UNODC
United Nations Office on Drugs and Crime

Current NPS Threats

Volume IV
November 2021

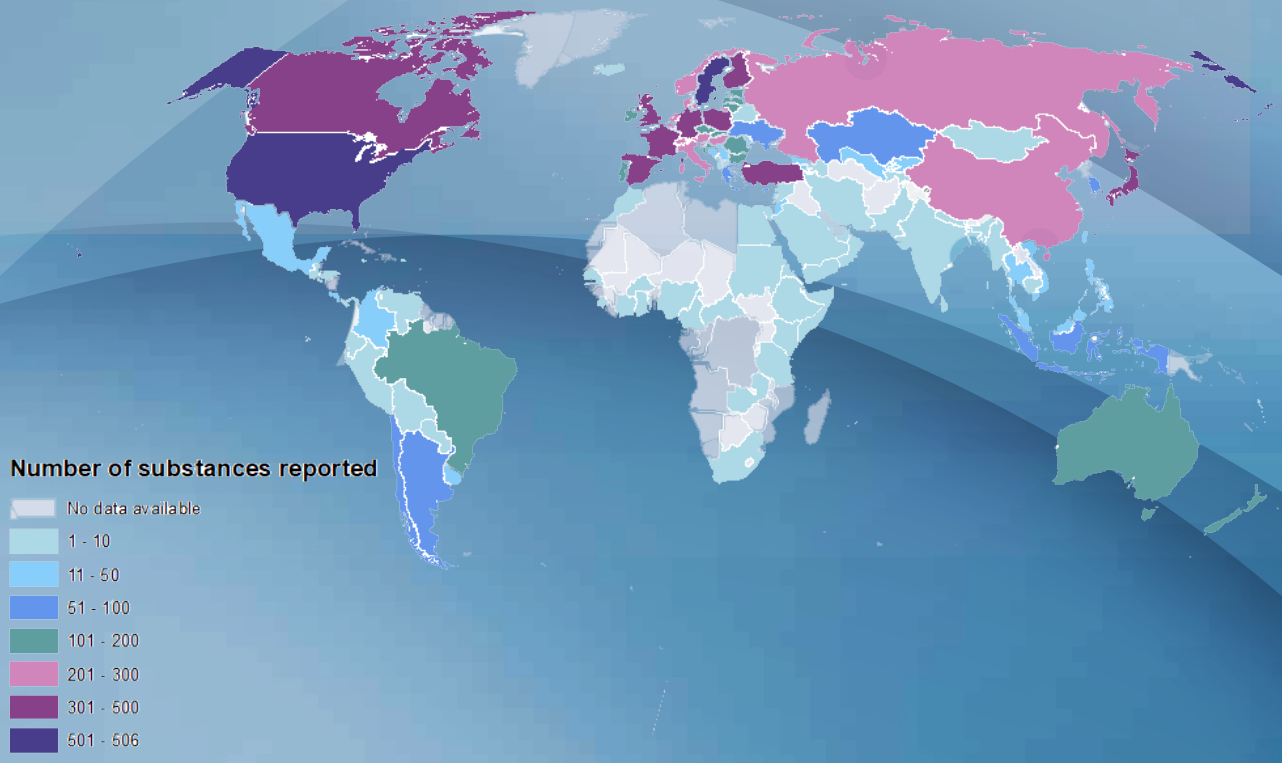


Figure 1: UNODC Early Warning Advisory NPS Portal database
*Data: Number of NPS reported by country/territory, 2021**

UNODC Early Warning Advisory Toxicology Highlights

- **Over 1100 NPS from 133 countries and territories have been reported to the UNODC Early Warning Advisory on New Psychoactive Substances**
- **Benzodiazepine-type substances are a primary NPS threat, identified in 68% of toxicology cases**
- **Poly-drug use continues to be a major feature of toxicology reports, particularly in cases concerning fatalities and driving under the influence of drugs**

2021

What is the UNODC Early Warning Advisory (EWA)?

Established in 2013 under the United Nations Commission on Narcotic Drugs Resolution 56/4 (2013), the UNODC Early Warning Advisory (EWA) was 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, 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, UNODC EWA has served as a voluntary 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 analysis of over 1500 cases submitted from toxicology laboratories within 17 Member States from the Americas, Europe, Asia and Oceania between May 2020 and April 2021.

Trend analysis of NPS reported by Member States

Currently, over 1100 individual NPS have been reported to the UNODC EWA by 133 countries and territories. The NPS situation globally is characterized by a marked heterogeneity as 105 countries and territories have reported the emergence of fewer than 100 NPS while 11 countries have reported more than 300 substances 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 2010 to 2020 is shown in Figure 2. Up to November 2021 and considering all NPS reported since monitoring began in 2008, stimulants constitute the largest group of NPS at 35 per cent, followed by synthetic cannabinoid receptor agonists at 29 per cent. Year on year trends indicate fluctuations within the number of substances reported within each group. In 2020, the number of substances reported in most groups declined, however it is notable that reports of synthetic opioids continued to increase as has been the case for several years.

NPS toxicology case reports

Since the previous volume of Current NPS Threats published in October 2020 the trends observed at that time have continued into 2021. Specifically, the persistence of benzodiazepine-type NPS, synthetic opioids and synthetic cannabinoid receptor agonists (SCRAs), along with Kratom and dissociatives, in particular ketamine, with stimulants and hallucinogens accounting for the remainder of substances reported in toxicology cases. Over the data collection period, more than 1500 toxicology cases involving a total of 58 individual NPS were reported to UNODC. Of these cases, 55% were classified as driving under the influence of drugs (DUID), 23% post-mortem (PM), 7% clinical admissions and 15% were other case types, e.g. drug facilitated sexual assault) (Figure 3).

Figure 3: Types of toxicology cases reported between May 2020 and April 2021

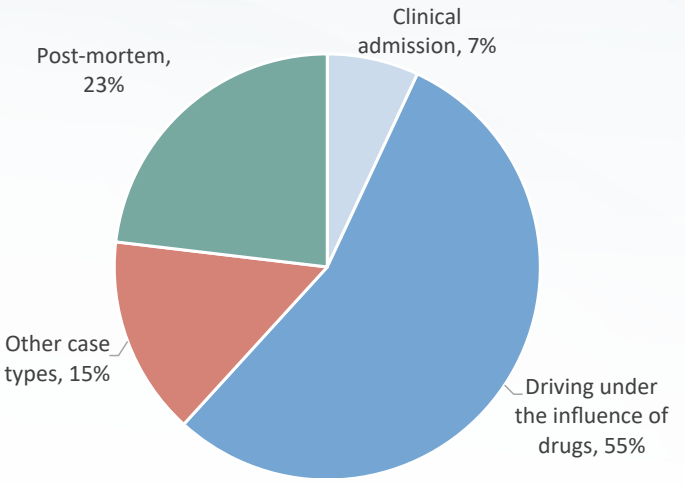
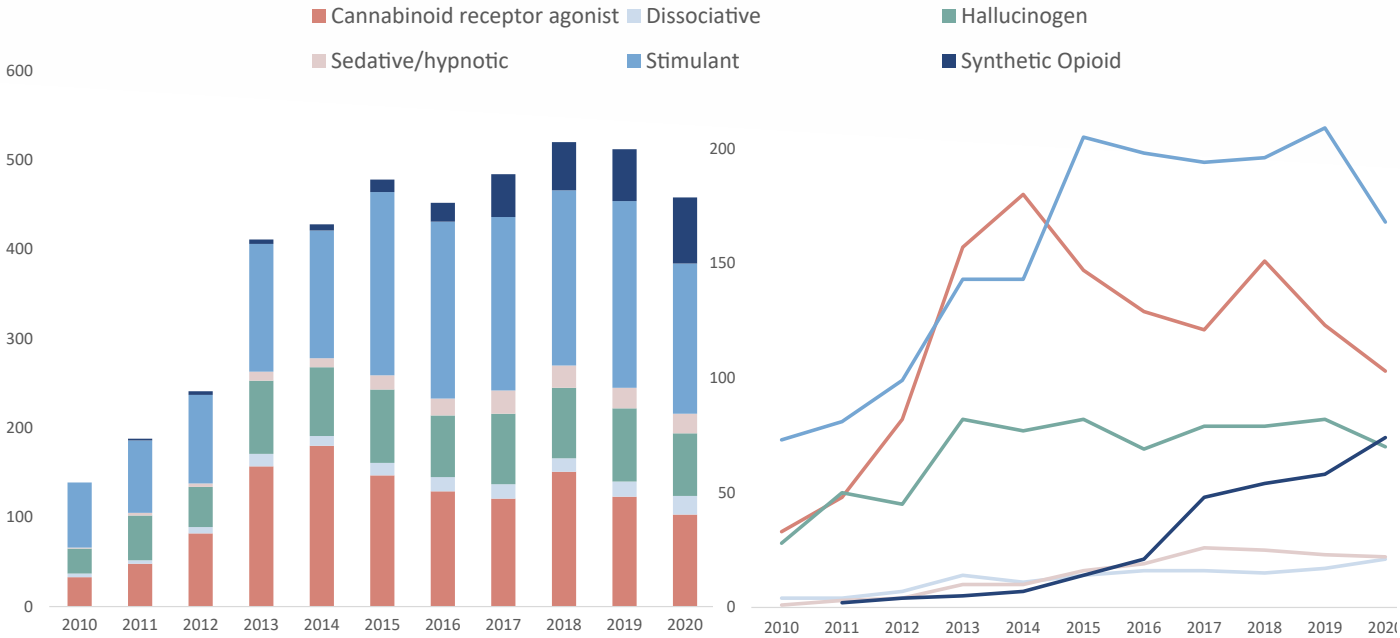


Figure 2: Emergence of NPS by effect group reported to the UNODC EWA 2010 - 2020



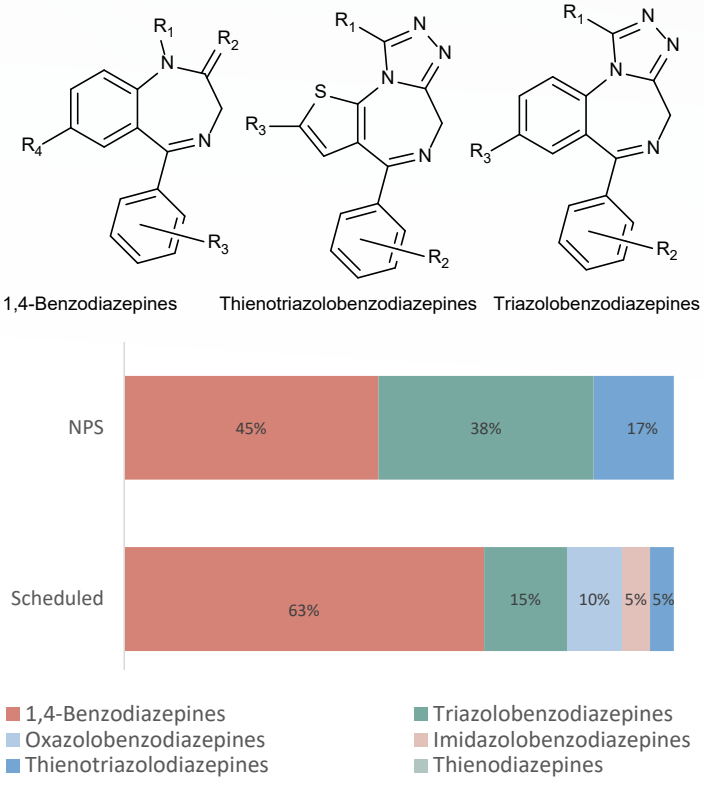
Furthermore, of the nearly 1900 instances of NPS reported in all the submitted cases, 69% were in relation to benzodiazepine-type NPS, very similar to the value of 68% reported in NPS Threats Volume III from 2020. Reported instances of benzodiazepines were also across all case types, namely post-mortem cases, clinical admissions, driving under the influence of drugs (DUID) and drug-facilitated sexual assault, demonstrating that they are a primary current NPS threat.

Benzodiazepine-type NPS

Benzodiazepines are a structural group of central nervous system depressants that are widely used in medicine as anticonvulsants, anxiolytics, hypnotics, sedatives, skeletal muscle relaxants and tranquilizers. The depressant properties of benzodiazepines are derived from their effects on a combination of receptors in the $GABA_A$ receptor complex in the brain. In total, 38 benzodiazepines are under international control with a further three (clonazolam, diclazepam and flubromazolam) to be added to Schedule IV of the 1971 Convention on Psychotropic Substances by the end of 2021.

The benzodiazepines currently under international control can be divided in to 6 different substructural groups (Figure 4) with the 1,4-benzodiazepine core being most prevalent, representing 63% of substances. With regard to benzodiazepine-type NPS, 28 individual substances have been reported to the UNODC Early Warning Advisory and within this group of NPS there has been less variability, with only 3 core structures being reported (1,4-benzodiazepines - 45%, thienotriazolodiazepines - 17% and triazolobenzodiazepines - 38%). Of the most commonly reported benzodiazepine-type NPS, clonazolam, flualprazolam and flubromazolam are triazolobenzodiazepines, etizolam is a thienotriazolodiazepine and diclazepam has a 1,4-benzodiazepine structure.

Figure 4. Structural classification of benzodiazepines under international control and benzodiazepine-type NPS that have been reported to UNODC

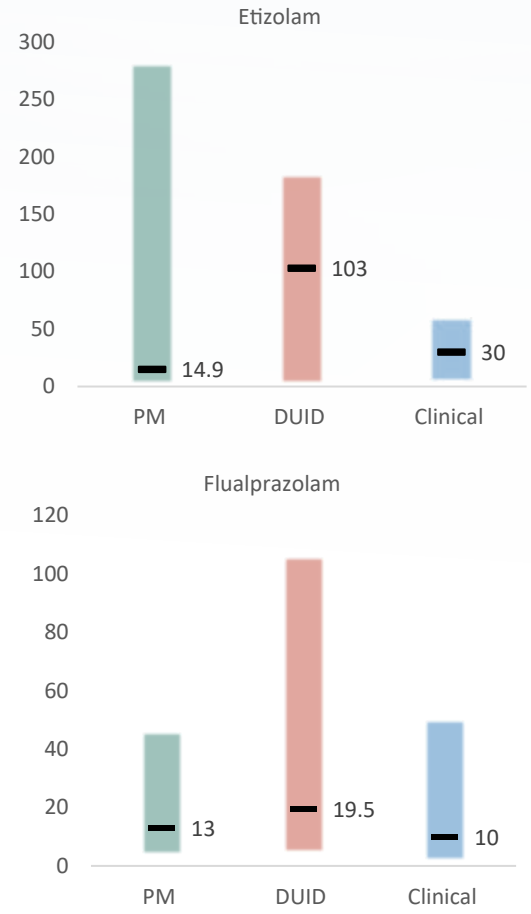


As previously described, benzodiazepine-type NPS continue to constitute the greatest number of NPS reported in the Tox-Portal. Where case circumstances and categorisation information were available, they accounted for 49% of all NPS instances within a post-mortem setting, 32% of NPS detections in clinical admissions and significantly, 85% of all driving cases.

Of the drugs reported, the most common were flualprazolam (n=494), etizolam (n=371), flubromazolam (n=271) and clonazolam (n=152) with diclazepam in 3 cases and phenazepam in 1 (post-mortem) case. Of some note, the vast majority of cases in which clonazolam was reported were related to driving, whereas flualprazolam, etizolam and flubromazolam were frequently reported across all case types.

Concentration data, shown in figure 5 were only available for etizolam (n=133), flualprazolam (n=92), flubromazolam (n=3) and phenazepam (n=1). For etizolam; PM n=38 (14.9 ng/mL median, range 3.4-281); Clinical n=6 (30.0 ng/mL median, range 5-60); Driving n=89 (103.0 ng/mL median, range 2.4-184). For flualprazolam; PM n=14 (13.0 ng/mL median, range 4-46); Clinical n=11 (10.0 ng/mL median, range 2-50); Driving n=67 (19.5 ng/mL median, range 4.7-106). Flubromazolam was measured in 3 post-mortem cases with two cases involving heroin and cocaine (8.1 and 13 ng/mL flubromazolam found) and the remaining case being an alternative cause of death (hanging) with a flubromazolam concentration of 13 ng/mL.

Figure 5. Concentration data for etizolam and flualprazolam showing concentration ranges and median reported values in ng/ml for post-mortem (PM), driving under the influence of drugs (DUID) and clinical admission cases.



Selected analytical methods for the analysis and identification of benzodiazepine-type NPS

•Blood concentrations of designer benzodiazepines: Relation to impairment and findings in forensic cases, G. Heide, G. Høseth, G. Middelkoop, Å.M.L. Øiestad, Journal of Analytical Toxicology, 2020, 44, 905–14. https://doi.org/10.1093/jat/bkaa043
•Development and validation of an LC-MS-MS method for the detection of 40 benzodiazepines and three Z-drugs in blood and urine by solid-phase extraction, S. Sofalvi, E.S. Lavins, C.K. Kaspar, H.M. Michel, C.L. Mitchell-Mata, M.A. Huestis, L.G. Apollonio, Journal of Analytical Toxicology, 2020, 44, 708–17. https://doi.org/10.1093/jat/bkaa072
•The Development and Validation of a Novel Designer Benzodiazepines Panel by LC-MS-MS, Mastrovito RA, Papsun DM and Logan BK.. Journal of Analytical Toxicology, 45(5):423-428 (2021)
•Short Communication for the Analysis of Flualprazolam in TIAFT Bulletin 50(2):43 (2020)

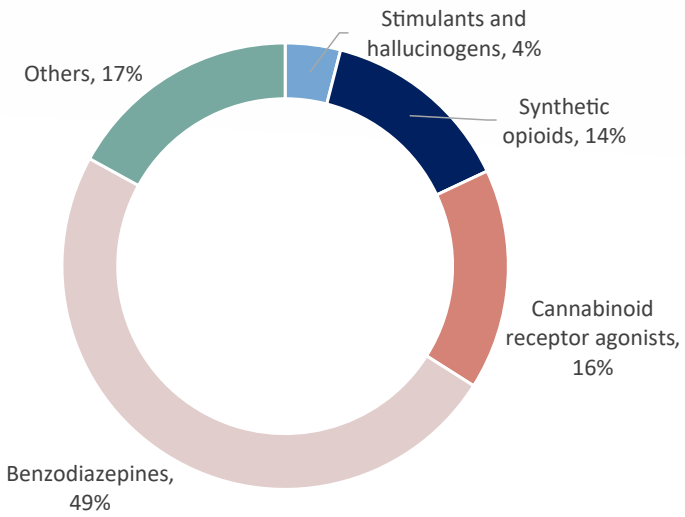
Post-mortem cases

Within the 2020/21 post-mortem NPS case data (n=397), stimulants and hallucinogens accounted for 4% of the NPS detected in fatalities, followed by synthetic opioids (14%) and SCRAs (16%) with benzodiazepine-type NPS accounting for 49% of all cases. The remaining cases (17%) predominantly involved Kratom (Figure 6).

Whilst not frequently reported across all case types, stimulants and hallucinogens featured exclusively in post-mortem cases and clinical admissions. Where assessment was possible, for the stimulants (N-ethylheptedrone, N-ethylhexedrone, mephedrone, benzylone, alpha-PVP and alpha-PHP) the substance was deemed to have medium or high contribution to death, with one case involving sibutramine where a causal relationship could not be established.

Of the hallucinogens, 25E-NBOH, 25I-NBOMe and 2C-E were reported solely within the South American region whereas 3- and 4-MeO-PCP, 3-MeO-PCE and 5-MeO-DMT were reported within Europe. In cases associated with fatalities, the cause of death was predominantly mechanical in nature (i.e. hanging, gunshot, etc). Nevertheless, the continued detection of both stimulants and hallucinogens indicates an on-going requirement for the toxicological analysis of such drugs.

Figure 6. Effect groups of NPS associated with fatalities



Cases involving Synthetic opioid NPS

Of all cases in which synthetic opioid NPS were reported, 81% were deaths, and of those, 63% of cases involved acetylfentanyl which has been encountered for a number of years and was internationally controlled in 2016. Similarly, carfentanil, (internationally controlled in 2018) accounted for 11% of cases (n=5) being solely reported in North America.

Brorphine, a newly emerging synthetic opioid NPS, has only been reported in one clinical admission case. Whilst a number of 2-benzylbenzimidazole opioids often referred to as nitazenes have been recently reported to the UNODC Early Warning Advisory (Figure 7) and elsewhere, only isotonitazene (placed under international control in 2021) was reported in this data collection period of toxicology cases and was solely related to 13 cases involving fatalities in North America.

However, as more literature is published reporting emergence of both brorphine and other nitazenes, their absence in toxicology cases could be related to a lack of validated analytical methods for their detection at the low concentrations they tend to be present in as well as challenges with access to reference materials.

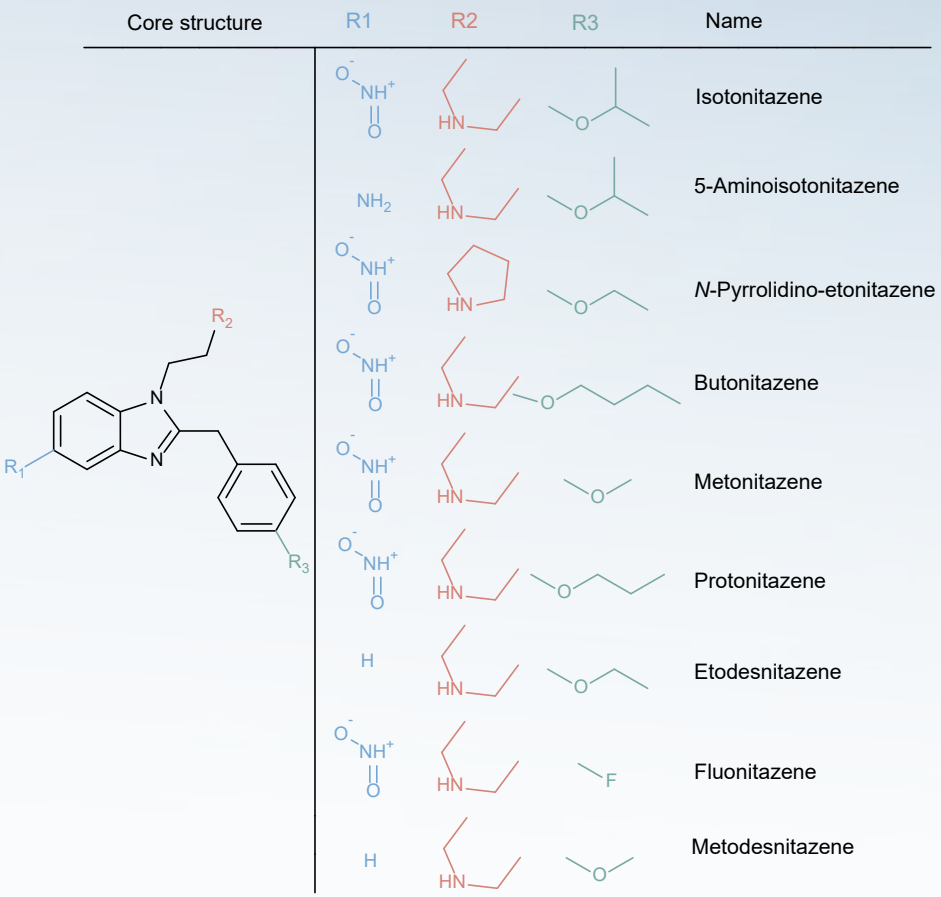
Cases involving synthetic cannabinoid receptor agonists (SCRAs)

SCRAs were reported in 172 cases in the current data collection. In 45 post-mortem cases involving SCRAs, 4F-MDMB-BINACA, 5F-MDMB-PICA and MDMB-4en-PINACA were predominant, representing 87% of reports. The SCRAs reported were deemed causal or contributory in 56% of post-mortem cases and in 36% of cases, more than one synthetic cannabinoid was identified and no other controlled substances were present.

Within cases of clinical admissions and driving under the influence of drugs, the same three synthetic cannabinoids were predominant, with some additional cases involving the use of FUB-AMB (AMB-FUBINACA). The patterns of use emerging from asubmitted cases indicates that in the majority of cases (67%) the SCRAs were consumed alone or accompanied by another SCRA, while combination with other controlled substances is less common.

IIn 19% of the cases a stimulant was also identified, but opioids and sedatives/hypnotics were only been found in 3% of the cases. The identification of cannabis in 17% of reports might suggest that the SCRAs are be applied on and consumed along other cannabis products, possibly unbeknownst to the user.

Figure 7. Nitazene opioids that have been reported to the UNODC Early Warning Advisory



Selected analytical methods for the analysis and identification of fentanyl and its analogues and nitazene opioids.

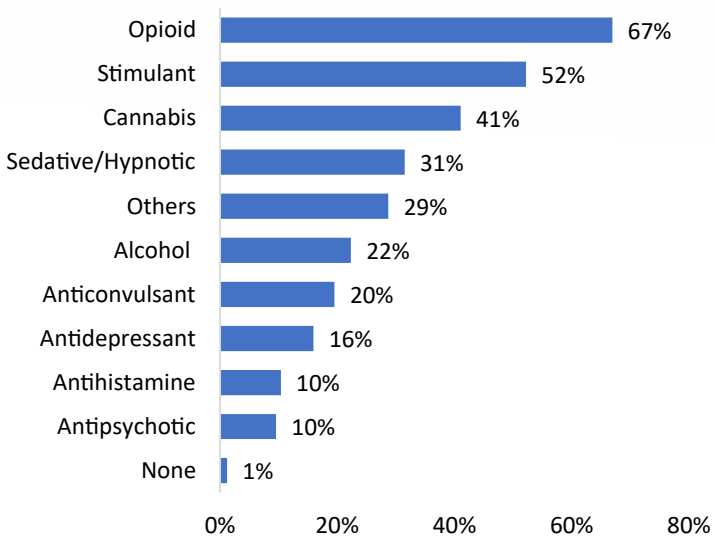
•UNODC Recommended methods for the Identification and Analysis of Fentanyl and its Analogues in Biological Specimens (link)
•Krotulski AJ, Papsun DM, Kacinko SL, Logan BK. Isotonitazene Quantitation and Metabolite Discovery in Authentic Forensic Casework. Journal of Analytical Toxicology 44(6):521-530 (2020)
•Short Communication for the Analysis of Isotonitazene in TIAFT Bulletin 50(2):47 (2020)
•Krotulski AJ, Papsun DM, Walton SE, Logan BK. Metonitazene in the United States-Forensic toxicology assessment of a potent new synthetic opioid using liquid chromatography mass spectrometry. Drug Test Anal. 13(10):1697-1711 (2021)
•Vandeputte MM, Van Uytfanghe K, Layle NK, St Germaine DM, Iula DM, Stove CP. Synthesis, Chemical Characterization, and μ-Opioid Receptor Activity Assessment of the Emerging Group of "Nitazene" 2-Benzylbenzimidazole Synthetic Opioids. ACS Chem Neurosci. 12(7):1241-1251 (2021)

Poly-drug use across different case types

As in previous Current NPS Threats reports, poly drug use continues to be an important feature and consideration in NPS casework. In post-mortem cases associated with the use of NPS, 79% of involved more than one substance. Substances under international control such as opioids, stimulants, cannabis and sedatives/hypnotics were most often identified. However, a range of medicines including antidepressants, antipsychotics and antihistamines among others were also identified (Figure 8).

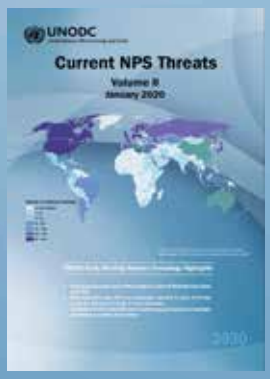
The diversity in the type of substances identified in poly drug use cases highlights the complexity of analytical toxicology and one of the continuing challenges faced by toxicologists in their work. The role of the UNODC toxicology portal in the early identification of threats and the subsequent provision of appropriate scientific information and assistance to forensic toxicologists and forensic service providers worldwide continues to be of utmost importance.

Figure 8. Substances identified in post-mortem cases involving poly drug use

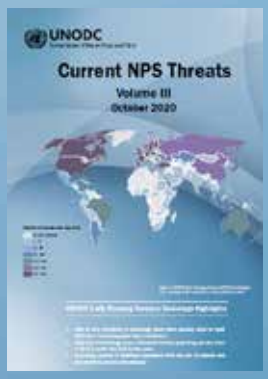


UNODC
United Nations Office on Drugs and Crime

Recent publications



Current NPS Threats
Vol. II, Jan. 2020
(English)



Current NPS Threats
Vol. III, Oct. 2020
(English, Spanish, Russian)

Global SMART Update
Volume 25
(English and Spanish)

Global Synthetic Drugs Assessment 2020
(English)

Acknowledgments

UNODC would like to thank The International Association of Forensic Toxicologists (TIAFT) for their collaboration and contribution to the development of the toxicology portal of the UNODC EWA and Dr. Simon Elliott for the preparation of the final draft of this report. UNODC would like to recognise the following contributors for sharing case information:

Abuelgasim Alhassan, Alain Verstraete, Alex Krotulski, Amanda Moore, Béatrice Garneau, Bertrand Brunet, Biljana Milosavljevic, Chelsea Yacovazzi, Christiana Cosma, Craig Triebold, Dani Mata, Diana Kappatos, Dimitri Gerostamoulos, Elizabeth Smalley, Eunmi Kim, Fatih Ordu, Gary Kunsman, Giovanni Serpelloni, Heesun Chung, Helena Fels, Hooi Yan Moy, Janet Schultz, Jean-Michel Gaulier, Jose Luiz Costa, Juliet Kinyua, Kaddour Salma, Karen Valencia, Katerina Liveri, Kelly Virkler, Kirsten Turner, Kristen Steward, Liliya Rizvanova, Mareta Ibragimova, Maria Franck, Maria Antonia Martinez, Maria Chiara David, María de los Angeles Sancho Brens, Mariana Peres, Martine Lamarche, Matthew Di Rago, Pai-Shan Chen, Pauline Sibille, Pirkko Kriikku, Rieska dwi widayati, Rossella Gottardo, Ruby Javed, Sandra Bishop-Freeman, Sandra Staeheli, Sanggil Choe, Serap Annette Akgur, Sharmilah Kuppusami, Simon Elliott, Stalin Hoyos, Stephen Trobbiani, Svante Vikingsson, Theerin Sinchai, Vajrapani Karunaratne, Xuan Truong Nguyen, Yannick Oyono and Yi Ju Yao.

UNODC would also like to acknowledge the Governments of Australia, Canada, China, Japan, New Zealand, Republic of Korea, Russian Federation, Singapore, Thailand, United Kingdom and United States for their financial support to the Global SMART Programme. In addition, UNODC would like to thank the European Monitoring Centre for Drugs and Drug Addiction, the International Narcotics Control Board, the World Customs Organization as well as many Member States around the world for making available information to the UNODC EWA.

*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).

Contact Details

UNODC Laboratory and Scientific Service
Vienna International Centre
P.O. Box 500
A-1400, Vienna
Austria
unodc-ewa-tox@un.org

Website
www.unodc.org
www.unodc.org/nps
www.unodc.org/tox
Social media
Twitter: @unodc_lab