for response are intended to remain useful across a range of plausible developments and are framed primarily for implementation by Member States and relevant competent authorities. They are informed by, and in some areas can draw on, existing EUDA functions and networks that support monitoring, information exchange and laboratory practice, including the EUDA's laboratory network and related early warning activities that support preparedness. Where HPSOs fall within the scope of the EU early warning system, these options should be understood as operating alongside existing national and EU arrangements for timely reporting, alerting and, where relevant, risk

assessments. Additional and more specific actions will be required depending on national the context and the nature of HPSO-related incidents or outbreaks. The list below should be read as a general priority set rather than an exhaustive response plan.

Options for response

1. **Maintain a shared understanding of the situation at the national level.** Maintain a regular, rapid national review arrangement to combine laboratory findings, acute harm signals and relevant law enforcement information into a brief joint update for designated national authorities and services, supporting timely interpretation and action.

2. **Strengthen national preparedness and contingency planning for HPSO-related harm events.** Ensure that Member States maintain or develop coordinated preparedness and response plans, including predefined escalation mechanisms, surge capacity for services, and cross-sector coordination arrangements to enable rapid response to suspected HPSO-related incidents.

3. **Set national toxicological screening priorities and a rapid update process.** Maintain an agreed minimum set of national screening priorities for HPSOs and sedatives in defined high-risk situations, together with a clear process for rapidly updating those priorities when new substances or sedative admixtures emerge.

4. **Shorten the detection-to-action pathway for misrepresentation and unexpected opioid detections.** Ensure that suspected misrepresentation or unexpected opioid detections in products sold as non-opioids, or in people not known to have intended opioid use, lead to rapid targeted testing, timely risk communication and agreed follow-up actions across health and law enforcement services.

5. **Maintain mutual national support arrangements for surge laboratory testing and confirmation.** Maintain arrangements that allow designated national laboratories to provide toxicological testing and confirmatory support during suspected HPSO-related harm events. National arrangements should also make clear how smaller or non-specialist laboratories can rapidly request that support.

6. **Strengthen national and EU-level early warning, alert and risk communication arrangements for relevant HPSO events.** Where HPSOs fall within the scope of the EU early warning system, ensure timely reporting through competent national authorities and national focal points. Member States should use existing national early warning, alert, information exchange and risk assessment arrangements where these are in place and strengthen or establish national mechanisms where current

arrangements do not allow timely communication to affected services, frontline responders or at-risk populations.

7. **Strengthen surge-capable take-home naloxone distribution and low-barrier access to OAT.** Ensure arrangements are in place, including legal and regulatory provisions, that allow rapid expansion of take-home naloxone distribution when harm indicators rise. Ensure also low-barrier access to OAT, including rapid initiation or re-entry at appropriate scale. Both take-home naloxone and low-barrier access to OAT should be widely available in the community and custodial settings. Together, these measures can reduce overdose risk, support engagement with care, and lessen pressure on ambulance services and emergency departments.

8. **Agree on predefined indicators and thresholds for rapid cross-sector review and action.** Agree on a set of key indicators and thresholds that, when reached, prompt rapid cross-sector convening, evaluation of the signals and early response measures, including risk communication and operational prioritisation. Examples may include an unusual cluster of non-fatal poisonings or drug-induced deaths in a specific area, repeated detection of HPSOs in misrepresented products or the detection of opioids in products sold as non-opioids.

9. **Use agreed minimum templates for information exchange between health and law enforcement agencies during suspected HPSO-related harm events.** Where useful, use agreed minimum specifications and simple templates within existing national information exchange arrangements so that key information can be shared quickly and consistently during suspected HPSO-related harm events. This may include, where relevant, the substance or product involved, the date and place of detection, the type of event or harm observed, the analytical status, whether the product was misrepresented, any known exposure circumstances and contact points for follow-up.

10. **Maintain rapidly updated guidance for clinical management of overdoses.** Maintain a process for rapid updates and dissemination of short, practice-oriented guidance for complex overdoses, including where sedatives and other adulterants are involved.

Conclusions

At the current time, this scenario-based assessment indicates a plausible risk of the further emergence of HPSOs in Europe. The scale and pattern of harms are likely to vary across Member States and may be shaped not only by differences in laboratory capacity, local drug market conditions and the reach of key interventions such as OAT and naloxone but also by the level and nature of exposure to HPSOs.

The current assessment is based primarily on early signals, laboratory detections, targeted monitoring sources, clinical observations and salient law enforcement seizures rather than on representative prevalence measurement and should therefore be read as a structured summary of the available evidence rather than a quantified estimate of prevalence and harms. Within these constraints, available signals indicate continuing change in substances, product presentations and exposure pathways that can extend beyond established opioid-using populations, particularly via misrepresented products and falsified medicine tablets.

Recent European experience also illustrates that severe outcomes can concentrate in local contexts where detection, treatment and harm reduction coverage and cross-sector coordination are more constrained. This reinforces the case for prioritising minimum readiness across Member States, including timely laboratory confirmation, predefined indicators for cross-sector review and action, clear arrangements for information exchange and the ability to scale protective measures rapidly during spikes in the number of localised HPSO-related harm events.

International experience from North America and Australia indicates that patterns of harm linked to HPSOs can change within short time frames. This does not imply a similar trajectory for Europe, but it underlines the importance of maintaining preparedness arrangements that support early recognition, timely laboratory confirmation, clear situational understanding, and effective response when HPSO-related harms increase or when misrepresented products are detected.

Taken together, the assessment supports a preparedness approach that strengthens early detection and interpretation, reduces vulnerabilities associated with uneven readiness and supports effective response to spikes in localised harm events and acute opioid toxicity. Member States should therefore remain alert not only to new nitazenes but also to the emergence of other high-potency opioid families, including orphines.

The EUDA can support Member States through its monitoring, threat assessment, alerts and laboratory network activities. Preparedness also requires attention to wider conditions that can accelerate change, including instability in established illicit opioid supply, shifts in production and trafficking patterns following controls and disruptions, increased misrepresentation in tablet products, and changes in the availability of key harm reduction and treatment interventions.

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Glossary

Drivers are factors already influencing highly potent synthetic opioid (HPSO) emergence, supply, exposure pathways, harms or system readiness; drivers in this threat assessment are used to explain the current baseline and to inform scenario logic.

Falsified medicines are medicines that are fake and resemble legitimate medicines. In this report, the term is used for fake medicine-like products that pose a public health risk because their identity, composition or potency is not what they are presented or sold to be. This use follows the European Medicines Agency distinction between falsified medicines and counterfeit medicines.

HPSOs (highly potent synthetic opioids) are, within the scope of this threat assessment, synthetic opioids that pose a substantial overdose risk due to high potency at low doses. This includes, but is not limited to, nitazene derivatives (e.g. isotonitazene, metonitazene, etonitazene), highly potent fentanyl analogues such as carfentanil and other newly emerging potent synthetic opioids that are newly appearing or re-emerging in novel forms or contexts, including in falsified pharmaceutical products or in ways that may displace traditional opioids in established markets. Fentanyl and less-potent fentanyl analogues are considered only where they coexist or interact with higher-potency opioids or materially shape HPSO risk pathways; heroin, morphine, methadone, buprenorphine, tramadol and other drugs traditionally not considered HPSOs are outside the scope of this threat assessment.

Misrepresented products are illicit drug products whose identity, composition or potency is presented or is likely to be perceived as something other than what it actually is, in ways that materially increase overdose risk. The harm arises primarily from false expectations about substance class and potency, rather than from adulteration alone. This includes falsified medicines (e.g. opioid-, benzodiazepine- or stimulant-branded pills) that contain highly potent synthetic opioids; tablets or powders mis-sold as heroin; non-opioid drugs (e.g. benzodiazepines or stimulants) adulterated with synthetic opioids; and products whose branding, colour, logos or street names mimic a familiar drug while masking markedly different pharmacological content.

Naloxone (availability and distribution) is an umbrella term used in this report to cover naloxone access across settings, including community take-home naloxone programmes where implemented, and naloxone carriage/access/use in frontline response settings (e.g. ambulance/emergency medical services, emergency departments, custodial settings and, where applicable, police or outreach services).

Signals are early indications of potential emergence, change or increased risk, drawn from sources such as early warning system notifications, law enforcement seizures, sentinel

toxicology, clinical surveillance or drug checking; signals are used for early warning interpretation and scenario framing and are not treated as prevalence measures.

Take-home naloxone is naloxone distributed to the community and intended for lay administration (e.g. by peers, family members or service staff) to reverse opioid overdose outside clinical settings. This term is used in this report only when this specific programme modality is intended.

Uncertainty refers to a factor relevant to highly potent synthetic opioid (HPSO) risk that could plausibly evolve in more than one direction over the assessment two-year time frame and where different plausible states would materially change exposure pathways, harm patterns, or the feasibility and prioritisation of response options. In this report, uncertainties are used to structure scenario development and to test preparedness under alternative but plausible conditions; they are distinct from drivers, which are factors already observable and shaping the current baseline.

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Annexes

Annex 1. EUDA scenario-based health and security threat assessment: methods and limitations

This threat assessment applied the EUDA's scenario-based threat assessment approach to assess the evolving risk posed by HPSOs over a two-year period. The approach combines structured synthesis of available European signals with expert input to identify key drivers and uncertainties, develop contrasting but plausible scenarios, and formulate implications and priority options for response. The assessment is scenario-based and is intended to support preparedness and decision-readiness under uncertainty rather than to forecast a single expected trajectory. The analytical approach applied in this assessment was adapted from common foresight methodology, including horizon scanning, trend and driver analysis, the identification of critical uncertainties and scenario development, drawing on the United Nations Development Programme foresight manual and the EUDA foresight toolkit for the drugs field (UNDP, 2018; EUDA, 2025a).

Expert input

Internal and external subject-matter experts (SMEs) contributed input at inception, during the review of stage 1 outputs (signals, drivers and uncertainties), through structured ranking of uncertainties by likelihood and impact, and through a structured workshop to test scenarios, implications, options for response and key messages. Internal EUDA input drew on five SMEs spanning policy, security analysis, health expertise and early warning information, supporting cross-domain interpretation of signals and response feasibility. External expert input was multidisciplinary and included experts from Belgium, Bulgaria, Denmark, Estonia, Ireland, Greece, the Netherlands, Poland, Portugal, Finland and Sweden, and included participation from the European Union Agency for Law Enforcement Cooperation (Europol). Expertise represented included clinical and emergency medicine and poison information, forensic and analytical toxicology (including post-mortem), public health and early warning information, drug market research, and law enforcement and strategic intelligence analysis. While this engagement strengthened triangulation and helped identify overstatements and missing considerations, expert consultation is not a representative sample of all national perspectives or professional communities, and views may differ across sectors and countries. The assessment therefore treats expert contributions as structured judgement used to support sense-making and scenario testing rather than as consensus evidence or formal endorsement of conclusions.

Process and timeline

The threat assessment was launched on 10 November 2025 and progressed through staged outputs and iterative review. A baseline situational picture was developed, including a structured compilation of signals and an assessment of drivers and uncertainties. A short national focal point pulse survey was fielded in parallel to capture a rapid snapshot of exposure status and perceived readiness. Drivers and uncertainties were reviewed through internal and external expert input. Uncertainties were then prioritised and used to define the scenario axes. Scenario narratives, implications and options for response were drafted and tested through internal review and a half-day workshop with external SMEs (26 January 2026). A consolidated draft (v1.0) was issued on 2 February 2026 and prepared for written review by internal and external SMEs. AI-supported scientific editing tools were used for editorial support and internal consistency checks. All outputs were reviewed and revised by the authors.

Signal identification and synthesis

Signals were defined as early indications of potential emergence, change or increased risk related to HPSOs. Signals were drawn from multiple complementary sources, including EU early warning system notifications, law enforcement seizure information, toxicology and sentinel monitoring including syringe residue analysis data from the European Syringe Collection and Analysis Project Enterprise (Escape), hospital emergency data from the European Drug Emergencies Network (Euro-DEN Plus), and other relevant analytical or reporting streams available to the agency. Signals were included where they plausibly indicated the presence, emergence or changing characteristics of HPSOs and could have implications for harm, exposure or preparedness, including where evidence was incomplete. Both analytically confirmed and suspected signals were retained to reflect the early warning purpose of the assessment. Confirmed findings (e.g. laboratory-verified detections) were distinguished from provisional observations (e.g. early clinical reports or field intelligence), which were interpreted cautiously and not treated as evidence of prevalence or trend.

Where the same underlying event or episode was reported across multiple sources, signals were linked and consolidated to avoid double counting. Multiple references to the same event were treated as triangulation, increasing interpretive confidence without inflating signal frequency. Curation prioritised (i) first detections or first appearances of relevant substances or product forms at the national or sub-national level and (ii) high-salience events likely to alter risk or preparedness needs (e.g. poisoning clusters, marked mortality changes or significant seizures of falsified medicine tablets). Each signal was characterised, where information allowed, by signal type (e.g. analytical detection, clinical observation, seizure, alert), substance or product form, exposure context or affected population, geographic scope and time window.

Geographic scope covered the EU Member States, with Norway and Türkiye included where signals were available. Selected non-EU neighbouring countries (e.g. Switzerland, the United Kingdom) were included as contextual reference points. The resulting signal synthesis informed the situational picture and subsequent analytical stages rather than as a comprehensive or representative inventory.

National focal point pulse survey (exposure and readiness)

A short national focal point pulse survey was administered via EUSurvey to Reitox network national focal points in the Member States plus Norway and Türkiye to capture a rapid, structured snapshot of national exposure status and perceived readiness to respond to HPSO-related risks (*N* = 28 responses). The survey captured (i) an ordinal exposure status item with explicit definitions (unknown / not enough data; no exposure / very early stage; early signs; established exposure); (ii) self-rated readiness on a 1–5 scale across early warning and detection systems, laboratory/forensic capacity, coordination between institutions and emergency response capacity; (iii) short free-text inputs on two key national factors influencing the situation and one priority uncertainty over the next two years; and (iv) perceived change in heroin availability over the past five years and, where decreased, likely reasons for change. Outputs were used to characterise heterogeneity and to inform preparedness profiling, and these points were interpreted as indicative inputs rather than as a performance assessment.

Drivers and uncertainties

Drivers were treated as factors currently shaping the HPSO situation and influencing how risk may evolve over the near-term two-year period. Uncertainties were formulated as factors that could plausibly take different directions over the period and materially change exposure pathways, harm patterns or response requirements. Drivers and uncertainties were developed through structured synthesis of the situational picture and expert input and then consolidated for use in scenario framing.

Uncertainty prioritisation (expert ranking survey)

Key uncertainties were prioritised through a structured expert ranking exercise using EU Survey. Experts scored each uncertainty on two dimensions over the near-term two-year period: likelihood and potential impact (both on 1–10 scales). A total of 17 responses were received (4 internal and 13 external SMEs). Results were used to identify the highest-salience uncertainties for scenario framing and to support transparency regarding why specific uncertainties were selected as scenario axes. The ranking was treated as structured

expert judgement to inform scenario construction rather than as a predictive model or a statistical estimate.

Scenario framing and development

Scenarios were constructed using a 2 × 2 matrix anchored in the two highest-salience uncertainties over the near-term two-year period, generating contrasting but plausible evolutions of exposure and harm. Scenario narratives were developed to explore different exposure pathways and escalation dynamics, recognising that elements of these pathways have already been observed in some Member States. Scenarios were used as analytical devices to test preparedness and response under uncertainty and to identify implications and options that remain relevant across futures, rather than to select a single expected outcome.

Implications and options for response

Implications were developed by assessing how each scenario could affect preparedness domains, including detection and monitoring, coordination and governance, and response capacity and service delivery. Options for response were formulated as a general priority set intended to strengthen preparedness across plausible developments, with emphasis on measures that can be scaled in proportion to risk and remain useful under different patterns of HPSO emergence and harm events.

Expert review and iteration

Draft outputs were iteratively reviewed internally and externally. External SMEs contributed both to the refinement and prioritisation of uncertainties and to the validation of scenario implications and response options through a structured half-day workshop (26 January 2026) with breakout discussions by scenario. Workshop inputs were synthesised from meeting transcripts and structured whiteboard outputs. The consolidated draft (v1.0) issued on 2 February 2026 incorporates recurrent expert feedback and refinements to implications, options for response and key messages. These points were prepared for written review by internal and external SMEs.

Limitations

This assessment is constrained by heterogeneous data coverage, data quality and reporting timeliness across Member States, including differences in toxicology practice, post-mortem investigation, case ascertainment and the availability of sentinel monitoring. The situational picture relies substantially on signal-based information (e.g. drug seizures, alerts, residue

analysis, poisoning clusters) that is well suited to early warning notifications and scenario framing but is not designed to generate representative prevalence or incidence estimates, nor is it able to support comparative burden measurement across countries. Signal frequency is influenced by monitoring intensity and investigative activity and therefore cannot be interpreted as a proxy for underlying exposure levels, and apparent geographic clustering may reflect where monitoring and confirmation systems are more developed rather than where HPSOs are absent or present at lower levels. Delays between market emergence, clinical events, detection, confirmation and reporting can obscure early diffusion and distort apparent timing or sequencing, and some mortality, toxicology and seizure data remain provisional and may be revised as investigations and reporting are completed.

Cross-country comparability is further limited by heterogeneity in opioid market structures and baseline opioid use patterns (e.g. heroin-dominant versus other synthetic or pharmaceutical opioids), which constrains the generalisation of substitution dynamics. In addition, darknet, social-commerce and peer-to-peer distribution channels are only partially captured in routine monitoring, and their contribution to availability, misrepresentation and diffusion remains uncertain. Survey inputs reflect self-reported information and structured expert judgement and may be affected by reporting and comparability biases.

Annex 2. Drivers of highly potent synthetic opioid emergence and spread in Europe

Definition of ‘drivers’: observable, directional and independent forces already acting in the EU that shape HPSO emergence, early diffusion, harm severity and detection frictions over the next 24 months.

This annex summarises drivers already influencing the emergence, supply, exposure pathways and harms of HPSOs in Europe. Each driver is classified using a ‘Pestle’ domain (‘political’, ‘economic’, ‘social’, ‘technological’, ‘legal’ or ‘environmental’). The ‘driver’ column names the factor, ‘directional impact on HPSO risk’ provides a short statement of its current effect on HPSO-related risk (e.g. increasing supply, lowering barriers to distribution, increasing exposure, worsening health outcomes) and ‘description’ briefly explains what the driver is and why it matters operationally. ‘Trajectory (↑/↓/↔)’ indicates whether the driver is increasing, decreasing or broadly stable. ‘Trajectory’ is used here as an indicative qualitative expert judgement on the recent direction of each driver (increasing, decreasing or broadly stable), based on the evidence reviewed for this assessment. It does not represent a quantitative trend estimate or forecast. ‘Scope of influence’ indicates how widely the driver applies across Member States (EU-wide, regional or localised) and is included as contextual information to support expert review and downstream scenario analysis; it does not quantify impact or priority. ‘Source/notes’ provides short references or clarifying comments on the basis for inclusion.

Political drivers

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory: ↑ increasing/↓ decreasing/↔ stable	Scope of influence	Source/notes
Political	External supply shocks (e.g. the opium ban in Afghanistan)	Risk-increasing	Politically driven disruptions in heroin supply (availability, purity, price) can alter market conditions and purchasing behaviour, creating incentives for higher-potency opioid products in some contexts. Effects are not uniform and	↔	EU-wide	EUDA and Europol 2024; EUDA, 2025c

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory: ↑ increasing/↓ decreasing/↔ stable	Scope of influence	Source/notes
			may vary by route, market structure and national conditions.			
Political	Exposure linked to geopolitical trafficking corridors	Risk-increasing	Border controls and geopolitical disruption can drive adaptive rerouting and cross-border micro-flows via alternative corridors, particularly affecting eastern and Baltic-adjacent Member States. In parallel, closures or intensified controls on some routes may suppress specific corridors, creating a mixed and rapidly shifting exposure picture.	↔	Regional	NFP survey input
Political	EU-level prioritisation of synthetic opioids (EWS / European multidisciplinary platform against criminal threats / European Ports Alliance)	Risk-reducing	EU-level prioritisation can accelerate cross-sector attention, information sharing and mobilisation of analytical and operational support. Translation into measurable preparedness gains depends on national resourcing and implementation.	↔	EU-wide	EUDA and Europol 2024 (emphasis on logistics hubs and coordination); EU drug strategies Contextual references: United Nations Office on Drugs and Crime early warning advisory; UK early warning reporting (as external comparator)
Political, legal	EU-level legal frameworks revision	Risk-reducing	Discussions are ongoing to revise the national legal framework based on EU regulations (Council Regulation (EC)	↑	EU-wide	National hearing in the French Senat, 2025

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory: ↑ increasing/↓ decreasing/↔ stable	Scope of influence	Source/notes
	to improve detection and seizures		No 111/2005 of 22 December 2004 laying down rules for the monitoring of trade between the Community and third countries in drug precursors and related acts).			
Political	Regional and international cooperation	Risk-reducing	Dialogue and cooperation between the EU, in sourcing and transit contexts, and affected partner countries (including the United States and the United Kingdom) supports intelligence sharing, joint situational awareness and faster interpretation of emerging signals.	↔	EU-wide	EUDA, 2025b; European Commission, 2025 Contextual references: UK early warning reporting (as external comparator); US reporting on synthetic opioid market complexity
Political	Increased national preparedness activities to respond to HPSOs	Risk-reducing	Preparedness activity is increasing in some Member States (e.g. expanded toxicology panels, protocols, naloxone initiatives, guidance updates), but progress depends on sustained resourcing and political will. Maturity and implementation phase vary substantially across Member States, creating uneven readiness.	↔	Regional	Examples: a preparedn from the Netherlands (Kools et al., 2025), a national hearing in the French Senat (Sénat, 2025) and Ireland's national naloxone programme.
Political	War and geopolitical instability affecting	Risk-increasing	War and geopolitical instability can reduce state control in specific areas, creating opportunities for illicit production, trafficking adaptation and route diversification. These	↔	EU-wide	EUDA, 2025b

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory: ↑ increasing/↓ decreasing/↔ stable	Scope of influence	Source/notes
	production and trafficking		dynamics can increase uncertainty about source areas, intermediaries and product composition reaching European markets.			
Political, social, economic	Cuts in social and health policy fundings	Risk-increasing	Shifts in political priorities and constrained public budgets can reduce or delay investment in harm reduction, treatment and monitoring. Even where strategies exist, uneven adoption and implementation can weaken coverage, increasing population vulnerability and slowing detection and response.	↔	Regional	EUDA (2024b)

NB: EDR, European drug report; NFP, national focal point.

Economic drivers

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory (↑/↓/↔)	Scope of influence	Source/notes
Economic	High-potency / low-volume economics	Risk-increasing	The value-to-weight advantage of HPSOs sustains viability through micro-shipments and concealment.	↔	EU-wide	EUDA and Europol, 2024
Economic	Grey-market online access to medicinal opioids	Risk-increasing	Unregulated online vendors expand access to adulterated/falsified opioid medicines containing HPSOs.	↔	EU-wide	NFP survey input
Economic	Falsified pill channels expanding	Risk-increasing	Pressed tablets and falsified products increase profitability and can extend exposure beyond established opioid-using populations.	↔	EU-wide	Friedman and Ciccarone (2025); Kools et al., 2025
Economic	Limited but documented mixing and packaging signals in the EU	Risk-increasing	Documented examples of small-scale mixing/packaging of pill/tablet forms within the EU indicate feasibility of short local supply steps; evidence remains sparse and uneven across Member States.	↔	EU-wide	EU drug market: NPS (mixing/packaging; see the case from Latvia from 2020); Ireland forensic reporting example (nitazene-related packaging seizure)

NB: NFP, national focal point.

Social drivers

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory (↑/↓/↔)	Scope of influence	Source/notes
Social	Changes in the traditional opioid-using population	Risk-increasing	Shifts away from heroin use in some contexts, combined with changing consumption preferences and product formats (including tablets and other non-injectable forms), can create openings for higher-potency opioids within existing markets. Effects are uneven across Member States.	↔	Regional	EUDA and Europol, 2024
Social	Uneven awareness of HPSO risks among users	Risk-increasing	Limited or delayed awareness of HPSO potency, duration of action and adulteration risks can increase overdose risk, particularly among people with low or no opioid tolerance. Awareness levels vary substantially across Member States and user groups.	↔	EU-wide	NFP survey input
Social	Sedative co-use and polysubstance patterns	Risk-increasing	Co-use of non-opioid sedatives alongside opioids can amplify overdose risk and complicate clinical management. Naloxone remains recommended for suspected opioid effects but does not reverse non-opioid sedatives, which may prolong or complicate response	↔	EU-wide	Euro-DEN Plus; Escape; international clinical guidance
Social	Stigmatising ‘zombie drug’ narratives	Risk-increasing	Stigmatising narratives associated with highly visible intoxication can increase social exclusion, reduce help seeking and create barriers to harm reduction and treatment access, including for HPSO users.	↔	EU-wide	Media analysis; SME input

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory (↑/↓/↔)	Scope of influence	Source/notes
Social	Official-looking packaging and misrepresentation	Risk-increasing	Official-looking packaging and pharmaceutical presentation can create false perceptions of safety and dosing certainty, increasing the likelihood of accidental exposure and overdose.	↔	EU-wide	NFP survey input; drug-checking services
Social	Declining heroin purity or availability in specific contexts	Risk-increasing	Reductions in heroin purity or availability observed in some Member States can increase market volatility and experimentation with alternative opioids; this pattern is not uniform across the EU.	↔	Regional	NFP survey input
Social	Ageing opioid-using populations and comorbidities	Risk-increasing	Older age and higher prevalence of comorbidities among some opioid-using populations can increase vulnerability to high-potency opioids and adverse outcomes.	↔	EU-wide	EUDA and Europol, 2024
Social	Uneven coverage of harm reduction services	Risk-increasing	Uneven access to harm reduction measures (including drug checking and take-home naloxone formulations) across Member States creates different levels of protection against HPSO-related harms.	↔	EU-wide	NFP survey input; national reports

NB: Escape, European Syringe Collection and Analysis Project Enterprise; Euro-DEN Plus, European Drug Emergencies Network; NFP, national focal point.

Technological drivers

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory (↑/↓/↔)	Scope of influence	Source/notes
Technological	Online retailing, encrypted communications and micro-shipments	Risk-increasing	Encrypted communications, online marketplaces and parcel logistics can sustain availability and distribution; disruption effects are often short-lived and adaptive.	↔	EU-wide	Broadhurst et al., 2021 on darknet seizures/displacement
Technological	Falsified tablet production and small-batch mixing	Risk-increasing	Low-cost tablet presses, small-batch mixing and local packaging can facilitate tablet diffusion and increase exposure through misrepresented products, including among non-injecting groups.	↔	EU-wide	EUDA and Europol, 2024
Technological	Expansion of monitoring (wastewater monitoring, syringe residue testing, test purchases, drug checking)	Risk-reducing	Sentinel tools are being promoted/used in some Member States, shortening detection-to-action times; coverage remains uneven.	↑	Regional	EUDA, 2025b
Technological	Detection and toxicology coverage	Mixed	Screening expansion since 2023 has reduced blind spots in some settings, but coverage, turnaround	↔	EU-wide	EWS and European drug alert system surveys and publications

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory (↑/↓/↔)	Scope of influence	Source/notes
	improving but uneven		and panel breadth remain variable across Member States.			
Technological	Cross-border online retail spillover	Risk-increasing	High online availability in neighbouring regions may contribute to cross-border exposure through e-commerce and informal supply, though patterns are uneven.	↔	Regional	NFP survey input
Technological	Use of EU logistics hubs for trafficking	Risk-increasing	Criminal use of major ports/parcel networks persists, implying displacement risks.	↔	Regional	EUDA and Europol.2024
Technological, legal	Precursor availability and chemical innovation	Risk-increasing	Global chemical supply chains and clandestine production capacity can enable rapid development of new opioids and precursor substitutions, potentially outpacing controls and sustaining analogue turnover.	↔	EU-wide	EUDA and Europol, 2024; EUDA 2025c

NB: EDR, European drug report; EWS, EU early warning system; NFP, national focal point.

Legal drivers

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory (↑/↓/↔)	Scope of influence	Source/notes
Legal	EU/national rapid control and EWS coordination	Risk-reducing	Faster notices, risk communications and joint actions are in effect; timeliness and implementation vary across national systems.	↔	EU-wide	EUDA, 2025b; EWS reports
Legal	Scheduling of drugs in the origin countries	Mixed	Controls in major source countries, particularly China, can reduce the availability of some synthetic opioids and relevant precursors, but may also contribute to substitution of new compounds, alternative opioid families or precursor routes, thereby sustaining innovation pressure.	↔	EU-wide	EUDA 2025c; EUDA and Europol, 2024
Legal	Routine toxicology limitations in detecting HPSOs	Risk-increasing	Routine forensic/toxicology workflows in some Member States cannot reliably detect emerging HPSOs (including at very low concentrations), sustaining detection blind spots and delays.	↔	Regional	NFP survey input
Legal	Uneven access to OAT and naloxone	Risk-increasing	Uneven coverage and access to opioid OAT and take-home naloxone across Member States sustains population vulnerability and contributes to unequal outcomes.	↔	EU-wide	EUDA, 2025b (response gaps); legal and policy correspondents' meeting, 2025

NB: EDR, European drug report; EWS, EU early warning system; NFP, national focal point.

Environmental drivers

Domain	Driver	Directional impact on HPSO risk	Description	Trajectory (↑/↓/↔)	Scope of influence	Source/notes
Environmental	Sentinel environments expanding (Emergency departments, syringe residue, wastewater monitoring)	Risk-reducing	Expanded sentinel environments improve local signal capture and can support more targeted alerts and outreach; coverage remains uneven across Member States.	↑	Regional	EUDA, 2025b; Giraudon et al., 2025
Environmental	Regional clustering in the Baltic states with wider spillover signals	Risk-increasing	High mortality and recurrent detections in the Baltic region, alongside identifications in multiple Member States, indicate an uneven footprint with potential for episodic spillover beyond core hotspots.	↔	Regional	EUDA, 2025b; EUDA and Europol, 2024

Annex 3. Uncertainties shaping highly potent synthetic opioid emergence and spread

Definition of ‘uncertainties’: an uncertainty is a critical unknown with two or more plausible states whose resolution within 24 months would materially change HPSO risk or response.

This annex summarises the main uncertainties that could materially change HPSO-related risks over the next 24 months. Unlike drivers, which describe pressures already acting on the current situation, uncertainties concern future developments that could plausibly evolve in different directions and lead to different implications for exposure, harms and preparedness.

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
Stability of OAT and other key medicines supply (commercial + shortage shocks): (A) stable OAT/medicine supply or (B) disruptions, withdrawals or pricing shifts reducing access	Treatment disruptions affect vulnerability to HPSOs.	24 months	Health; governance; markets	Commercial or regulatory shifts may interrupt OAT availability and destabilise protective treatment coverage.	European Medicines Agency notices; regulatory and market intelligence	European Medicines Agency; SME input; national regulatory bodies
Emergence of novel synthetic opioids: (A) incremental evolution within known classes (nitazenes/fentanyls) or (B) the rapid emergence of new high-potency opioid families (e.g. orphines or other potent synthetic opioids)	New opioid families may outpace detection and control systems.	24 months	Forensics; markets; health; governance	Rapid emergence of new opioid classes would challenge toxicology, legal frameworks and monitoring capacity across Member States.	First detections of new families; analogue clusters in drug-checking / post-mortem data; EWS ‘unknown opioid’ alerts; police and customs seizures; emergence signals from Estonia;	NFP pulse survey

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
					international comparator evidence	
Depth of heroin supply contraction: (A) contraction deepens, increasing substitution pressure or (B) supply stabilises, leading to low substitution pressure	Determines substitution momentum towards HPSOs.	24 months	Health; markets; law enforcement; governance	Falling heroin purity and availability accelerates synthetic opioid uptake; stable supply tempers substitution pressures.	Price/purity trends; heroin seizures; substitution reports from services; satellite imagery from opium-producing countries	Caulkins et al., 2024; NFP pulse survey
Effectiveness of China's nitazene controls: (A) controls reducing flow, and switching/substitution to other opioid families increasing or (B) controls weak, and nitazenes and other HPSO remaining prevalent	Shapes upstream availability and analogue evolution.	24 months	Markets; governance; law enforcement; forensics	Effective scheduling may suppress nitazenes but prompt analogue switching; weak enforcement sustains existing flows.	Nitazene detections in the EU; drug testing for nitazene contamination; emergence of new opioid analogues; postal/parcel routing changes; evidence of switching after control actions	EU drug market: NPS, 2024; Wang and Lassi 2022
Relocation of precursor and synthesis sourcing: (A) supply chains shifting to India / other regions or (B) China remaining the dominant source	Relocation alters trafficking routes and enforcement burdens.	24 months	Markets; law enforcement; governance	Shifts in precursor and synthesis sourcing may reconfigure exposure pathways and enforcement pressure points. May include more distributed/small-scale synthesis.	Mentions of new brokers; 4-anilino-*N*-phenethylpiperidine- and *N*-phenethyl-4-piperidone-analogue seizures; new courier or postal patterns;	Wang and Lassi, 2022; EUDA crime, markets and precursors monitoring

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
					alerts from newly engaged border control authorities	
Pace of falsified tablet diffusion: (A) broad diffusion across EU markets or (B) containment in specific niches/clusters	Determines exposure among opioid-naïve and younger users.	24 months	Health; markets; communications	Tablet formats enable discreet dosing and can broaden the at-risk population beyond traditional opioid users.	Pill-form HPSO seizures; youth toxicology positives; darknet/online pill listings; overdose deaths among people consuming tablets (thinking they were benzodiazepines), platform-based/social-commerce pill listings; tablet shift seen in Ireland (public reporting)	Friedman and Ciccarone, 2025; EUDA and Europol, 2024
Sedative admixture penetration: (A) sporadic and contained or (B) becoming widespread in opioid supply	Increases overdose severity and complexity of clinical management.	24 months	Health; forensics; communications	Widespread sedative mixing (e.g. xylazine/medetomidine) would complicate overdose management.	Co-detections in toxicology; persistent sedation by emergency medical services after naloxone; wound/necrosis presentations where relevant	Copeland et al., 2024; EUDA, 2025b; evidence from the United States

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
Online supply resilience under enforcement, and platform moderation and payment/parcel controls in place: (A) sustained suppression of key markets or (B) rapid vendor displacement and resilient supply	Determines persistence and accessibility of online HPSO markets.	24 months	Law enforcement; markets; governance	Enforcement shocks can temporarily disrupt supply but markets may rapidly adapt and migrate. Outcomes depend on platform policies, parcel oversight and payment anonymity regulation (not only in law enforcement operations).	Darknet monitoring; darknet takedowns; vendor migration to new platforms; short-term price and availability changes, platform policy changes; payment restrictions; parcel screening changes	Broadhurst et al., 2021 on darknet seizures/displacement; EUDA and Europol, 2024
Forensic/toxicology capacity: (A) scaling up and a reduction in detection lag or (B) patchy capacity with persisting delays	Detection gaps delay alerts and responses.	24 months	Forensics; governance; health	Variable capacity and slow method adoption increase the risk of blind spots that mask HPSO spread. Capacity depends on staffing and equipment, and (in some Member States) there is limited access to post-mortem toxicology.	Panel expansion; EWS time-to-alert; lab backlogs versus additional resourcing; post-mortem toxicology coverage / turnaround times / validation backlogs / external quality assurance participation	EUDA, 2025b Note: Post-mortem kinetics/stability can affect detectability.
Coverage and continuity of OAT: (A) expanding coverage and improving continuity or (B) stagnating/contracting	OAT coverage and continuity reduce overdose risk and stabilise	24 months	Health; governance; communications	Changes in OAT coverage/continuity materially shape population vulnerability to high-potency opioids	OAT coverage estimates (harm reduction / opioid users in treatment); policy changes	EUDA national treatment indicators; national health ministry reporting

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
coverage and persisting continuity gaps	high-risk opioid use populations; uneven provision can amplify vulnerability under HPSO market shocks. Linked drivers include uneven OAT access; policy/funding shifts; service capacity.			and the severity of harm waves. Divergent Member State trajectories can widen readiness gaps.	affecting eligibility/retention; waiting times / clinic capacity indicators	
Access to and implementation of take-home naloxone: (A) expanding access and improving implementation or (B) access remaining limited and implementation remaining patchy	Wider naloxone availability and effective delivery models can reduce fatal outcomes during HPSO-related overdose waves; limited access can increase mortality and strain emergency services. Linked	24 months	Health; emergency response; governance	The public-health impact of HPSO events is strongly shaped by naloxone coverage and operational delivery (distribution channels, training and uptake). Cross-country differences can produce markedly different outcomes under similar exposure.	Regulatory changes for take-home naloxone / supply; distribution volumes / coverage proxies; implementation signals (training uptake / programme scale)	EUDA harm reduction reporting; national programme documents; expert judgement

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
	drivers include regulatory constraints; funding; first-responder/public readiness.					
Public-health funding for opioid response: (A) funding maintained or increased or (B) funding eroded due to competing priorities	Funding determines the resilience of prevention, treatment and early warning systems, as well as impacting laboratory surge capacity and monitoring.	24 months	Governance; health; social	Geopolitical and economic pressures may divert budgets away from harm reduction, OAT and monitoring, weakening response capacity.	Budget lines for harm reduction, OAT and EWS; reports of service reductions; delays in naloxone rollout	NFP pulse survey (including experts in Germany, Latvia, Romania and Sweden); EUDA 2024b
An ageing cohort versus a new opioid-user generation: (A) no substantial new cohort and demand contracts or (B) new recruits emerging and demand stabilising or growing	Shapes long-term susceptibility and market size for HPSOs.	24 months	Social; markets; health	An ageing heroin cohort reduces demand unless younger users emerge as a result of falsified pills or prescription misuse.	Average age of treatment entrants; trends in under-25 opioid clients; overdose demographics by age	TDI; DRD
Quality of risk communication and level of public trust: (A) trusted, practical communications	Influences service uptake, help seeking	24 months	Communications; governance; health	Stigmatising discourse increases social distance and may deter	Media content analyses; stigma surveys; harm	Sumnall et al., 2025; national media monitoring

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
ensuring service use or (B) fragmented/sensationalised communications reducing service uptake	and public support.			people from engaging with services.	reduction service utilisation trends	
Geographic diffusion trajectory: (A) concentrated in a few Member States or clusters or (B) multi-country urban outbreaks emerging	Determines the scale of coordination and the resource needs.	24 months	Health; markets; law enforcement	Current clusters (e.g. the Baltic states, Ireland and the United Kingdom) may remain localised or use may expand to other major EU urban centres.	First detections in new capitals; wastewater/syringe positives in new areas; EWS and Europol alerts	EUDA, 2025b; EUDA and Europol, 2024
Port/logistics system resilience: (A) strengthening controls, reducing exploitation or (B) increasing displacement to secondary routes	Shapes HPSO entry vectors and displacement patterns.	24 months	Law enforcement; governance; environmental	Port hardening and joint operations may reduce exploitation, but traffickers can shift to secondary hubs and parcel channels.	Implementation of European Ports Alliance measures; container/parcel risk scores; insider threat investigations	EUDA and Europol, 2024
EU-based production trajectory: (A) remaining limited to sporadic mixing/packaging (B) or expanding into stable small-cell production	Local production would increase resilience and availability of HPSOs.	24 months	Economic; technological; law enforcement	Documented mixing/packaging sites demonstrate feasibility; scaling would materially alter local risk; expansion depends on whether networks see a stable EU market for HPSOs.	Laboratory dismantlement; precursor/reagent sourcing patterns; forensic profiling linkages	EUDA and Europol, 2024
Relocation of opium/heroin production: (A) shifting to new producing regions or	Alters heroin availability trajectory and	24 months	Markets; governance; law enforcement	Relocation to neighbouring or new regions could sustain	EUDA crime, markets and precursors	EUDA and Europol, 2024; EUDA crime,

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
(B) remaining concentrated in Afghanistan, despite contraction	thus substitution pressure.			heroin supply and delay synthetic substitution. A large-scale shift should be observable through multiple indicators.	monitoring; satellite/cultivation reports where available; regional intelligence; forensic analysis alerts on adulterated heroin seizures	markets and precursors monitoring
Market behavioural trajectory for HPSOs: (A) misrepresentation and accidental use predominating or (B) preference-driven demand becoming common	Consumer behaviour determines how quickly and how far HPSOs diffuse.	24 months	Social; markets; governance	A shift towards intentional preference for HPSOs would accelerate supply chain adaptation and entrenchment. It should be noted that current youth demand tends towards stimulants; preference-driven HPSO demand would require a distinct market shift.	Drug-checking data; darknet vendor marketing; repeat use patterns in cohorts	EUDA and Europol, 2024; EUDA, 2025c
Involvement of global trafficking networks: (A) minimal and niche or (B) major transnational cartels entering the HPSO market	Determines the scale, sophistication and resilience of HPSO supply.	24 months	Markets; law enforcement; governance	Entry of large cartels would dramatically increase availability, diversification and corruption risks. Major entry is probable only if	Intelligence links to major cartels; seizure patterns mirroring cocaine/heroin networks; crypto-	French Senat hearing, 2025; EDMR 2024; Organized Crime and Corruption Reporting Project investigations (United States)

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
				EU market profitability is sufficient.	payment infrastructure	
Cross-drug contamination: (A) HPSOs remaining confined to opioid products or (B) HPSOs frequently adulterating benzodiazepines, stimulants and other drugs	Expands overdose risk to opioid-naïve populations. This uncertainty includes the contamination of non-opioid markets on one hand and falsified opioid-like tablets on the other.	24 months	Health; forensic; communications	If HPSOs contaminate non-opioid substances, accidental overdoses and detection complexity will increase substantially.	Non-opioid toxicology positives; drug-checking alerts; overdose clusters among non-opioid users	French Senat hearing, 2025
High-profile incident(s) triggering policy shift: (A) no major incident, and gradual policy evolution or (B) mass event forcing emergency measures	Shapes speed and intensity of political and regulatory response.	24 months	Governance; communications	Single mass-casualty or symbolic events can catalyse sweeping policy changes that reshape markets and services.	Media coverage spikes; emergency ministerial meetings; rapid legislative/budget initiatives	French Senat hearing, 2025; national crisis responses
Prescribing environment shift: (A) stable or improving pain management or (B) abrupt crackdown or diversion surge	Prescribing dynamics influence both diversion and unmet medical needs.	24 months	Health; governance; markets	Cautious stability reduces risk; abrupt tightening without support can drive patients to illicit markets.	Trends in opioid prescribing; reports of unmet pain needs; diversion case reports	French Senat hearing, 2025; EUDA prescribing trends; national health agencies; evidence from the United States

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
Political prioritisation of HPSOs: (A) becoming a high-level EU/national priority ↔ or (B) remaining a low-salience issue	Determines policy momentum, funding and coordination.	24 months	Governance; communications	High levels of political salience unlock budgets and cross-sector action; low salience constrains responses. Political salience may remain low without a high-profile incident.	Ministerial speeches; strategic documents; budget allocations	Internal SME judgement; EU policy texts
Policy framing (health versus security): (A) health-led framing or (B) security-/enforcement-led framing	Shapes the balance between harm reduction and enforcement responses.	24 months	Governance; communications	Health-led framing tends to favour services and prevention; security-led framing may prioritise control and penalties.	Government communications; allocation between harm reduction and law enforcement budgets; institutional leadership signals	Internal SME judgement; comparative policy analyses
Drug-checking services: (A) legalised, expanded and normalised or (B) restricted, marginal or rolled back	Impacts early detection capability and individual risk reduction.	24 months	Health; governance	Expansion of drug checking strengthens sentinel detection and user awareness; restriction weakens early warning capacity.	Legal reforms; service coverage maps; user uptake and sample volumes	EUDA; national harm reduction reports
National system readiness for detection and response: (A) systems ready for highly coordinated, rapid detection and action or (B)	System-level coordination capacity determines the capacity of Member States	24 months	Health; forensics; governance	Several Member States noted weak preparedness, gaps in detection and limited interinstitutional coordination, making	EWS lag times; clinical early warning feedback speed; frequency/quality of inter-agency	NFP pulse survey; EUDA, 2025b; Killeen et al., 2024

Uncertainty	Why it matters / linked driver(s)	Period	Domains	Rationale	Early indicators	Source/note
fragmented, slow systems with delayed response	to contain HPSO outbreaks at an early stage.			early containment uncertain.	coordination exercises	

NB: DRD, drug-related death; EWS, EU early warning system; NFP, national focal point; TDI, treatment demand indicator.

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