UNODC
United Nations Office on Drugs and Crime

Current NPS Threats

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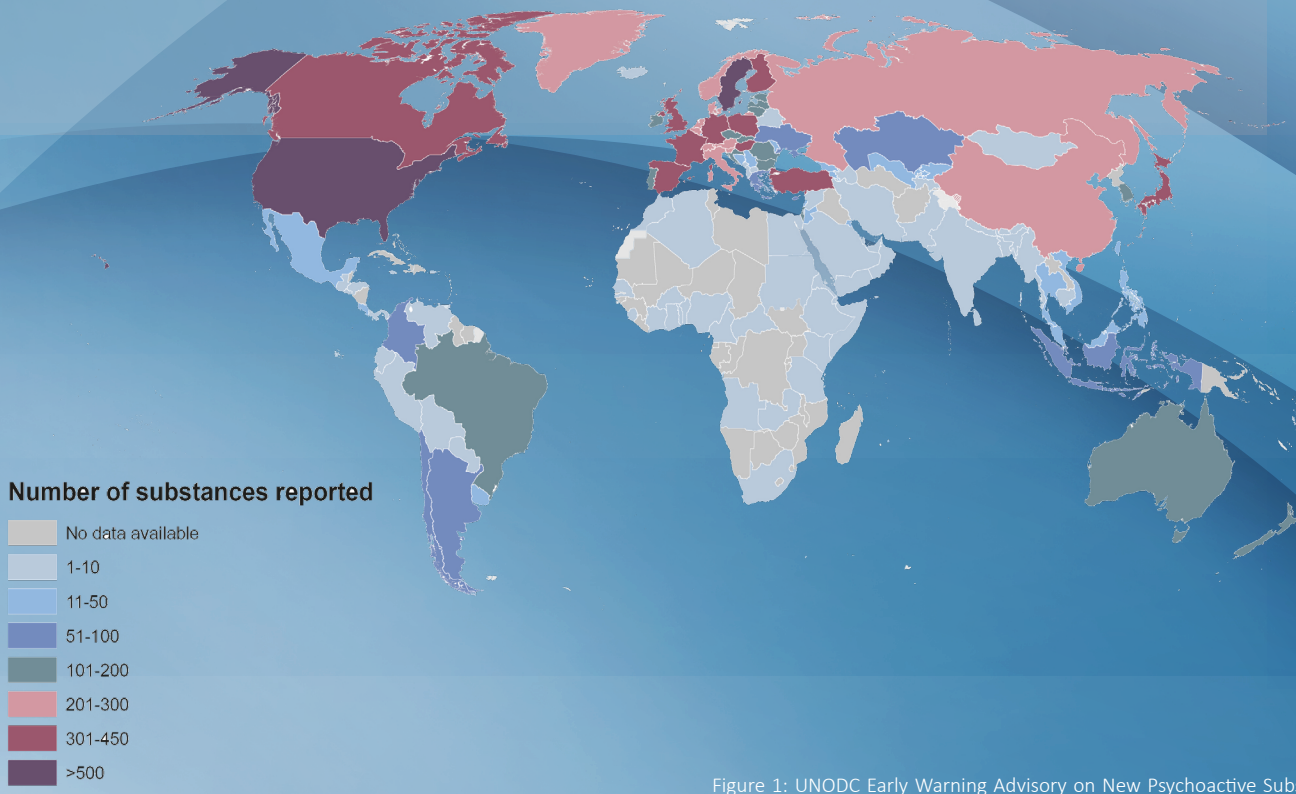


Figure 1: UNODC Early Warning Advisory on New Psychoactive Substances (NPS). Number of NPS reported by country/territory up to 2022

UNODC Early Warning Advisory Toxicology Highlights

- **Over 1150 NPS from 137 countries and territories have been reported to the UNODC Early Warning Advisory on New Psychoactive Substances**
- **Benzodiazepine-type substances continue to be a primary NPS threat, reported in 47% of post-mortem and 67% of drug driving cases**
- **Synthetic opioid NPS are the second highest group of NPS reported in both post-mortem and drug driving cases**

2022

What is the UNODC Early Warning Advisory?

Established in 2013 under the United Nations Commission on Narcotic Drugs Resolution 56/4, the UNODC Early Warning Advisory (EWA) is the first global monitoring system on new psychoactive substances (NPS). Managed by the UNODC Laboratory and Scientific Service's Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART) Programme, the UNODC EWA serves as a tool for effective, evidence-based policy responses by monitoring, analysing and reporting global and regional trends on NPS. Since its inception, EWA serves as a online data system that gathers and consolidates both regular and ad hoc submissions from forensic drug testing laboratories, Member States and partner organisations on NPS found in seized materials.

Since 2018, the EWA enhanced its features by including toxicology data to help identify the most persistent, prevalent and harmful NPS which pose the greatest threat to public health, thus, assisting in the prioritisation of substances for placement under international control, as well as legislative responses at the national level. The following report presents the latest information on NPS that have been reported to UNODC and an analysis of 1453 cases submitted from toxicology laboratories within ten Member States from the Americas, Europe, Asia and Oceania between May 2021 and April 2022.

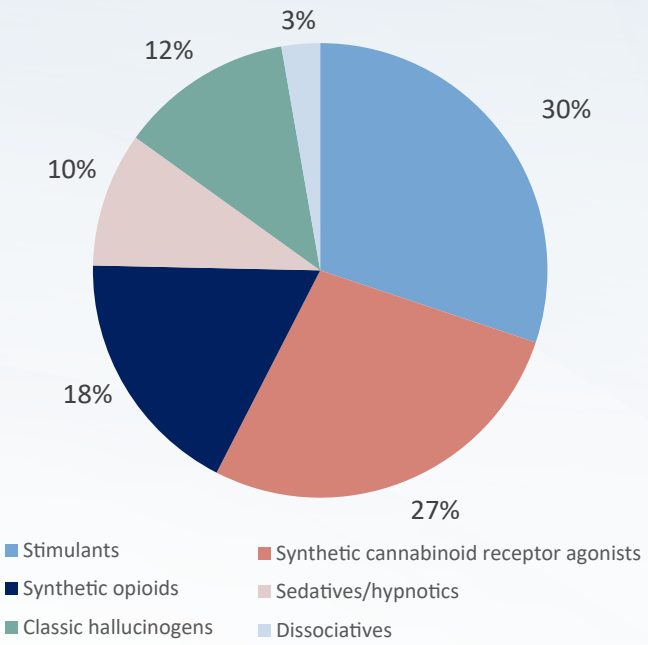
Trend analysis of NPS reported by Member States

Currently, over 1150 individual NPS have been reported to the UNODC EWA by 137 countries and territories. The NPS situation globally continues to be quite diverse and poses differing challenges in different regions of the world. For example, while 12 countries have identified more than 300 individual substances, 90 countries have identified less than 50 as shown in Figure 1.

NPS can be classified into six groups based on their mode of action and the number of reports of substances within each of these groups from 2011 to 2021 is shown in Figure 2. Current data indicates that while there are fluctuations in year on year reporting within substance groups, the overall number of substances reported each year has remained steady and has been over 500 for each of the last four years. Synthetic opioids in particular have continued to increase both in the reporting of fentanyl analogues and in the increased emergence of other NPS with opioid effects such as a variety of nitazenes and "U-series" substances.

In 2021 and up to October 2022, 76 individual new substances have been reported to UNODC. Of these, 30% (22) were stimulants, 27% (20) were cannabinoid receptor agonists, and the third largest group were synthetic opioids at 18% (13) as shown in Figure 3.

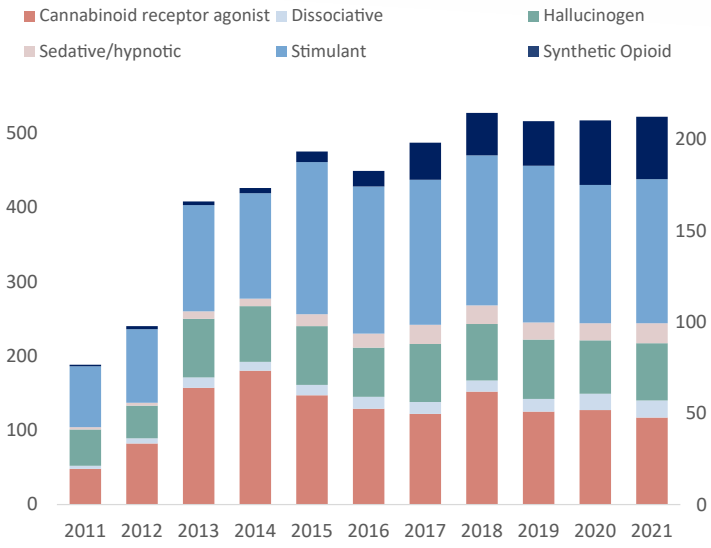
Figure 3: New Substances reported to UNODC in 2021-22



NPS toxicology case reports

Over the data collection period for this report, more than 1400 toxicology cases involving 63 individual NPS were reported to UNODC and trends observed in previous NPS threats reports have continued. The substance groups most frequently reported across the three main case types (post-mortem (PM), driving under the influence of drugs (DUID) and clinical admissions) were benzodiazepine-type NPS, synthetic cannabinoid receptor agonists (SCRAs), and synthetic opioids as shown in Figures 4 and 5. There were also a large number of drug use cases in individuals within the criminal justice system from East Asia involving ketamine and SCRAs. Stimulants (invariably cathinones) and kratom accounted for the remainder of substances reported.

Figure 2: Emergence of NPS by effect group reported to the UNODC EWA 2010 - 2021



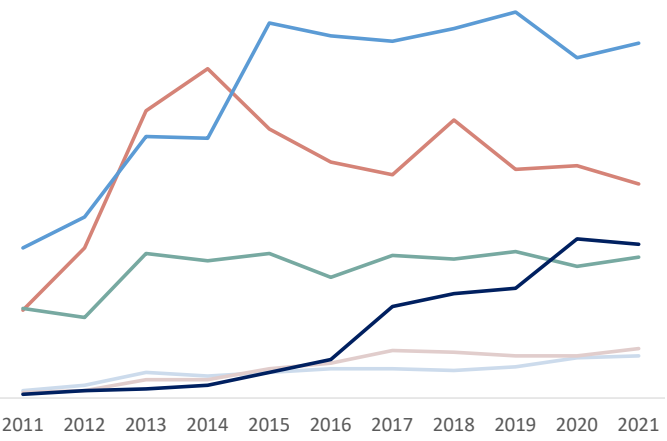


Figure 4: Types of toxicology cases reported

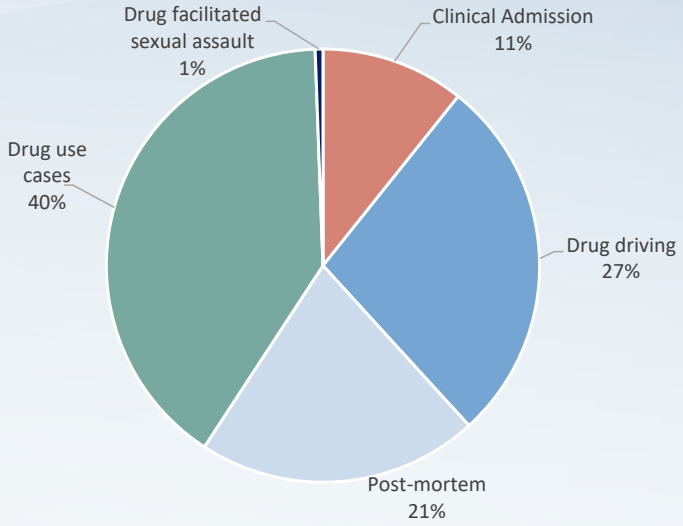
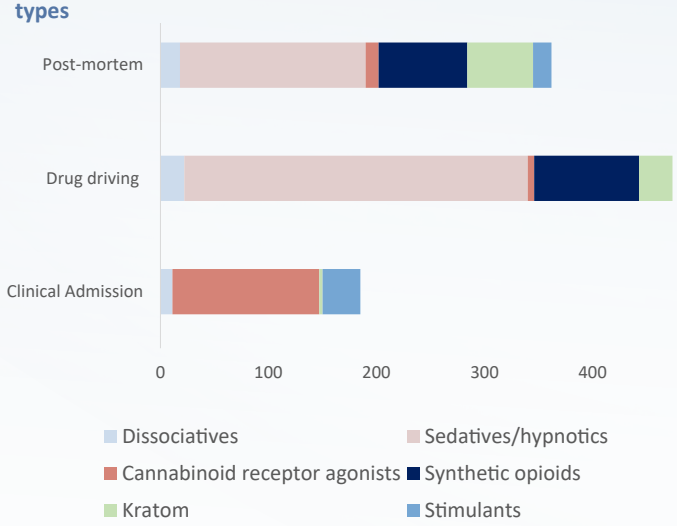


Figure 5: Substance groups reported across main toxicology case types

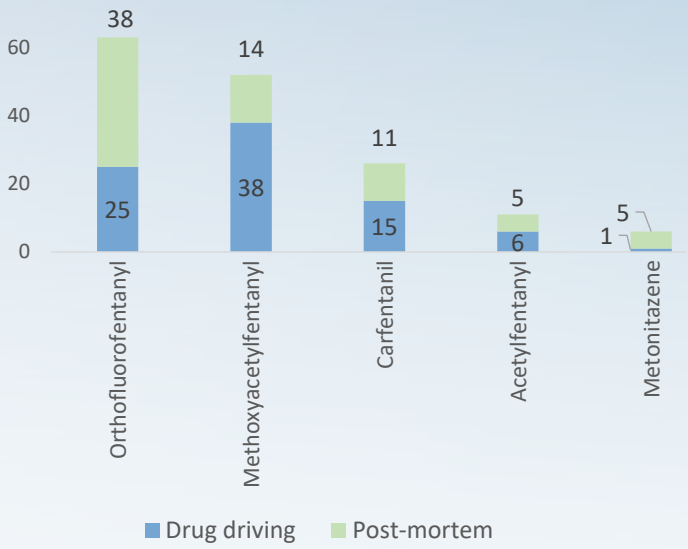


Within 154 clinical admission cases, SCRAs and cathinones constituted the highest proportion of cases, whereas in cases of drug facilitated sexual assault (DFSA), benzodiazepine-type NPS predominated. Indeed, benzodiazepine-type NPS accounted for nearly 59% of all NPS reported in relation to DUID and PM cases. This is less than in the 2020 and 2021 NPS threats reports (where they accounted for 68% and 69% of cases, respectively) but demonstrates a persistence in the threat posed. In terms of other NPS types, synthetic opioids (21%) were the next most common NPS reported in DUID and PM cases, while SCRAs predominated in clinical admissions accounting for 74% of reported substances.

Synthetic opioids and persistence of carfentanil

Synthetic opioid NPS such as fentanyl analogues and nitazenes continue to be reported in toxicology casework and constitute the second highest group of NPS reported in this data collection perioid, overtaking SCRAs. NPS opioids featured in both cases of drug driving and fatalities (see Figure 6), which demonstrates the continued potential harm of such drugs. Orthofluorofentanyl and methoxyacetylfentanyl accounted for 65% of all reports but there were also first time reports of nitazenes such as metonitazene which was reported in five fatalities and one DUID case.

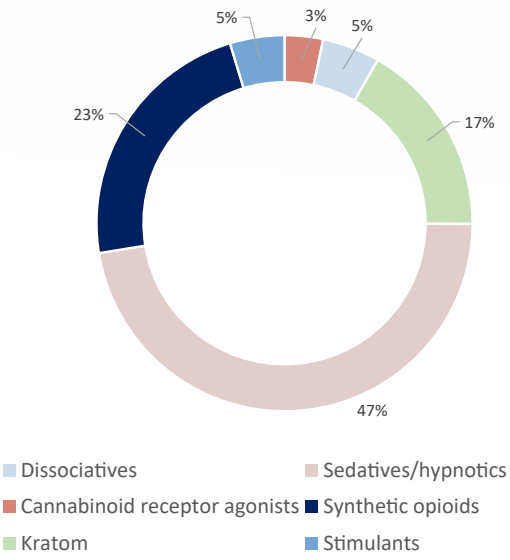
Figure 6: Top 5 NPS with opioid effects reported across post-mortem and drug driving cases



Of particular note and concern is the continued presence of carfentanil (placed under international control, in 2018) which was reported in 10 deaths and 15 DUID cases in North America. Whilst other controlled substances in particular fentanyl, heroin/morphine, methamphetamine and cocaine were reported in many of the cases (where known), the pharmacological nature of carfentanil presents a significance risk of toxicity. This also extends to the cases involving other synthetic opioids, where despite other drugs being present (again especially fentanyl, heroin/morphine, methamphetamine, cocaine and benzodiazepines), the detected NPS opioids were deemed to have caused or contributed to the death or driving intoxication.

In the fatalities where carfentail was detected, the individuals were predominantly found deceased with no ante-mortem symptomology to conclusively determine the mechanism of death (i.e. whether specific opioid-induced respiratory depression contributed). This is typical of post-mortem situations and should be considered given that across all reported fatalities, synthetic opioids were identified in 23% of cases. In additon, benzodiazepine-type NPS were detected in 47% of cases, Kratom in 17%, dissociatives in 5%, stimulants in 5% and SCRAs in 3% of PM cases as shown in Figure 7.

Figure 7: Effect groups of NPS reported in post-mortem cases



Benzodiazepine-type NPS

Benzodiazepine-type NPS continue to constitute the greatest number of NPS reported to the Tox-Portal. Where case circumstances and categorisation information were available, they accounted for 47% of all reports within a post-mortem setting and 67% of all DUID cases. Of the substances reported, the most common were etizolam (n=141), clonazolam (n=140), flualprazolam (n=107) and flubromazolam (n=89). In addition, bromazolam was reported in 21 cases (19 PM and 2 DUID), flubromazepam reported in 4 cases and each of phenazepam and pyrazolam in one case. Concentration data for the most common benzodiazepines found in post-mortem and DUID cases are shown in Figure 8.

Drug-facilitated sexual assault (DFSA) cases

Whilst there were only 7 cases of DFSA within the data for this report, benzodiazepine-type NPS were reported in all cases and typically only one substance was present. In previous years, etizolam had been reported in a DFSA case in 2018, three cases in 2020, with one case in 2020 involving flualprazolam. Therefore, these recent data represent a concerning trend of the involvement of benzodiazepine-type NPS in such cases*.

Benzodiazepines have long been associated with DFSA typically with prescribed drugs such as diazepam, temazepam and flunitrazepam, but the increased potency of benzodiazepine-type NPS pose potentially greater risks through central nervous system depression. This also presents analytical challenges, as where detected, the concentrations found can be exceptionally low (<2 ng/mL in blood) with limits of detection <0.1 ng/mL. This demonstrates that forensic toxicology laboratories should ensure they can detect benzodiazepine-type NPS within investigative casework, especially as they may be the primary drug involved in DFSA incidents. This also includes having an understanding of the metabolism and analytical profiles of phase 1 and phase 2 metabolites given urine is often the only specimen available for analysis in DFSA cases.

Cases involving synthetic cannabinoid receptor agonists (SCRAs)

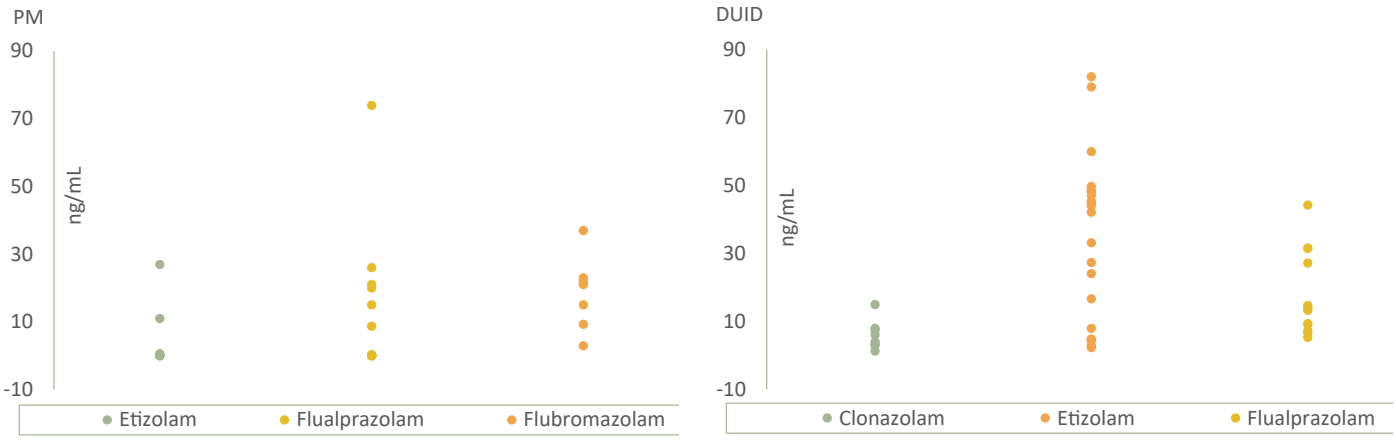
SCRAs were reported in 339 cases over the current data collection period. In total, 16 individual substances were reported, however, five indiviudal substances corresponded to 90% of reports (MDMB-4en-PINACA (42%), AB-PINACA (25%), 4F-MDMB-BINACA (9%) and ADB-BUTINACA (8%). While SCRA's were reported in 12 PM and 6 DUID cases, they were primarily identified in clinical admissions (40%) and drug use within criminal cases (65%).

Poly-drug use in NPS cases

Poly-drug use continues to be an important feature and consideration in toxicology cases associated with the use of NPS. Across all case types reported, 53% involved more than one substance. This poly-drug nature was even more frequent among PM cases in which 81% of cases involved multiple substances. The diversity of the substances reported in PM cases is illustrated in Figure 9. Opioids and stimulants were most often reported with fentanyl notably being identified in 46% of cases and methamphetamine idenfied in 21%. Other than controlled substances, a number of medicines were identified including 16 antidepressants and 15 anticonvulsants among others.

The clear diversity in the types of substances identified in poly-drug use cases associated with the use of NPS continues to highlight the complexity of analytical toxicology and the challenges faced by forensic toxicologists. This highlights the importance of the collaboration between UNODC and toxicology laboratories through the Tox-Portal in the early identification of threats and the subsequent provision of appropriate scientific information and assistance to forensic toxicologists and forensic service providers worldwide.

Figure 8: Blood concentrations (ng/ml) of benzodiazepines in post-mortem (PM) and driving under the influence of drugs (DUID) cases



*Perez Orts, M., van Asten, A., & Kohler, I. (2022). Journal of Analytical Toxicology,, bkac017. Advance online publication. https://doi.org/10.1093/ jat/bkac017)

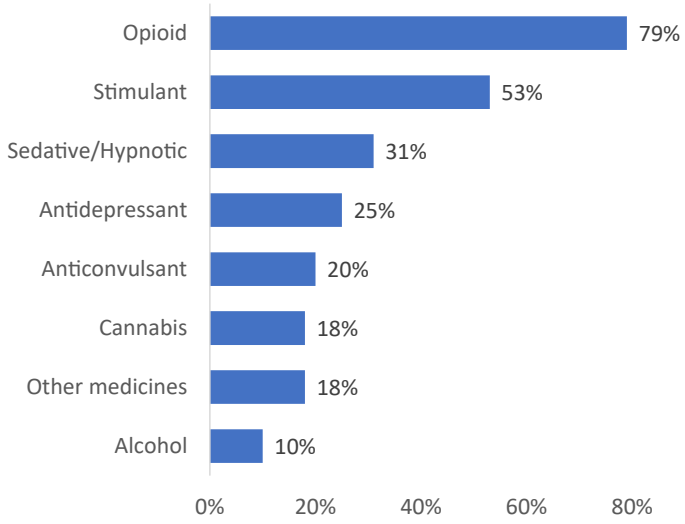
Metabolism of benzodiazepine-type NPS

The majority of the benzodiazepine-type NPS undergo hydroxylation with subsequent glucuronidation, and as such, approaches for analysis have focused on such metabolites using LC-MS/MS or HRMS and often utilise hydrolysis, especially as reference material for the corresponding glucuronides are not currently available. In situations where immunoassays may be used for presumptive testing, studies have indicated benzodiazepine-type NPS exhibit sufficient cross-reactivity for commercially available immunoassays for traditional benzodiazepines due to some shared structural similarity. But this cannot be assumed for all or for future compounds and use of LC-MS-MS or HRMS is more common in recent literature, for example.

- Puzyrenko A, Wang D, Schneider R, Wallace G, Schreiber S, Brandt K and Gunsolus IL., Journal of Analytical Toxicology, 2022, 46(7), 712-718
- Mastrovito RA, Papsun DM and Logan BK., Journal of Analytical Toxicology, 2021, 45(5), 423-428
- Mei V, Concheiro M, Pardi J and Cooper G., Journal of Analytical Toxicology, 2019, 43(9), 688-695
- van Wijk XMR, Yun C, Hooshfar S, Arens AM, Lung D, Wu AHB and Lynch KL., Journal of Analytical Toxicology, 2019, 43(4), 316-320

However, lack of available reference material for parent drugs, deuterated internal standards and phase 1 or phase 2 metabolites can hinder analysis. Furthermore, due to the wide ranging pharmacokinetics of benzodiazepines (including benzodiazepine-type NPS), the corresponding detection windows in biological material vary from a few hours to many days. As such and where possible, analysis of blood, urine and potentially hair may be beneficial, as per recommended in DFSA testing protocols (link).

Figure 9: Other substances identified in post-mortem cases of poly-drug use



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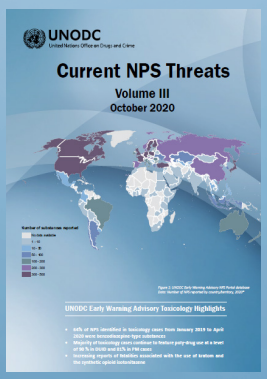

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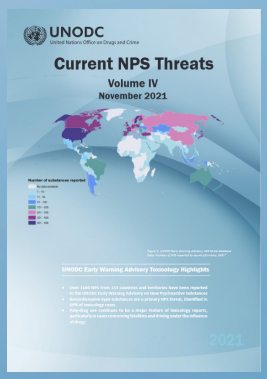
(English, Spanish, Russian)



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Global SMART Update
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(English Russian, Spanish)

Synthetic drugs in East and South East Asia
(English)

*Note: The boundaries and names shown and the designations in this document do not imply official endorsement or acceptance by the United Nations. Dashed lines represent undetermined boundaries. The dotted line represents approximately the Line of Control in Jammu and Kashmir agreed upon by India and Pakistan. The final status of Jammu and Kashmir has not yet been agreed upon by the parties. The final boundary between the Republic of Sudan and the Republic of South Sudan has not yet been determined. A dispute exists between the Governments of Argentina and the United Kingdom of Great Britain and Northern Ireland concerning sovereignty over the Falkland Islands (Malvinas).

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