AUGUST 2024

INFORMATION BULLETIN

# ADDRESSING THE INCREASE IN ILLICIT USE OF BENZODIAZEPINES IN THE AMERICAS

OAS | CICAD

INTER-AMERICAN DRUG ABUSE CONTROL COMMISSION (CICAD)

## OAS Cataloging-in-Publication Data

**Inter-American Drug Abuse Control Commission**

Information Bulletin: Addressing the Increase in Illicit Use of Benzodiazepines in the Americas; (OAS. Official documents; OAS/Ser.L)





Prepared and published by the Inter-American Drug Abuse Control Commission (CICAD), Organization of American States (OAS). Information Bulletin: Addressing the Increase in Illicit Use of Benzodiazepines in the Americas, Washington, D.C., 2024.


Comments on the document are welcome and can be sent to OID_CICAD@oas.org.

The contents of this document are presented exclusively for informational purposes and do not necessarily represent the opinion or official position of the Organization of American States, its General Secretariat, or its member states.

This Information Bulletin was prepared by the Inter-American Observatory on Drugs (OID, by its Spanish-language acronym) of the Inter-American Drug Abuse Control Commission (CICAD, by its Spanish-language acronym), located within the Secretariat for Multidimensional Security (SMS) of the Organization of American States (OAS).

## Executive Secretary

**Adam E. Namm**
Inter-American Drug Abuse Control Commission
Organization of American States

## Assistant Executive Secretary

**Angela Crowdy**
Inter-American Drug Abuse Control Commission
Organization of American States

## General coordination

**Marya Hynes**

## Technical review

**Juan Carlos Araneda**
**Pernell Clarke**
**Aurore Dehousse**
**Paula Demassi**
**Marya Hynes**

## Author

Antonio Pascale M.D., Toxicologist and professor at the Center for Biomedical Sciences of the University of Montevideo, Uruguay. Member of the Expert Committee on Drug Dependence of the World Health Organization (WHO).



The Executive Secretariat of CICAD (ES-CICAD) would like to thank the national drug commissions of the OAS member states, without whom this bulletin could not have been produced.

Special thanks to the Government of the United States for its support and funding of this bulletin.

# CONTENTS

# EXECUTIVE SUMMARY

Benzodiazepines are implicated in a high number of drug overdoses, including intoxications and fatalities, according to the National Poison Data System of the United States,[1]. They have been identified in cases of driving under the influence and traffic accidents. Benzodiazepines are associated with a higher risk of abuse and dependence compared to other types of tranquilizer drugs that are misused. They are frequently associated with poly-substance use, particularly with other central nervous system stimulants and depressants, which increase the risk of acute toxicity and death and have been identified as assault or date-rape drugs.

Each year, mounting evidence underscores their negative impact on public health. Consequently, the United Nations Commission on Narcotic Drugs and pertinent international conventions impose stringent controls.

1. *National Poison Data System (NPDS), available in: https://www.aapcc.org/*

The growing worldwide phenomenon of non-medical use and abuse of benzodiazepines is an extremely concerning problem in the Americas. The Hemispheric Drug Strategy 2020 of the Organization of American States (OAS) establishes that: "Member states take the necessary steps to prevent the diversion of pharmaceutical products with psychoactive properties for illicit use and ensure access for legitimate medical and scientific purposes."[2] Illicit, benzodiazepines, often referred to as new psychoactive substances (NPS), are synthetic versions of these medications. They mimic the effects of medically prescribed benzodiazepines but can be more highly potent and have long-lasting effects. The wide range of these illicit substances, along with the constant emergence of new versions, makes it challenging to regulate and control them effectively, complicating drug policy efforts.

Notably, challenges persist in accurately detecting benzodiazepines in laboratory settings, particularly in emergency departments, potentially leading to underreporting of cases. While substantial information exists in countries such as Canada and the United States and countries of the European Union, information remains scarce in Latin America and the Caribbean. In these subregions, early warning systems (EWS) could play a key role in toxicological surveillance to reduce morbidity and mortality from the use of these substances. The aforementioned OAS Hemispheric Drug Strategy and its corresponding Plan of Action (2021-2025) advise member states to establish and/or strengthen national EWS to promote collaboration and the exchange of information with other existing regional or international systems. Indeed, EWS have been identified by the United Nations Office on Drugs and Crime (UNDOC) as a best practice for identifying NPS, synthetics, and other emerging drug threats.

*2. Organization of American States, Secretariat for Multidimensional Security, Inter-American Drug Abuse Control Commission. Hemispheric Drug Strategy, 2020.*

# 1. INTRODUCTION - BENZODIAZEPINES

## 1.1. OVERVIEW

Benzodiazepines are among the world's most prescribed psychotropic substances.[3] Their medical use is consistent with their pharmacological profile: anti-anxiety, sedative, muscle-relaxation, anticonvulsive, and hypnotic. Aspects of their acute and chronic toxicity have been known for decades, as has their potential for abuse and/or dependence.[4] Over the past decade, there has been a notable expansion of the benzodiazepine market, predominantly fueled by their nonmedical and recreational uses. This surge coincides with the emergence of benzodiazepine-type NPS for recreational use either alone or in conjunction with other substances or even exploited as assault or date-rape drugs.

The term "synthetic benzodiazepines" refers to benzodiazepines utilized illicitly without therapeutic intent and, in most countries, lacking medical approval. Nevertheless, synthetic benzodiazepines exist for legitimate applications, for example, diazepam (Valium). Therefore, this paper, which focuses on their illicit use, applies the term "benzodiazepines for illicit use." Recognizing the escalating public health concerns associated with their misuse, international conventions list dozens of benzodiazepines for medical use as controlled substances and in 2023 extended their regulatory scope to encompass benzodiazepines used for illicit purposes.[5]

*3. Domínguez V, Collares M, Ormaechea G, Tamosiunas G. Uso racional de benzodiazepinas: hacia una mejor prescripción. Rev. urug. med. Interna 2016; 3: 14-24.*

*4. Murphy Y, Wilson E, Goldner EM, Fischer B. Benzodiazepine use, misuse, and harm at the population level in Canada: A comprehensive narrative review of data and developments since 1995. Clinical Drug Investigation 2016, 36(7), 519–530. 10.1007/ s40261- 016- 0397- 8.*

*5. Among its recommendations for classification of the psychoactive substances examined during the 46th annual meeting, held October 16–20, 2023, the Expert Committee on Drug Dependence (ECDD) of the World Health Organization (WHO) recommended that the benzodiazepine flubromazepam be kept under surveillance.*

### 1.1.1. CHEMICAL STRUCTURE, RELEVANT TOXICOKINETIC ASPECTS

When used for medical purposes -- e.g., diazepam, bromazepam, alprazolam, clonazepam, midazolam, and flunitrazepam--, the potency of benzodiazepines is linked to how long they stay in the body and their duration of action. Some diazepines are not recommended for adults over the age of 65 or those with liver disease. This is due to how the liver breaks them down, which can lead to harmful effects if not properly metabolized. Moreover, these substances interact with other medications and the metabolization process, affecting their levels in the body, further underscoring the importance of cautious use and close monitoring when prescribed.

### 1.1.2. MECHANISM OF TOXICITY

Benzodiazepines bind to a specific benzodiazepine receptor, which is part of the GABA A (GABA: gamma-aminobutyric acid) receptor system. GABA is an amino acid neurotransmitter that acts as the primary inhibitory neurotransmitter in the mammalian central nervous system (CNS). GABA receptors are found on at least 30–40% of nerve cells in the human brain. This interaction can produce either therapeutic or toxic effects. While benzodiazepines have a wide range of therapeutic uses, overdosing or acute intoxication with them can result in clinical manifestations such as depressed consciousness (which can lead to coma), dizziness, weakness, altered motor coordination, difficulty walking or speaking, anterograde amnesia, etc. The sedative effects of benzodiazepines can be reversed with a medication known as flumazenil, which works by blocking benzodiazepines at their receptor.[6]

*6. Domínguez V, Collares M, Ormaechea G, Tamosiunas G. Uso racional de benzodiazepinas: hacia una mejor prescripción. Rev. urug. med. Interna 2016; 3: 14-24.*

Serious problems can occur when people overdose on highly potent benzodiazepines, particularly those containing halogenic compounds that cause cardiovascular toxicity (e.g., flunitrazepam) when mixed or associated with other substances (notably those that can result in respiratory depression), injuries from falls, aspiration, and traffic accidents from driving under the influence.

Chronic use of benzodiazepines has been linked with altered psychomotor capacity in individuals, as well as cognitive decline and problems with memory and attention.[7,8]

Table 1 summarizes the effects of short and long-term use, as well as other associated complications.


*7. Sud P, Lee DC. Sedatives and hypnotics. In: Nelson, L., Howland, M.A., Lewin, N., Smith, S., Goldfrank, L., & Hoffman, R. eds. Goldfrank's Toxicologic Emergencies. New York: 11th ed. McGraw Hill. 2019; 72: 1084-1193.*

*8. Brunetti P, Giorgetti R, Tagliabracci A, Huestis MA, Busardò FP. Designer Benzodiazepines: A Review of Toxicology and Public Health Risks. Pharmaceuticals 2021, 14, 560. https:// doi.org/10.3390/ ph14060560.*


**Table 1.** Acute and chronic complications and risks associated with benzodiazepine use

| Clinical manifestations and acute complications | Chronic effects | Associated risks |
|---|---|---|
| Depressed /altered level of consciousness potentially leading to dizziness, weakness, altered motor coordination, difficulty walking or speaking, blackouts, and coma, among others. | Memory and attention deficit disorders.<br><br>Motor coordination disorders.<br><br>Abuse, dependence. | Traffic and workplace accidents.<br><br>Injuries, falls.<br><br>Assaults including date rape.<br><br>Risk of withdrawal syndrome in cases of dependence.<br><br>Polysubstance use with other stimulants, depressors and disruptors of the central nervous system. |
| Bradycardia, hypertension. | | |
| Aspiration. | | |

The use of benzodiazepines for medical purposes is recommended for short durations, usually around 2-3 months due to their adverse effects and potential for abuse and/or dependence.[9] In the case of benzodiazepine dependence, the abrupt cessation or sharp reduction in their use can lead to withdrawal syndrome. The severity and duration of withdrawal depend on the half of the specific benzodiazepine in the body and its potency, among other factors. Benzodiazepine withdrawal is characterized by irritability, insomnia, agitation, higher body temperature, seizures, and dysautonomia. In severe cases, if withdrawal is not treated properly, it can be life-threatening.[10]

*9. Domínguez V, Collares M, Ormaechea G, Tamosiunas G. Uso racional de benzodiazepinas: hacia una mejor prescripción. Rev. urug. med. Interna 2016; 3: 14-24.*

*10. Farrell S, Fatovich T. Benzodiazepines. In: Haddad and Winchester's clinical management of poisoning and drug overdose. Shannon, MW, Borron SW, Burns MJ, Haddad LM, Winchester JF eds. Philadelphia: 4th ed. Saunders, Elsevier. Año 2007; 35: 671-686.*

# 2. BENZODIAZEPINES FOR MEDICAL VS. ILLICIT SYNTHETIC NPS BENZODIAZEPINES AS EMERGING DRUGS

Since 2007 there have been growing reports of benzodiazepines for illicit use as emerging drugs.[11] These substances have the same chemical structure as classic benzodiazepines; however, small changes in their molecular composition have led to the synthesis of numerous compounds. These include primarily the 1,4-benzodiazepines, triazolo-benzodiazepines, and thienotriazolodiazepines.[12] The significance of these modifications lies not only in the enormous variety of these compounds but also in their heightened potency and duration of action. Consequently, small doses, either alone or in combination with other substances, can cause acute intoxication or more serious adverse effects.[13] Furthermore, some benzodiazepines exist whose mechanism of action is not fully understood, similar to NPS.

*11. Zawilska JB, Wojcieszak J. An expanding world of new psychoactive substances—designer T benzodiazepines. Neurotoxicology 2019; 73: 8–16. https://doi.org/10.1016/j.neuro.2019.02.015*

*12. Greenblatt HK, Greenblatt DJ. Designer Benzodiazepines: A Review of Published Data and Public Health Significance. Clin Pharmacol Drug Dev 2019; 8, 266–269.*

*13. Brunetti P, Giorgetti R, Tagliabracci A, Huestis MA, Busardò FP. Designer Benzodiazepines: A Review of Toxicology and Public Health Risks. Pharmaceuticals 2021, 14, 560. https:// doi.org/10.3390/ph14060560.*

# 3. THE EPIDEMIOLOGY OF BENZODIAZEPINES FOR ILLICIT USE IN THE AMERICAS IN THE PAST DECADE

## 3.1. THE MOST COMMON SUPPLY, DEMAND, AND RISK SCENARIOS

The use of tranquilizers without a medical prescription is a widespread public health concern in the countries of the Americas. In Brazil, Costa Rica, Peru, and Uruguay, benzodiazepines are among the three most prevalent drugs used for non-medical purposes. In many cases, these substances are medical-grade benzodiazepines that may not necessarily fall within the group of new synthetic benzodiazepines that do not have a therapeutic use. It is estimated that between 1% and 9% of the general population have tried them at least once in their lives.[14]

A study on the supply of benzodiazepines for medical use drawing from data provided by the Network of Medicine Information Centers of Latin America and the Caribbean (known by its Spanish-language name, "Red CIMLAC"), which includes professionals from Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela, revealed that each country has between 6 to 12 registered benzodiazepine drugs, with a median of 10. Some of these countries do not require a special prescription for certain benzodiazepines. Across all countries, general practitioners are authorized to prescribe them; however, in some Latin American countries, dentists and veterinarians also have prescribing authority. The authors of this study highlight the risk of non-medical use, given the different health policies governing prescription and oversight.[15]

*14. Organización de los Estados Americanos (OEA), Secretaría de Seguridad Multidimensional, Comisión Interamericana para el Control del Abuso de Drogas (CICAD). Informe sobre el consumo de drogas en las Américas 2019. Washington, D. C., 2019..*

*15. Speranza N, Viroga S, Naeko SA, Pimentel F, Calvo DM, Cañás M et al. Descripción de la disponibilidad y normas para el uso de las benzodiazepinas en algunos países de América Latina, 2022. Rev Méd Urug 2022; 38(2): e38202 doi: 10.29193/RMU.38.2.1.*

Despite the increasing number of drug seizures and clinical cases involving illicit benzodiazepines in North America, there is currently a dearth of information regarding the supply and usage of illicit benzodiazepines in Latin America and the Caribbean.[16,17]

NPS benzodiazepines are sold as pills, tablets, capsules, patches, and liquids. They are often illicitly marketed as legitimate benzodiazepines for medical use or may appear as adulterants of synthetic opioids, heroin, and synthetic cannabinoids.[18] These substances are frequently obtained on the dark web,[19] leading to less control over sales and underreporting of the supply through drug seizures. Because they are highly potent, the administration of adulterated or counterfeit benzodiazepines on the black market can lead to serious acute intoxications, including fatal ones. Additionally, they can cause severe alterations of consciousness, increasing the risk of assault such as sex offenses, traffic accidents, and workplace incidents.[20] Illicit benzodiazepines are among the drugs most commonly found as a factor in sexual assault cases.[21]

There is a high prevalence of illicit benzodiazepine use in the context of polysubstance use of stimulants, CNS depressors (opioids), and hallucinogens.[22] While this problem has been highly prevalent in recent years, the United States has since 2014 reported more frequent simultaneous use of drugs such as oxycodone, heroin, hydrocodone, methadone, and morphine with alprazolam and diazepam in deaths from overdose.[23]

Benzodiazepine users often combine these drugs with other depressants to enhance euphoria, and with psychostimulants to counteract undesirable effects.[24] The combination of illicit benzodiazepines with synthetic opioids creates a high-risk scenario, as both associated use and adulterations of these substances have been reported. The hypnotic and sedative effects of benzodiazepines, when combined with opioids, significantly increase the risk of overdose, coma, respiratory depression, and fatal intoxications. Researchers in Canada found that the concomitant use of illicit benzodiazepines and opioids increases the risk of hospitalization and emergency department visits by 13%, doubling the risk of death.[25]

*16. Inter-American Drug Abuse Control Commission (CICAD), Organization of American States (OAS). Information Bulletin: Online Sales of Illicit Substances in the Americas. September 2023*

*17. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2023.*

*18. Morgillo A, Marovino E, Mazzarella M, Merandi S, Giordano L, Morgillo CR et al. Old and "New Designer" Benzodiazepines as Crime Facilitating Drugs: A Review of Toxicological and Analytical Aspects. Qeios 2023; ID: 3AZW0Q · https://doi.org/10.32388/3AZW0Q*

*19. United Nations Office on Drugs and Crime (UNODC). The online trafficking of synthetic drugs and synthetic opioids in Latin America and the Caribbean. 2022.*

*20. Zawilska JB, Wojcieszak J. An expanding world of new psychoactive substances—designer T benzodiazepines. Neurotoxicology 2019; 73: 8–16. https://doi.org/10.1016/j.neuro.2019.02.015*

*21. United Nations Office on Drugs and Crime (UNODC). Current NPS Threats. Volume V, October 2022.*

*22. Brunetti P, Giorgetti R, Tagliabracci A, Huestis MA, Busardò FP. Designer Benzodiazepines: A Review of Toxicology and Public Health Risks. Pharmaceuticals 2021, 14, 560. https:// doi.org/10.3390/ph14060560*

*23. United Nations Office on Drugs and Crime (UNODC). Global Smart Update. Non-medical use of benzodiazepinas: a growing threat to public health? Volume 18, September 2017.*

*24. Russell C, Lawa J, Bonn M, Rehma, J, Alia F. The increase in benzodiazepine-laced drugs and related risks in Canada: The urgent need for effective and sustainable solutions. International Journal of Drug Policy 2023;111: 103933. https://doi.org/10.1016/j.drugpo.2022.103933*

The UNODC EWA NPS Portal and International Collaborative Exercise Portal indicate that in 2022 benzodiazepines were the most reported drugs, accounting for 47% of all post-mortem case reports and 67% of cases of driving under the influence. The most frequently reported benzodiazepines for illicit use were etizolam (n=141), clonazolam (n=140), flualprazolam (n=107), and flubromazolam (n=89).[26]

In 2023, the Portal reported 133 post-mortem cases in which 191 reports of benzodiazepines NPS were found, accounting for 52% of the drugs reported, including etizolam (n=30), flualprazolam (n=20), and flubromazolam (n=17).[27]

In the United States, the Centers for Disease Control and Prevention reported that, between April–June 2019 and April–June 2020, overdose deaths resulting from illicit benzodiazepine-involved overdose increased 519.5%, whereas deaths from prescriptions drugs increased only 21.8% Between January 2019 and June 2020, benzodiazepines were reported to be involved in approximately 7,000 fatal acute intoxications in 23 states, accounting for 17% of all overdose deaths in the country. Furthermore, NPS benzodiazepines were detected in 12,499 overdose deaths in the United States between 2019 and 2021.[28] The benzodiazepines most frequently involved in these deaths were etizolam, flualprazolam, clonazolam, flubromazolam, and diclazepam, leading to the control of these substances by the Drug Enforcement Administration.[29]

*25. Sharma V, Simpson SH, Samanani S, Jess E, Eurich DT Concurrent use of opioids and benzodiazepines/Z-drugs in Alberta, Canada and the risk of hospitalization and death: a case cross-over study. BMJ Open 2020; 10(11), Article e038692.*

*26. United Nations Office on Drugs and Crime (UNODC). Current NPS Threats. Volume V, October 2022: https://www.unodc.org/unodc/en/scientists/current-nps-threats.html*

*27. United Nations Office on Drugs and Crime (UNODC). Current NPS Threats. Volume VI, October 2023.*

*28. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report: Trends in Nonfatal and Fatal Overdoses Involving Benzodiazepines—38 States and the District of Columbia, 2019–2020. Vol. 70, No. 34. August 27, 2021.*

*29. Drug Enforcement Administration (DEA). Five Synthetic Benzodiazepine Drugs Deemed Imminent Hazard to Public Safety. Available at: https://www.dea.gov/es/node/220266 (consulted March 8, 2024).*

## 3.2. SYNTHETIC BENZODIAZEPINE CONTROL UNDER INTERNATIONAL CONVENTIONS

More than 30 benzodiazepines for medical use are listed in the 1971 Convention on Psychotropic Substances. In recent years, various benzodiazepines such as NPS have been added to List IV of that Convention:

**Flualprazolam:** Is a triazolo-benzodiazepine, detected in drug seizures as tablets and, less often, in powder, patch, or liquid form. Its chemical structure is similar to that of alprazolam and triazolam. Users report acute effects such as depressed consciousness, sedation, disinhibition, and memory issues. It has a dependency mechanism similar to that found in alprazolam users. Acute intoxication, traffic accidents, and more than 25 fatalities have been reported in individuals exposed to flualprazolam. The UNODC's NPS Early Warning Advisory (EWA) Portal included 42 reports involving flualprazolam between 2017 and 2019, 40 of them being clinical cases in the United States.[30]

**Etizolam:** Also known as thienobenzodiazepine has been used for medical purposes in some countries but is sold and distributed on the black market in tablet and powder form. Its effects are similar to those of other benzodiazepines, including the risk of abuse and dependence. It has been implicated in fatalities in combination with other drugs (synthetic opioids, synthetic cathinones, and other benzodiazepines) and detected in drivers.[31]

*30. WHO Expert Committee on Drug Dependence: Beardsley PM, Brands B, Ekwere IT, Elliott S, Jain R, Kaduri P, Kitanaka J, Pascale A, Rahimi-Movaghar A, Nudmamud-Thanoi S, White J, Forty-second report (WHO Technical Report Series; No. 1026). World Health Organization (2020). ISBN 978-92-4-000184-8 (electronic version). ISBN 978-92-4-000185-5 (print version). ISSN 0512-3054.*

*31. WHO Expert Committee on Drug Dependence: Beardsley PM, Best W, Brands B, Ekwere IT, Elliott S, Jain R, Kaduri P, Kitanaka J, Pascale A, Rahimi-Movaghar A, Nudmamud-Thanoi S, White J, Forty-third report (WHO Technical Report Series; No. 1034). World Health Organization (2021). ISBN 978-92-4-002302-4 (electronic version). ISBN 978-92-4-002303-1 (print version). ISSN 0512-3054.*

**Clonazolam:** Is a 1,4-triazolo-benzodiazepine with a similar structure to clonazepam, triazolam, and alprazolam. It is distributed on the black market in various forms, including tablets, powder, patches, and liquid. Clonazolam produces effects akin to other benzodiazepines, and its use has been linked to traffic accidents, and non-fatal acute intoxications. It also has the potential to lead to dependence.[32]

**Diclazepam:** A 2-chloro derivative of diazepam with similar effects, diclazepam is sold on the black market in tablet or liquid form. It metabolizes into other benzodiazepines such as lorazepam. Diclazepam increases the risk of unintentional opioid overdose due to its long elimination half-life, which can lead to accumulation and interactions when combined with other drugs. Its use has been reported among drivers involved in traffic accidents and as an assault or date-rape drug.[33]

**Bromazolam:** A triazolo-benzodiazepine, commonly found on the black market in tablets, capsules, powder, liquid, and chewable candies. It is often sold either in its pure form or as an adulterant mixed with other benzodiazepines for illicit purposes. Bromazolam is highly potent and has a short and intermediate elimination half-life. Its use is associated with hypnotic, sedative, and euphoric effects. There has been a steady increase in seizures of this substance, with laboratory confirmation of its presence in traffic accidents, as well as acute intoxications, including fatal overdoses.[34]

*32. WHO Expert Committee on Drug Dependence: Beardsley PM, Best W, Brands B, Ekwere IT, Elliott S, Jain R, Kaduri P, Kitanaka J, Pascale A, Rahimi-Movaghar A, Nudmamud-Thanoi S, White J, Forty-third report (WHO Technical Report Series; No. 1034). World Health Organization (2021). ISBN 978-92-4-002302-4 (electronic version). ISBN 978-92-4-002303-1 (print version). ISSN 0512-3054.*

*33. WHO Expert Committee on Drug Dependence: Beardsley PM, Best W, Brands B, Ekwere IT, Elliott S, Jain R, Kaduri P, Kitanaka J, Pascale A, Rahimi-Movaghar A, Nudmamud-Thanoi S, White J, Forty-third report (WHO Technical Report Series; No. 1034). World Health Organization (2021). ISBN 978-92-4-002302-4 (electronic version). ISBN 978-92-4-002303-1 (print version). ISSN 0512-3054*

*34.WHO Expert Committee on Drug Dependence. Forty-sixth Meeting. Bromazolam-critical review. World Health Organization 2023. Available at: https://cdn.who.int/media/docs/default-source/46th-ecdd/bromazolam_46th-ecdd-critical-review_public-version.pdf?sfvrsn=4f1bccfa_1 (consulted March 3, 2024).*

**Flubromazolam:** Is a 1,4-triazolo-benzodiazepine available on the black market in tablet and liquid forms. It is highly potent and long acting, with effects similar to those of alprazolam and triazolam. Users have reported tolerance and withdrawal syndromes, indicating its potential for dependence. Flubromazolam use by itself has been related to traffic accidents, and there are cases of its use in combination with opioids. Additionally, it is sometimes sold on the black market as a benzodiazepine intended for medical use.[35]

*35. Among the recommendations of the Expert Committee on Drug Dependence (ECDD) of the World Health Organization on classification of the psychoactive substances examined at its 46th annual meeting, held October 16–20, 2023, was that the benzodiazepine flubromazepam be kept under surveillance.*

# 4. PUBLIC HEALTH IMPACT OF THE ILLICIT USE OF BENZODIAZEPINES IN THE AMERICAS

## 4.1 ACUTE INTOXICATIONS: POLYSUBSTANCE USE, RISKY BEHAVIOR, AND POTENTIAL FOR ABUSE AND DEPENDENCE

NPS benzodiazepines share a similar structure with classic benzodiazepines; however, their molecular alterations often result in increased affinity for receptors in the central nervous system, leading to stronger effects on the body and brain, including acute and chronic toxicity. Clinical manifestations may include dizziness, muscle weakness, altered motor coordination, depressed consciousness potentially progressing to coma, confusion, hallucinations, and cardiovascular issues such as bradycardia and hypertension. The risk of respiratory depression is heightened when these substances are combined with other depressants like alcohol or synthetic opioids. Blackouts associated with their use can expose individuals to significant risks including involvement in criminal activities, road accidents, workplace incidents, or be indicative of assault or coercion.[36]

Tolerance, where habitual users require higher doses to achieve the same effects, is common among benzodiazepine users. Withdrawal syndrome, which can start at different times and last varying durations, has been observed in those who use benzodiazepines illicitly. Symptoms may include agitation, seizures, paranoia, and delirium, which can result in lasting neuropsychiatric effects or even fatalities.[37]

*36Liebrenz M, Schneider M, Buadze A, Gehring MT, Dube A, Caflisch C. High-dose benzodiazepine users' perceptions and experiences of anterograde amnesia. Journal of the American Academy of Psychiatry and the Law Online 2016; 44(3), 328–337.*

*37. Lann MA, Molina DK. A fatal case of benzodiazepine withdrawal. American Journal of Forensic Medicine and Pathology 2009; 30(2), 177–179. 10.1097/PAF.0b013e3181875aa0.*

## 4.2. CASE REPORTS

Reported cases of illicit benzodiazepine use involve acute intoxications, fatal overdoses, incidents of driving under the influence, traffic accidents, robberies, and sex offenses, as they are often utilized as assault or date-rape drugs. Etizolam, flualprazolam, flubromazepam, clonazolam, diclazepam, bromazolam, and adinazolam are among the NPS benzodiazepines cited in these incidents. Data from poison control centers in the United States indicate that they are the most frequently encountered substances in overdose cases.[38] As mentioned earlier, polysubstance use is prevalent, making it challenging to attribute deaths to a single substance, especially when combined with highly toxic drugs like fentanyl and its derivatives.[39] Nonetheless, the use of illicit benzodiazepines and the associated risks are increasingly concerning.

## 4.3. THE TOXICOLOGY LABORATORY FOR THE IDENTIFICATION OF ILLICIT BENZODIAZEPINES

Cross-reactivity between new synthetic benzodiazepines and traditional medical ones has been observed due to their similar basic structure. As a result, immunoassays are highly sensitive but may yield positive results for classic benzodiazepines when in fact the substance is an NPS. Accurate identification remains limited with conventional techniques used in hospital emergency departments, which lack the sophistication of more advanced analytical confirmation methods. Furthermore, even with improved analytical techniques, the absence of protocols to identify specific substances or their metabolites in illicit benzodiazepines hampers detection capabilities. Additionally, the wide variety of pharmacokinetic properties of these substances creates a broad window for detection, ranging from an hour to several days.[40]

The abundance of new synthetic benzodiazepines presents challenges in optimizing analytical techniques, which are predominantly used in forensic scenarios or cases with forensic implications. Currently, there are limitations in detecting them in hospital emergency departments, particularly in cases of non-fatal acute intoxication, especially in Latin America and the Caribbean.

*38. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report: Trends in Nonfatal and Fatal Overdoses Involving Benzodiazepines—38 States and the District of Columbia, 2019–2020. Vol. 70, No. 34. August 27, 2021.*

*39. Canadian Centre on Substance Use and Addiction (CCSA). (2022). Sedatives chrome- extension://efaidnbmnnnibpcajpcglclefindmkaj/ Available at: https://www.ccsa.ca/sites/default/ files/2022- 06/CCSA- Canadian- Drug- Summary- Sedatives- 2022- en_0.pdf (consulted March 8, 2024).*

*40. United Nations Office on Drugs and Crime (UNODC). Current NPS Threats. Volume V, October 2022.*

## 4.4. ROLE OF EARLY WARNING SYSTEMS IN THE COMMUNICATION OF EMERGING CASES AND RISKS:

### PUBLIC ALERTS

CICAD's Hemispheric Drug Strategy and Plan of Action underscore the significance of establishing national EWS as a pivotal measure to tackle the challenges posed by NPS, synthetics, and other emerging substances while promoting collaboration and information sharing with other existing regional or global systems. The significance of sharing NPS information globally is further reinforced by the United Nations Commission on Narcotic Drugs (CND) Resolution 56/4.

CICAD's Inter-American Observatory on Drugs (OID, by its Spanish-language acronym) directs and oversees the Early Warning System of the Americas (SATA, by its Spanish-language acronym), which was established in 2019. The SATA relies on alerts generated by national EWS and functions as a conduit for communicating and distributing emerging drug alerts throughout the Western Hemisphere, thereby fostering international collaboration.

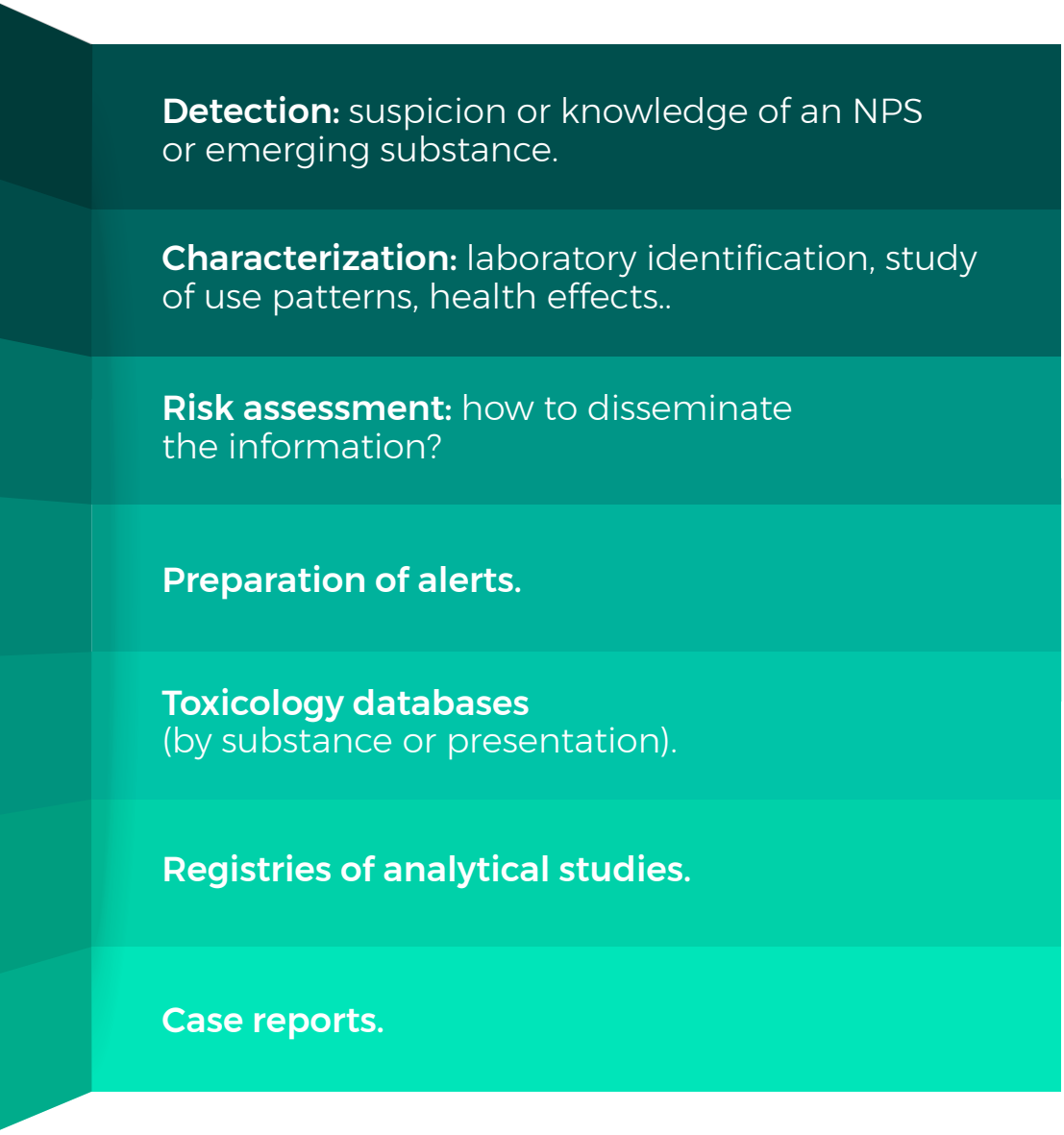
As highlighted on the UNODC's NPS EWA Portal, the information provided by national early warning systems is crucial for evaluating the supply and demand issues related to NPS, particularly benzodiazepines.

National EWS play a vital role in the early detection and reporting of NPS, including benzodiazepines (see Figure 1). These systems monitor emerging drug trends and provide timely information on new and potentially dangerous substances. They are key players in toxicological surveillance, which is crucial for identifying acute intoxications and public health threats posed by NPS benzodiazepines. By collecting and analyzing data on drug-related incidents, EWS inform public health responses and policy decisions, leading to the issuance of public health alerts and warnings about new substances. This increased awareness and preparedness among healthcare providers, law enforcement, and the public helps prevent harm.

The SATA enhances the efforts of national EWS across the Americas by coordinating and integrating their activities. It promotes the sharing of information and best practices, improving the collective understanding and response to emerging drug threats. By facilitating communication between national EWS and international bodies like the UNODC, SATA strengthens the global response to NPS benzodiazepines.

SATA also supports the development and implementation of policies and strategies aimed at reducing the supply and impact of NPS benzodiazepines. In alignment with the OAS Hemispheric Drug Strategy and its Plan of Action, the OID advises member states on establishing and strengthening their EWS. Furthermore, the OID, in collaboration with international partners, enhances the analytical capabilities of national laboratories, addressing the technical challenges associated with the detection of NPS benzodiazepines. This includes improving the accuracy of identification techniques and managing issues like cross-reactivity.

**Figure 1.** Stages and resources utilized by the national EWS.



OAS | CICAD

INTER-AMERICAN DRUG ABUSE CONTROL COMMISSION (CICAD)

INFORMATION BULLETIN

# ADDRESSING THE INCREASE IN ILLICIT USE OF BENZODIAZEPINES IN THE AMERICAS