UNODC
United Nations Office on Drugs and Crime

Current NPS Threats

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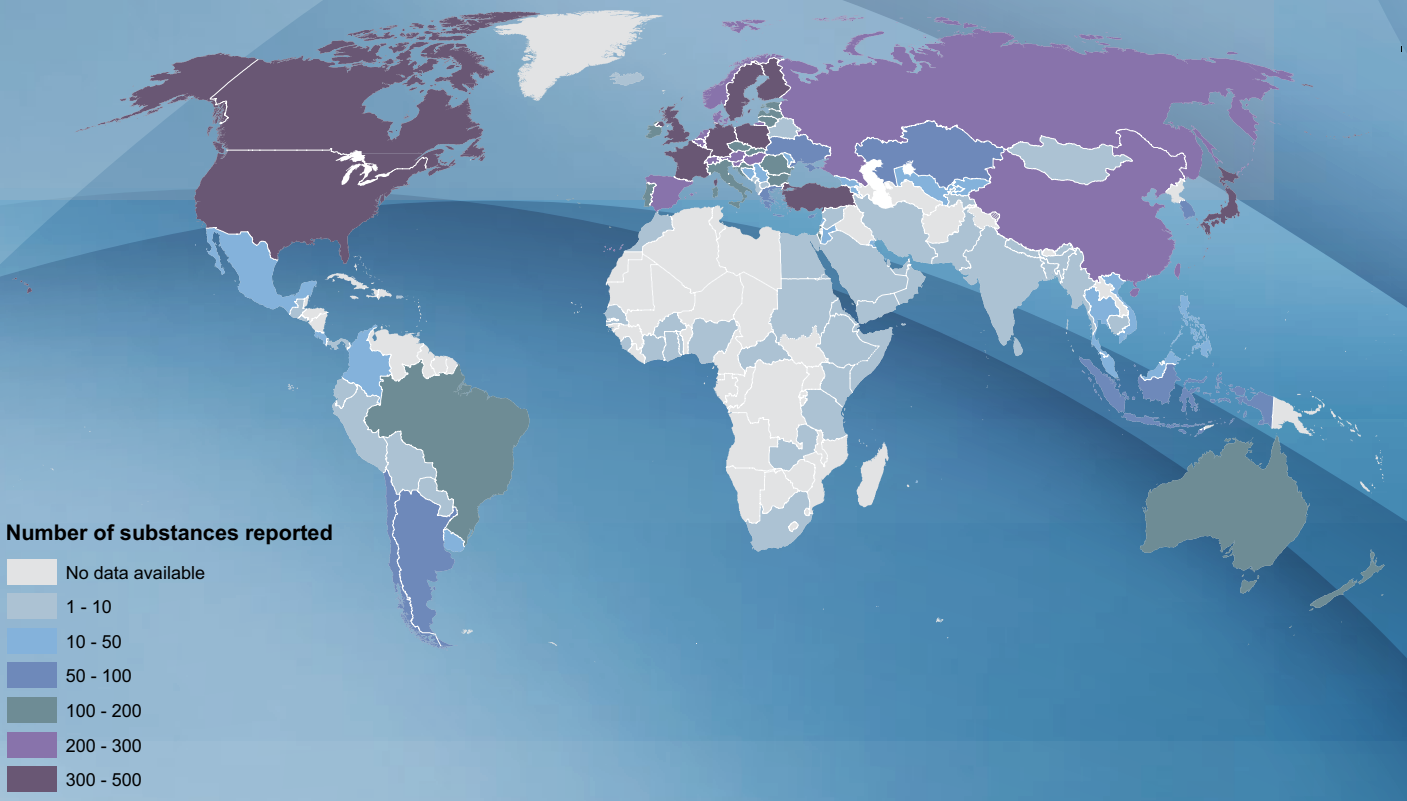


Figure 1: UNODC Early Warning Advisory NPS Portal database
*Data: Number of NPS reported by country/territory, 2020**

UNODC Early Warning Advisory Toxicology Highlights

- 64% of NPS identified in toxicology cases from January 2019 to April 2020 were benzodiazepine-type substances
- Majority of toxicology cases continue to feature poly-drug use at a level of 90 % in DUID and 81% in PM cases
- Increasing reports of fatalities associated with the use of kratom and the synthetic opioid isotonitazene

2020

What is the UNODC Early Warning Advisory (EWA)?

In 2013, the United Nations Office on Drugs and Crime (UNODC) established the Early Warning Advisory (EWA) on New Psychoactive Substances (NPS) in response to the Commission on Narcotic Drugs (CND) Resolution 56/4 (2013) entitled "Enhancing international cooperation in the identification and reporting of new psychoactive substances". The EWA serves as a tool for effective, evidence-based policy responses by monitoring, analysing and reporting global and regional trends on NPS. The UNODC EWA is a voluntary online data system that consolidates regular and *ad hoc* submissions from forensic drug testing and toxicology laboratories, Member States and partner organisations on NPS found in seized materials and toxicology cases.

Since 2018, the EWA has enhanced its features by including toxicology data in order to identify the NPS which pose the greatest threat to public health, thus, assisting in the prioritisation of substances assessed for international control as well as legislative responses at the national level.

The following report represents a snapshot analysis of the most recent cases submitted from toxicology laboratories within 13 Member States between January 2019 and April 2020. The reporting countries arise from geographical regions which include North America, Europe, Asia and Oceania. Although the analysis allows for a broader understanding of the associated harm of NPS, it is not an exhaustive representation of the variety and toxicity of NPS present globally.

Trend analysis of NPS reported by Member States

Currently, approximately 1004 individual NPS have been reported to the UNODC EWA by 125 countries and territories. These substances 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 2009 to 2020 is shown below.

The information highlights a dynamic NPS market. Overall, stimulants account for the largest group of substances reported, followed by synthetic cannabinoid receptor agonists (SCRAs) and classic hallucinogens. In recent years, reports of substances in most groups have either plateaued or even decreased following an initial rapid increase from 2012-2015. However, certain groups of NPS such as synthetic opioid receptor agonists continue to be on the rise with an almost four fold increase from 2016 until mid-2020. The group of sedative/ hypnotics has also shown a steady increase in recent years.

NPS toxicology case reports

Over the period from January 2019 to April 2020, 670 toxicology cases involving 46 individual NPS were reported to UNODC. Of these cases, 62% were classified as driving under the influence of drugs (DUID), 26% post-mortem (PM), 4% clinical admissions and 8% were cases grouped as "other" (e.g. drug facilitated sexual assault) (Figure 3).

Figure 3: Types of toxicology cases reported between 2019 and April 2020

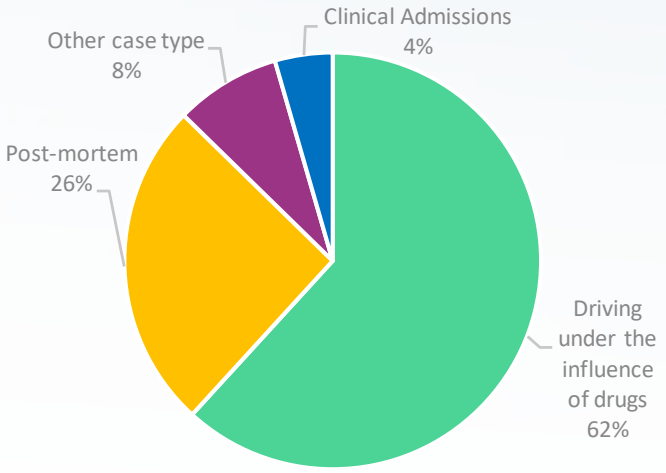
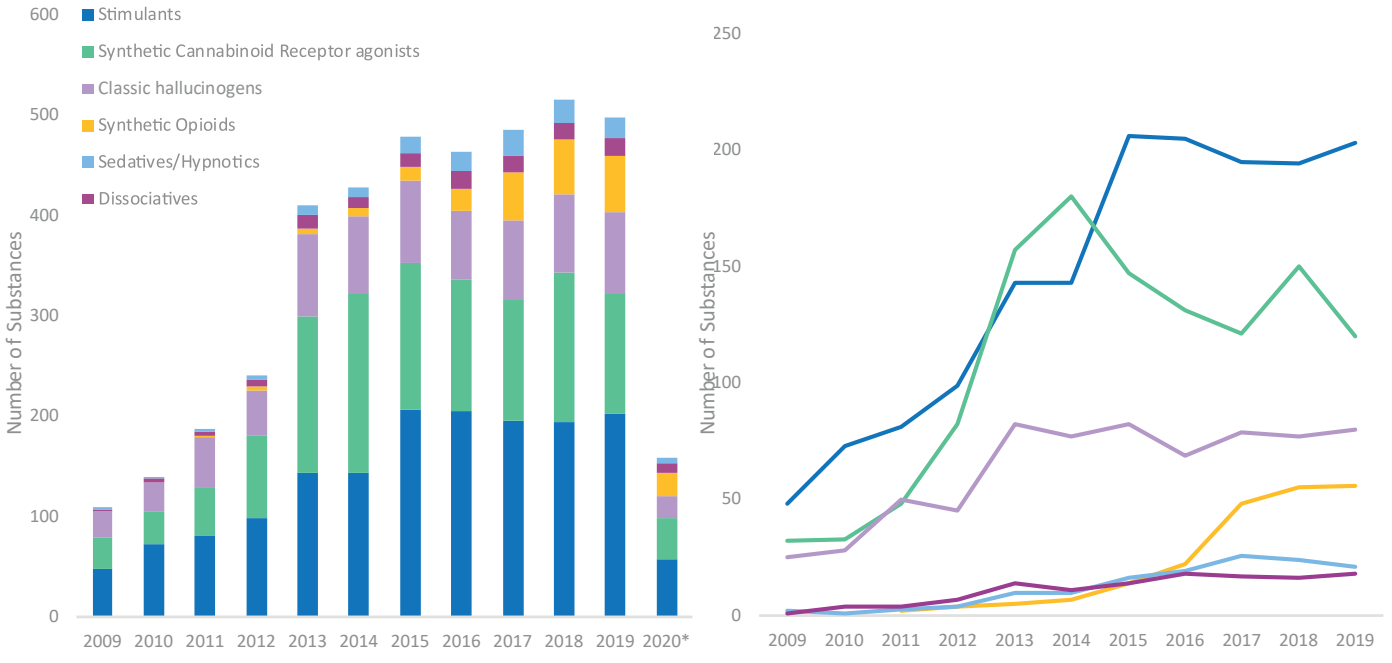


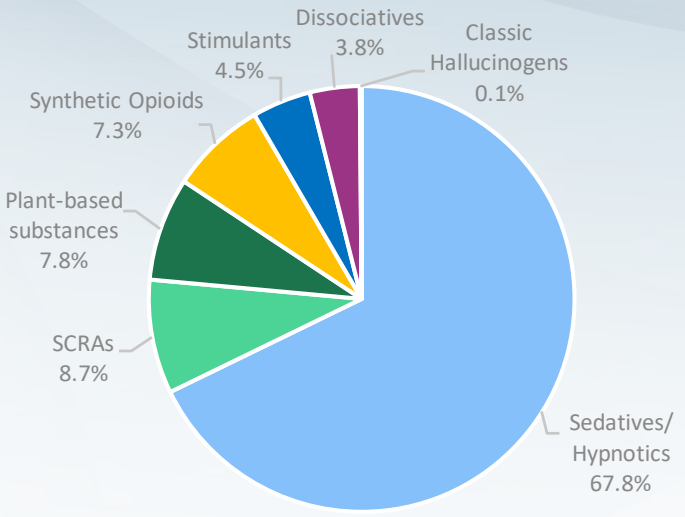
Figure 2: Emergence of NPS by effect group reported to the UNODC EWA 2009 - 2020



**Note*: 2020 data not finalised

In volume II of Current NPS Threats published in January 2020 (https://www.unodc.org/unodc/en/scientists/current-nps-threats.html) toxicology case reports received by UNODC showed the growing importance of benzodiazepine-type NPS with sedative/hypnotic effects. This increasing trend has continued well into 2020 with sedatives/hypnotics accounting for the largest group (68%) of NPS in toxicology reports, followed by SCRAs, plant-based substances in particular kratom and synthetic opioids (Figure 4).

Figure 4: NPS reported within toxicology cases



Benzodiazepines in toxicology cases

As of July 2020, 34 individual sedative/hypnotic substances have been reported by 49 countries and territories, of which 29 are benzodiazepine-type NPS and 5 are derivatives of the CNS depressant methaqualone. Between 2019 and April 2020, a total of 10 individual benzodiazepine-type NPS were identified in toxicology cases reported to UNODC with etizolam, flualprazolam and flubromazolam accounting for 64% of all identified NPS*. Their individual distribution across toxicology case types is shown in Figure 5.

Benzodiazepines are widely used in medicine as anticonvulsants, sedatives and tranquilizers and there are a total of 38 substances in this class under international control following the recent placement of phenazepam (2016), etizolam and flualprazolam (both in March 2020) in Schedule IV of the 1971 Convention on Psychotropic Substances**. Benzodiazepines, both legitimate medicines and benzodiazepine-type NPS, are often detected in drug overdose cases and can contribute to serious adverse health effects and death, particularly in combination with opioids.

A large proportion (83%, N=402) of DUID cases identified the presence of benzodiazepine-type NPS, with flualprazolam and flubromazolam representing the two most reported NPS at 51% and 22% respectively.

**Note*: Case reports were predominately recorded in the United States with some cases also reported in Canada, Australia, Finland, Sweden and Switzerland.

***Note*: International control of etizolam and flualprazolam comes into force on November 3, 2020. Flubromazolam will be subject to critical review at the 43rd Expert Committee of Drug Dependence of the World Health Organisation in October 2020.

Benzodiazepine-type NPS were also identified in 48% of PM cases (N=197). In case reports, etizolam, flualprazolam, flubromazolam and phenazepam were assessed to have either contributed to or been the cause of death in 48% of PM cases within this category (N=111), clearly indicating their potential to cause harm. Additionally, etizolam and flubromazolam, both with two cases each, have been causal to death in the absence of any other substance identified (e.g. controlled drug, medicines or alcohol). Yet, the fact that (fatal) overdoses involving benzodiazepine-type NPS are typically poly-substance cases adds complexity in understanding their potential to cause harm

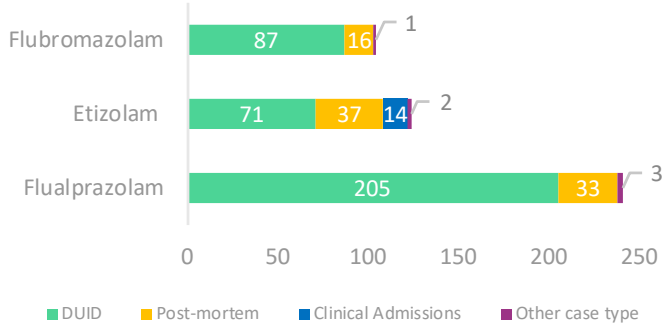
The proportion of cases involving the three most frequently reported NPS (etizolam, flualprazolam, and flubromazolam) that were categorized as poly-drug use was generally very high, between 80-90%. In particular, controlled substances, such as cannabis, but also medicines were frequently identified in addition to NPS. The proportion of cases in which more than one NPS was identified was between 10% and 16% and mainly involved a combination of these three substances.

When possible, blood concentration ranges of these benzodiazepine-type NPS were determined and reported. In fatal cases, these ranged between 12.0 and 80.0 ng/mL (cardiac blood, n=5) for etizolam, between 100 and 500 ng/mL (femoral blood, n=5) for flualprazolam, 37.0 and 130 ng/mL (cardiac blood, n=2) for flubromazolam and between 10.0 and 119 ng/mL (femoral blood, n=2) for phenazepam.

For some comparison, in DUID cases the reported peripheral blood concentrations were between 2.50 and 373 ng/mL (n=23) and between 5.50 and 26.0 ng/mL (n=4), for etizolam and flualprazolam respectively. Blood concentrations of phenazepam in non-fatal cases were reported between 30.0 and 47.7 ng/mL (n=2). There is a notable overlap between concentrations in fatal and non-fatal cases involving etizolam and phenazepam, which is not uncommon in toxicology and could be attributed to a number of factors; e.g. tolerance in long-term users.

The analysis presented here reveals that benzodiazepine-type NPS can play an important role in contributing to serious harm, either alone or in combination with other psychoactive substances. Thus, forensic laboratories should ensure that they have appropriate analytical methods available for their detection in case work.

Figure 5: Toxicology case type distribution of the top three reported NPS



Poly-drug use across different case types

Poly-drug use was identified as an important consideration in cases associated with the use of NPS in previous volumes of Current NPS Threats and the latest information shows that this continues to occur across all types of toxicology cases. Overall, poly-drug use was identified in 81% of all toxicology cases reviewed (N=670), with a similar proportion in the 171 post-mortem cases analysed. In about half of the cases, at least one controlled substance such as methamphetamine or cocaine were identified, while medicines as well as alcohol were present in 82% of post-mortem cases. The proportion of post-mortem cases in which more than one NPS was identified was 19%.

In DUID cases, poly-drug use seems to be even more widespread, with a combination of substances used in over 90% of DUID cases. Controlled substances were found in 81% of these cases and 51% were found to have consumed medicines, mostly prescription benzodiazepines and opioids. In 13% of cases the driver was under the influence of multiple NPS.

Isotonitazene, Kratom and Brorphine

Cases featuring Isotonitazene

NPS with opioid-like effects, continue to emerge on illicit drug markets. One recent example is isotonitazene, a synthetic opioid that has emerged in Europe and North America and until recently had not appeared in any toxicology cases. Since June 2019 however, eight instances of fatalities associated with isotonitazene have been reported to UNODC from the United States. Furthermore, in all but one case, the substance was assessed to have been causal to the death of the individual. Reported blood concentrations ranged between 0.4 and 4.40 ng/mL (n=8). However, due to its novelty and opioid-like effects which might be misinterpreted as heroin overdoses, it is possible that many cases remain undetected to this day. Isotonitazene will be subject to critical review by the 43rd Expert Committee on Drug Dependence (ECDD).

Increasing reports of fatalities involving Kratom

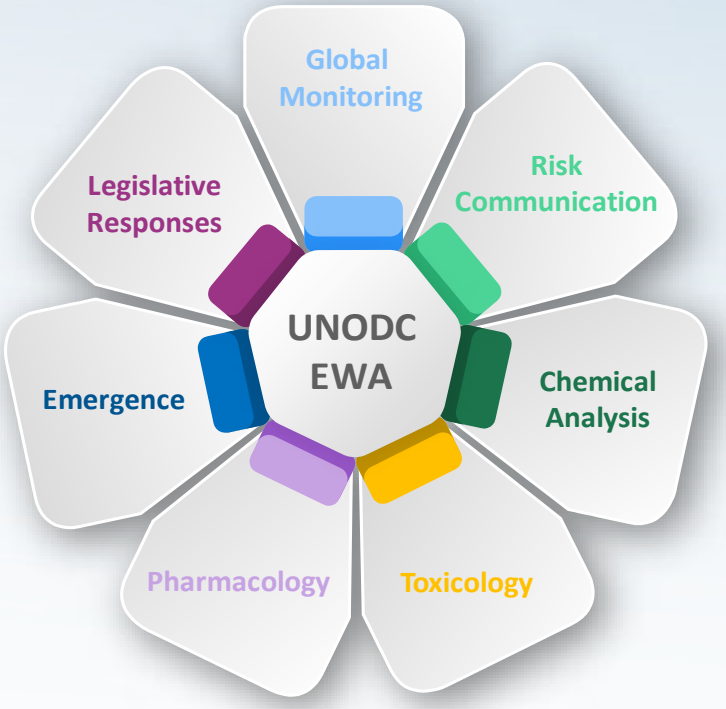
Recently, another NPS that has shown its potential to cause serious harm, including fatalities, is Kratom, a plant material derived from the tropical evergreen tree Mitragyna speciosa. The leaves contain pharmacologically active alkaloids especially mitragynine and 7-hydroxymitragynyine, which show opioid as well as stimulant effects. Cases involving Kratom were evenly split between DUID and PM cases, with 90% of all Kratom cases involving the concomitant use of other substances. In the previous volume of Current NPS Threats, Kratom cases accounted for 46% of all NPS detected in fatalities. Nevertheless, there had not been a single case reported in which Kratom was causal to the outcome. However, since July 2019, at least 14 cases have been identified where Kratom was deemed causal (n=7) or contributory (n=7) to the fatality. Of the seven causal PM cases, two where labelled single drug use cases. In fatal PM cases where blood concentrations had been determined, cardiac mitragynine concentrations of between 113 and 4280 ng/mL (n=5) were reported. For comparison, analysed blood mitragynine concentrations in DUID cases were between 10.7 and 333 ng/mL (n=24).

Brorphine - a new synthetic opioid

First reported to the UNODC EWA in July 2019, Brorphine ((1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one), a piperidine benzimidazolone classified as a synthetic opioid, started to make its way onto the NPS market in Canada and the United States. More recently, in June/July 2020 this substance was found during seven post-mortem cases in the USA and once during a clinical admission in Belgium. An initial study[1] on the patient showed that the substance appeared to have a long half-life and high potency compared to medicinal opioids such as hydromorphone. Toxicologial screening of serum samples of the patient using immunoassay and enzymatic methods gave a negative result highlighting one of the main challenges faced by toxicologists when analysing and identifying new and emerging substances.

[1] Verougstraete, N., Vandeputte, M., Lyphout, C., Cannaert, A., Hulpia, F., Van Calenbergh, S., Verstraete, A., Stove, C., Journal of Analytical Toxicology, published ahead of print on 03 August 2020.

Features of the UNODC Early Warning Advisory on New Psychoactive Substances



Modules of the United Nations Toolkit on Synthetic Drugs

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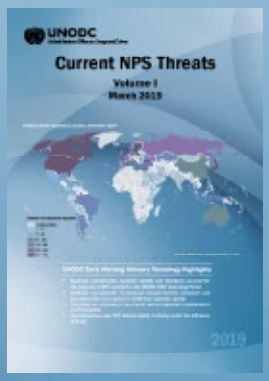
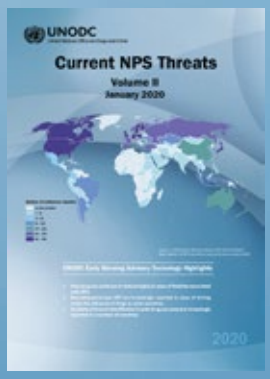
Available publications

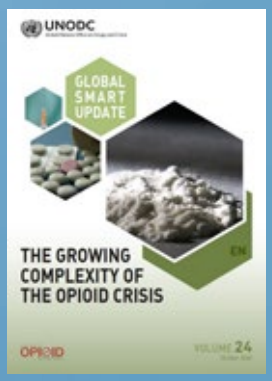


Current NPS Threats
Vol. I, Mar. 2019
(English)



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

Global SMART Update
Volume 23
(English and Spanish)



Global SMART Update
Volume 24
(English)

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Contact Details

UNODC Laboratory and Scientific Section
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