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WHO Expert Committee on Drug Dependence

Forty-seventh report

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WHO Expert Committee on Drug Dependence: forty-seventh report (WHO Technical Report Series No. 1065)

ISBN 978-92-4-010764-9 (electronic version)
ISBN 978-92-4-010765-6 (print version)
ISSN 0512-3054

Contents

Acknowledgements

The World Health Organization (WHO) is grateful for the contribution of many individuals and organizations to this Expert Committee. The 47th meeting of the Expert Committee on Drug Dependence (ECDD) was organized under the overall direction of Yukiko Nakatani (Assistant Director General, Division of Access to Medicines and Health Products, WHO) and Deusdedit Mubangizi (Director, Department of Health Products Policy and Standards, WHO). Dilkushi Poovendran (Technical Officer, Expert Committee on Drug Dependence, WHO) coordinated the work of the meeting. Technical support to the meeting was provided by Michelle Coghlan (Consultant, ECDD) and Ana Munoz Arranz (Consultant, ECDD), Tina Lam (Monash University, Australia), Jason White (Yeltana Consulting, Australia), and Suzanne Nielsen (Monash University, Australia). Administrative support was provided by Rosa Andolfato and Samia Chaibi.

The WHO secretariat gratefully acknowledges the technical guidance and input of all contributors.

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Technical editing

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Provision of data
The WHO secretariat gratefully acknowledges the participation of the United Nations Office on Drugs and Crime (UNODC) and the International Narcotics Control Board (INCB) in the meeting and for providing data. Technical data were also received from the European Union Drugs Agency (EUDA) and from Member States, which contributed to prioritization of substances and provided information to the secretariat on the Member State questionnaire.

Abbreviations

AUC	area under the dose–concentration curve
BRET	bioluminescence resonance energy transfer
C_{max}	maximum concentration
CAS	Chemical Abstracts Service
CB	cannabinoid
CBD	cannabidiol
CI	confidence interval
3-CMC	3-chloromethcathinone
CYP	cytochrome P
EC_{50}	half maximum concentration
ECDD	Expert Committee on Drug Dependence
ED_{50}	median effective dose
E_{max}	maximum effect
ELISA	enzyme-linked immunosorbent assay
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EWA	Early Warning Advisory
GABA	γ-aminobutyric acid
GC	gas chromatography
HHC	hexahydrocannabinol
INCB	International Narcotics Control Board
InChI	International Chemical Identifier
INN	International Nonproprietary Name
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
K_i	dissociation constant

LC	liquid chromatography
MOR	μ-opiod receptor
MS	mass spectrometry
NFLIS	National Forensic Laboratory Information System
NMR	nuclear magnetic resonance
NPS	novel psychoactive substance
3-OH-PCP	3-hydroxyphencyclidine
pO_2	partial pressure of oxygen
pCO_2	partial pressure of carbon dioxide
PCP	1-piperidinyl)cyclohexyl]phenol
QTOF	quadripole time-of-flight
SMILES	simplified molecular input line entry system
THC	tetrahydrocannabinol
TLC	thin-layer chromatography
UNODC	United Nations Office on Drugs and Crime
UV	ultraviolet
WEDINOS	Welsh Emerging Drugs and Identification of Novel Substances
WHO	World Health Organization

Executive summary

The International Drug Control Conventions of 1961 and 1971 mandate WHO to make recommendations to the United Nations Secretary-General on the necessity for and level of international control of psychoactive substances according to the advice of its independent scientific advisory body, the Expert Committee on Drug Dependence (ECDD).

At its 47th meeting, the ECDD critically reviewed seven new psychoactive substances, comprising one synthetic cannabinoid (CB) (hexahydrocannabinol, HHC), four novel synthetic opioids (protonitazepyne, metonitazepyne, etonitazepipne, *N*-desethyl isotonitazene), one dissociative-type substance (3-hydroxyphencyclidine) and one cathonine/stimulant (*N*-ethylheptedrone). It also reviewed the medicine carisoprodol. A critical review was undertaken of data on the use of each substance and its effects, so that the Expert Committee could determine whether the information available on these substances justified scheduling in the 1961 or 1971 Convention.

After the 47th meeting of the ECDD, WHO endorsed and submitted the following recommendations to the United Nations Secretary-General for further consideration by the Commission on Narcotic Drugs.

Recommendation	Substance name	International Union of Pure and Applied Chemistry (IUPAC) name
To be added to Schedule I of the Single Convention on Narcotic Drugs (1961)	**Etonitazepipne**	IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1H-benzoimidazole Alternate names: *N*-piperidinyl etonitazene
	***N*-Desethyl isotonitazene**	IUPAC name: *N*-ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine Alternate names: norisotonitazene
	***N*-Pyrrolidino metonitazene**	IUPAC name: 2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole Alternate names: metonitazepyne
	***N*-Pyrrolidino protonitazene**	IUPAC name: 2-[(4-Propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole Alternate names: protonitazepyne
To be added to Schedule II of the Convention on Psychotropic Substances (1971)	**Hexahydrocannabinol**	IUPAC name: 6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol Alternate names: HHC

To be added to Schedule IV of the Convention on Psychotropic Substances (1971)	**Carisoprodol**	IUPAC name: 2-[(carbamoyloxy)methyl]-2-methylpentyl(1-ethylethyl)carbamate International nonproprietary name: Carisoprodol
To be kept under surveillance	**3-Hydroxyphencyclidine**	IUPAC name: 3-[1-(1-Piperidinyl)cyclohexyl]phenol) Alternate names: 3-OH-PCP
	***N*-Ethylheptedrone**	IUPAC name: 2-(Ethylamino)-1-phenylheptan-1-one Alternate names: *N*-ethylnorheptedrone

In addition, the Forty-seventh ECDD received an informal update from the secretariat regarding a critical review of coca leaf planned for 2025.

1. Information meeting

WHO Expert Committee meetings are closed to the public. On 14 October 2024, a public information meeting was held so that individuals and entities external to WHO could listen to an update on current and future activities of the ECDD secretariat, and to provide comment on issues on the ECDD agenda.

The session was attended by 172 participants from 48 countries, representing governments, academia, civil society, international organizations and private entities.

1.1 Welcome and opening of the meeting

The 47th ECDD Information Session was opened and chaired by Deusdedit Mubangizi, Director of WHO Department of Health Product Policy and Standards, who outlined the primary objectives of the meeting and highlighted the significant role of WHO and the ECDD in evaluating psychoactive substances under international conventions. He noted the ECDD's comprehensive substance assessment approach, including the prioritization and review of novel psychoactive substances (NPS) due to their rapid emergence and serious public health threats. Mubangizi welcomed the diverse perspectives and acknowledged contributions from written statements and oral presentations, stressing the value of this input in enriching the Committee's deliberations and supporting comprehensive public health protection efforts.

1.2 Role and mandate of the WHO Expert Committee on Drug Dependence (ECDD)

Dilkushi Poovendran, Technical Officer, ECDD, outlined WHO's mandate under the 1961 and 1971 international drug control conventions. Through its ECDD, WHO evaluates substances for international control based on their potential for dependence, abuse, and public health risks, while considering possible therapeutic applications.

1.2.1 WHO ECDD review procedure and processes

WHO convenes the ECDD in accordance with WHO Regulations on Expert Advisory Panels and Committees. The processes and procedures undertaken by WHO to fulfil its treaty responsibilities are described in full in the Guidance on the WHO review of psychoactive substances for international control. Poovendran described the multi-stage review process, methods of initiation of a review process, as well as the technical stages of review where WHO gathers scientific

data, collaborates with global health and drug monitoring bodies, and consults stakeholders to build comprehensive profiles of each substance. It was explained that the 47th ECDD is reviewing eight substances for international control recommendations, as well as an informal update on coca leaf, which will be ongoing a critical review in 2025, with input solicited from multiple stakeholders. WHO ECDD's pre-review and critical review reports are widely accessible, supporting global efforts to manage psychoactive substances responsibly.

1.3 WHO traditional, complementary, and integrative medicine

Pradeep Dua, Technical Officer for Traditional, Complementary, and Integrative Medicine, discussed the cultural and medicinal uses of coca leaves, traditionally consumed as tea or chewed in regions like South America and parts of Asia. He noted that coca leaf is employed in homeopathic and traditional medicine for a range of conditions, including stomach issues, fatigue, altitude sickness, and as a topical anesthetic. While coca leaves and their constituent, cocaine, are classified as Schedule I substances under the 1961 Single Convention, Dua emphasized that effective regulatory provisions need to be in place to curb the illegal isolation and usage of the psychoactive compounds like cocaine by virtue of unwarranted use of herbs like Erythroxylon coca, used as regulated traditional medicine in few member states. He highlighted the importance of comprehensive scientific reviews and controlled trials to assess the safety and efficacy of coca leaves in medical applications.

1.4 Presentations and statements from participants

The 47th ECDD information session received 13 oral statements and 23 written statements for consideration. The 13 oral statements included 12 interventions on the informal update on the ECDD review of coca leaf (Diego Pacheco Balanza, Vice Presidency of the Plurinational State of Bolivia, Bolivia; Álvaro Enrique Ayala Mélendez, Colombia Permanent Mission to the UN, Colombia; Carlos Figueroa Henostroza, National Commission for Development and Drug-Free Life, Peru; Vivian Tatiana Camacho Hinojosa, Traditional Medicine Health Ministry, Bolivia; Hernan Vales, OHCHR, Indigenous Peoples and Minorities Section, Switzerland; Luis Fernando Rojas Terrazas, Universidad Tecnica Privada Cosmos, Bolivia; Eduardo Chilon, Aymara Tupak Katari Bolivian University, Bolivia; Jesus Gomez Paye, Bolivian Institute of Kallawaya Traditional Medicine, Bolivia; Marie Nougier, International Drug Policy Consortium, United Kingdom; Zara Snapp, Instituto RIA, AC/Acción Técnica Social, Colombia; Iván Lorenci de Francisco, Sikh Human Rights Group, Switzerland; Ana Pamela Quezada, International Mental Health Network, Peru) and one intervention on the critical review of hexahydrocannabinol (Mukesh Ambwani, Red Crescent Medical and Diagnostic

Centre, Pakistan). The 23 written statements included 20 contributions to the informal update on the ECDD review of coca leaf (Diego Pacheco Balanza, Vice Presidency of the Plurinational State of Bolivia, Bolivia; Álvaro Enrique Ayala Mélendez, Permanent Mission to the UN and other international organisations, Colombia; Carlos Figueroa Henostroza, Permanent Mission of Peru, Peru; Vivian Tatiana Camacho Hinojosa, Health Ministry, Bolivia; Hernan Vales, OHCHR, Switzerland; Luis Fernando Rojas Terrazas, Universidad Tecnica Privada Cosmos, Bolivia; Eduardo Chilon, Aymara Tupak Katari Bolivian University, Bolivia; Jesus Gomez Paye, Bolivian Institute of Kallawaya Traditional Medicine, Bolivia; Kunihiro Seki, High Altitude Pulmonary and Pathology Institute, Japan; Marie Nougier, International Drug Policy Consortium, United Kingdom; Diego Garcia-Devis, Open Society Foundations, Colombia; Constanza Sánchez Avilés, ICEERS, España; Natalia Rebollo, ICEERS, Mexico; Martin Jelsma, Transnational Institute, Netherlands (Kingdom of the); Iván Lorenci de Francisco, Sikh Human Rights Group, Switzerland; Dora Lucila Troyano Sanchez, Alianza Coca Para la Paz, Colombia; Zara Snapp, Instituto RIA/Acción Técnica Social, Mexico/Colombia; Ana Pamela Quezada, International Mental Health Network, Peru; Kenneth Headrick, United States; Anthony Henman, United Kingdom), two contributions to the critical review of hexahydrocannabinol (Nikolaos Avgerinos, Organization Against Drugs, Greece; Mukesh Ambwani, Red Crescent Medical and Diagnostic Centre, Pakistan) and one contribution to the critical review of carisoprodol (Nikolaos Avgerinos, Organization Against Drugs, Greece). The information from the oral and written interventions was compiled as a report and provided to the Committee.

2. Meeting report of the 47th Expert Committee on Drug Dependence

The 47th meeting of the WHO ECDD was convened on 14–18 October 2024 and coordinated from WHO headquarters in Geneva, Switzerland. A list of participants to the meeting can be found in Annex 2.

2.1 Opening of meeting and welcoming remarks

Deusdedit Mubangizi welcomed all participants on behalf of the WHO Director-General and thanked the ECDD members for their work in reviewing the substances on the agenda. He recalled WHO's mandate under the 1961 Single Convention on Narcotic Drugs *(1)* and the 1971 Convention on Psychotropic Substances *(2)*, which is to assess psychoactive substances with potential for abuse and dependence that harm health and, when relevant, to assess therapeutic use of the substances. He recalled that evidence-based assessment of psychoactive substances as mandated by the international drug control conventions is central to the work of the ECDD. He reminded participants that they were acting in their personal capacities and not as representatives of their governments.

2.2 Procedural matters

A representative of the WHO Office of the Legal Counsel said that the Expert Committee was convened in accordance with WHO's Regulations for Expert Advisory Panels and Committees *(3)* and the Guidance on the WHO review of psychoactive substances for international control *(4)*. The functions of the ECDD are therefore to review the information provided to it on the substances being considered for international control and for exemptions and to advise the Director-General on such control. ECDD members were also reminded of the confidentiality of the ECDD's deliberations.

A representative of the WHO Office of Compliance, Risk Management and Ethics explained that competing interests in health care may result in conflicts of interest, in biased generation or assessment of evidence and in misinformed health-care policies. WHO has a stringent policy on avoiding conflicts of interest, particularly in the preparation of official guidance documents that affect health care. As a declaration of conflicts of interest is insufficient to neutralize potentially harmful effects, the Organization has mechanisms for accurate identification of relevant conflicts of interest and approaches to managing any conflicts (such as exclusion of members, recusal from participation in meeting sessions, restricting

participation), thus ensuring the validity, transparency and credibility of the Expert Committee's decisions.

In accordance with WHO policy, all members of the Expert Committee and all temporary advisers attending the meeting were asked to submit written disclosures of potential conflicts of interest that might affect, or might reasonably be perceived to affect, their objectivity and independence in relation to the subject matter of the meeting. The WHO ECDD secretariat received several disclosures and sought the advice of the Office of Compliance, Risk Management and Ethics in addressing them. It was determined that none of the interests declared by members of the Expert Committee or temporary advisers would prevent their participation in the work of the group.

The members of the Expert Committee elected Simon Elliott as Chair, Afarin Rahimi-Movaghar as Vice-Chair and Pamela Kaduri as Rapporteur. The Chair welcomed all participants, and the meeting approved the agenda proposed by the secretariat.

2.3 Updates on WHO ECDD meetings and recommendations

2.3.1 Recommendations and outcomes of the 46th ECDD

The Committee noted that the 46th ECDD, which convened on 16–20 October 2023, made the following recommendations.

To be added to Schedule I of the Single Convention on Narcotic Drugs (1961):

- Butonitazene

To be added to Schedule II of the Convention on Psychotropic Substances (1971):

- 3-Chloromethcathinone
- Dipentylone
- Flurodeschloroketamine

To be added to Schedule IV of the Convention on Psychotropic Substances (1971):

- Bromazolam

The Committee recommended the following substance for critical review:

- Carisoprodol

The Committee recommended that the following substances be kept under surveillance:

- Flubromazepam
- Nitrous oxide

The WHO Director-General communicated the recommendations of the ECDD to the United Nations Secretary-General, who presented them to the Commission on Narcotic Drugs at its 66th session in December 2023. Subsequently, at its 67th session, on 19 March 2024, the Commission decided by 48 votes to none, with one abstention, to include butonitazene in Schedule I of the 1961 Convention (Decision 67/1).

The Commission decided by 50 votes to none, with one abstention, to include 3-chloromethcathinone in Schedule II of the 1971 Convention (Decision 67/2), to include dipentylone in Schedule II of the 1971 Convention (Decision 67/3), to include 2-flurodeschloroketamine in Schedule II of the 1971 Convention (Decision 67/4) and to include bromazolam in Schedule IV of the 1971 Convention (Decision 67/5).

Therefore, all the recommendations made by the 46th ECDD were accepted by the Commission on Narcotic Drugs, effectively placing five new psychoactive substances under international control.

2.3.2 Recommendations from working group on substance surveillance

On 13 May 2024, the ECDD working group met to consider substances to be reviewed at the 47th ECDD meeting in October 2024. More than 40 focal points from more than 20 countries and representatives of international organizations with access to data on NPS were approached for information on substances that are not under international control, but for which there is evidence of persistent harmful use. The focal points were selected according to their geographical spread to ensure regional representation and according to their capacity to collect and collate toxicological and epidemiological data related to substances of concern.

An initial literature scan and database search were conducted to find information on each substance identified by the focal points, in addition to substances currently under surveillance by the ECDD Secretariat and substances previously recommended for critical review after a pre-review. A list of 17 substances was made for which information had been found on their pharmacology, toxicology and their risk to public health. The information on each substance was presented to the working group during the meeting.

Substances formally notified to the WHO for review are considered separately and were not discussed at this meeting. Recommendation for pre-review or critical review was based on the availability of reliable information such as on abuse and dependence potential, the extent of use and harm to health arising from use of a substance. After reviewing the information for each substance, the working group recommended that the secretariat consider eight substances for critical review at the 47th ECDD meeting. These were:

- hexahydrocannabinol (HHC)
- *N*-pyrrolidino protonitazene (protonitazepyne)
- *N*-pyrrolidino metonitazene (metonitazepyne)
- etonitazepipne (*N*-piperidinyl etonitazene)
- *N*-desethyl isotonitazene
- *N*-ethylheptedrone
- 3-OH-PCP (3-hydroxyphencyclidine) and
- carisoprodol

The information on a further three substances was determined to be insufficient for a critical review; however, it was agreed that there was emerging evidence of either harmful effects or potential public health or social harm. These substances were placed under surveillance so further information could be collected to inform the need for a critical review. These substances were:

- ethyleneoxynitazene
- *N*-desethyl etonitazene and
- *O*-acetylpsilocin.

2.3.3 Updates on priorities from international agencies

WHO Division of Access to Medicines and Health Products

The Division addresses two areas of work related to the global drug problem: WHO work mandated by the international drug control conventions to be carried out by the ECDD and issues associated with access to controlled medicines.

A recent development is revision of the guidelines for access to and safe use of controlled medicines. A systematic review was commissioned for the guidelines, which is being completed, and a guideline development group met to finalize the recommendations and best practice statements, which will be included in the guidelines, with justifications. Four domains were identified as priorities for an updated systematic review for the guidelines: quantification, procurement and

supply of medicines; medicine regulation and control; prescribing, dispensing and administration; and education, knowledge and attitudes. Systematic reviews of evidence have been conducted in all four domains. A draft guideline is being prepared, to which an expert review group is contributing comments. The new guidelines will assist policymakers, programme managers and experts in countries in formulating and and implementing balanced policies that ensure access to and safe use of controlled medicines while preventing their diversion, nonmedical use and harm to health.

WHO Department of Global HIV, Viral Hepatitis, and Sexually Transmitted Infections

The priorities of the Department include development and oversight of implementation of global health sector strategies on HIV, viral hepatitis and sexually transmitted infections.

People who inject or use drugs for non-medical purposes are disproportionately affected by HIV, viral hepatitis and other infectious diseases. According to the latest WHO estimates, psychoactive drug use was attributed to resulted in almost 600 000 deaths in 2019 from infectious diseases (viral hepatitis B and C, HIV), drug use disorders (including drug overdose), road traffic injuries accidents and suicides. The priorities of the Department, guided by the Global Health Sector Strategies on HIV, viral hepatitis and sexually transmitted infections for 2022–2030, include: "putting people at the centre", addressing the unique priorities for each disease, using a shared, integrated approach to strengthening health and community systems, responding to swiftly changing health and development, and eliminating stigmatization, discrimination and other structural barriers. These strategies were noted with appreciation by the WHO General Assembly, which gave WHO a clear mandate to work with Member States on the new strategic framework until 2030. The guidelines for prevention of HIV, viral hepatitis and sexually transmitted infections include health interventions such as for harm reduction, including for people who inject drugs. The guidelines are a normative product of the Department and were developed in collaboration with people with lived experience of drug use. Other activities include scientific and technical support to the UNITAID programme on hepatitis C prevention and treatment of people who inject drugs and collaboration with Member States in introducing and scaling up use of evidence-based opioid agonist therapy and needle and syringe programs for preventing HIV and viral hepatitis and integrated care. The Department is also updating implementation guidance on needle and syringe programs, planning a regional meeting on evidence-based responses to drug use and infectious disease in the African Region, in which more than 10 countries will participate, and supporting and collaborating with UNODC in the Commission on Narcotic Drugs created by the United Nations General Assembly.

WHO Alcohol, Drugs and Addictive Behaviours Unit, Department of Mental Health, Brain Health and Substance Use

The Alcohol, Drugs and Addictive Behaviours (ADA) Unit works globally to improve health and well-being of populations by articulating, promoting and supporting evidence-informed policies, strategies and interventions to reduce the burden associated with alcohol, drugs and addictive behaviours, and by monitoring their implementation and impact.

Substance use and substance use disorders continue to be a major global health issue. Around 2.6 million deaths were caused by alcohol consumption in 2019 and about 400 million people (or 7% of world population aged 15+) having alcohol use disorders. Non-medical drug use has increased over the last decade to 292 million people (5.6% of 15-64 yr olds) with 64 million living with drug use disorders in 2022. At the same time, the treatment coverage in countries remains scarce, ranging from extremely low (0.3%) to a maximum of 35% for drug use disorders and 14% for alcohol use disorders, according to WHO data. This is confirmed by recent UNODC report, showing that only 1 in 11 people with drug use disorders receiving treatment, with the delivery of services being unequal in relation to gender and other sociodemographic variables.

Drug dependence is a chronic health condition that requires comprehensive, long-term treatment, including both pharmacological and psychosocial interventions. WHO supports countries by developing, disseminating and supporting use of technical guidelines, standards and tools. WHO further supports countries by generating, compiling and disseminating reliable information on the health impacts of psychoactive substance use, the effectiveness of prevention and treatment and the capacity of health systems.

There is a range of products recently published or under development by the unit, such as:

- In 2024, the ADA unit published a Global status report on alcohol and health and treatment of substance use disorders, with a comprehensive overview of the situation with substance use, related harms, policy and health system responses, concluding with broad directions for international action to accelerate progress towards achievement of SDG health target 3.5;
- The ADA unit continues to work on implementation of the UNODC–WHO Programme on Drug Dependence Treatment and Care with direct country support and global advocacy. Within the joint programme, the implementation toolkit is currently being develop for

the WHO/UNODC International Standards for the Treatment of Drug Use Disorders. A training manual on community management of opioid overdose as part of the Stop-Overdose-Safely initiative is about to be launched;

- Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders was updated during recent years, followed by the update of the mhGAP implementation guide;
- The unit has started updating WHO guidelines on treatment of opioid dependence and community management of opioid overdose, to be published in 2026;
- Non-medical cannabis use and related harms continue to be an important issue in many countries, and a new edition of a WHO technical document on the health and social effects of non-medical cannabis use is about to be published;
- The unit is co-chairing the Thematic Group on Addressing Substance Use and Disorders Due to Substance Use in Humanitarian Settings within IASC MHPSS Reference Group, and about to launch an orientation course on substance use and substance use disorders for humanitarian actors who work with communities;
- Two training courses were recently developed within WHO Academy on substance use and substance use disorders: on integration of mental health into primary care (the Mental Health Gap Action Programme e-learning course); and on behavioural counselling in primary care for noncommunicable disease risk factors.

The unit contributes to generation of evidence through international research projects, such as the multisite study on community management of opioid overdose implemented in Kazakhstan, Krygyzstan, Tajikistan and Ukraine; and a multicenter study of the acceptability, feasibility and cost-effectiveness of delivering long-acting depot buprenorphine for treatment of opioid dependence in low- and medium-income countries.

The unit organizes biannual WHO Forum on Alcohol, Drugs and Addictive Behaviour. The next one is planned to take place in Geneva, Switzerland in 2025.

UNODC

Scheduling of substances under the three international drug control conventions continues to be a cornerstone of the rules-based system of ensuring access to

substances for medical and scientific purposes while preventing their abuse. The role of UNODC has been to provide information to Member States about the procedures and scientific and technical reasons for the recommendations of relevant treaty bodies to ensure effective implementation of scheduling decisions. UNODC is therefore involved when possible in risk assessments by WHO with support from scientific advisory groups or expert panels. Since 2014, the Commission on Narcotic Drugs has taken decisions to place 83 substances under various schedules of the 1961 and 1971 Conventions. In addition, seven precursors of fentanyl and its analogues and 21 precursors of amphetamine-type stimulants have been scheduled under the 1988 Convention.

UNODC has continued its programme of developing and disseminating best practice guidelines and manuals for laboratory identification of controlled substances. The UNODC programme for testing the proficiency of national forensic laboratories, the International Collaborative Exercises, conducted tests in 320 forensic drug testing and toxicology laboratories in 90 countries in the past year. The UNODC Early Warning Advisory (EWA) is monitoring over 1258 new psychoactive substances reported in 141 countries and territories and is providing evidence for identification of the most harmful, persistent, prevalent NPS through its toxicology portal. The seventh report in the series of "current NPS threats" was published recently, which continues to provide information for prioritization of substances for action by treaty bodies. This should also ensure early identification and anticipation of threats, timely reductions in the associated risks and appropriate support to enable Member States and the international community to implement appropriate strategies to reduce supplies.

The aim of the UNODC synthetic drug strategy is to support countries in addressing the problem of synthetic drugs, including those causing the opioid crisis. The guidance presented in the strategy is based on four spheres of action: multilateralism and international cooperation, early warning of synthetic drug threats, promoting science and informed health responses, and strengthening country narcotic capacity and international operations to disrupt trafficking and synthetic drugs. To further support implementation of the synthetic drug strategy, the tool kit on synthetic drugs includes more than 500 cross-coding tools and practical resources from the United Nations system, including WHO and the International Narcotics Control Board (INCB). The toolkit now has over 200 000 users worldwide. Its resources are organized into 15 specialized modules, which are available in all six official United Nations languages.

INCB

The mandate and focus for INCB are to:

- limit use of controlled substances to medical, scientific and industrial purposes;
- control requirements for medical use of cannabis;
- ensure respect for human rights in the design and implementation of drug control policies;
- categorically reject extrajudicial responses to drug-related activities;
- possibly adopt alternative measures to address drug-related crime;
- coordinate drug control by national stakeholders; and
- promote universal ratification of the drug control conventions.

The INCB has three goals for 2024. The first is to ensure uninterrupted trade in internationally controlled drugs during emergencies and other urgent situations. The second is to reduce the availability of non-scheduled chemicals, designer precursors and material and equipment for the manufacture of illicit drugs. The third is to ensure that relevant national industrial sectors cooperate proactively with competent national authorities to reduce the risk of exploitation of the industry by drug traffickers.

A current concern of the INCB is continued evolution of illicit drug manufacture, particularly to replace controlled chemical precursors with new substances and to recover controlled precursors from finished licit products available domestically. Currently, 33 chemical precursors are under international control under tables 1 and 2 of the 1988 Convention. An achievement related to the international scheduling of precursors since 2014 is the scheduling of esters of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) in 2024.

2.3.4 Informal update: ECDD review of coca leaf

In June 2023, WHO received an official request from a Member State to conduct a critical review of coca leaf. In accordance with the guidance on WHO review of psychoactive substances for international control, a critical review of coca leaf is planned in 2025 for consideration by the ECDD.

The ECDD Secretariat has finalized the scope of the critical review, which will include coca leaf and preparations of coca leaf, such as coca leaf powder and coca tea, as defined in the 1961 Single Convention. The critical review will exclude cocaine (methyl ester of benzoylecgonine) and preparations of cocaine (including

coca paste), which are currently controlled separately under Schedule I of the 1961 Single Convention. WHO will follow the guidance on the WHO review of psychoactive substances for international control, and the format of the critical review report will be used.

WHO issued an open call for contributions to the critical review report, which will systematically assess and consolidate information from published and unpublished sources, the Member State questionnaire and information received from a public consultation. The Secretariat has invited information, especially scientific evidence in the scope of the critical review, to be submitted for the informal update, and many countries and individuals have asked to share data and information with the ECDD.

The critical review report on coca leaf will be published in September 2025, and submission of data and comments on the critical review will be accepted until the 48th ECDD in October 2025.

2.4 Critical reviews: Recommendations on the scope of international control of psychoactive substances

At its 126th session, in January 2010, the WHO Executive Board approved the publication *Guidance on the WHO review of psychoactive substances for international control (4)*. In accordance with that document, WHO conducts either a pre-review or a critical review. A critical review is initiated by the Expert Committee in any of the following cases:

- a notification has been received from a Party to the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances concerning the scheduling of a substance;
- the Commission on Narcotic Drugs has explicitly requested a review of a substance;
- a pre-review of a substance has resulted in an Expert Committee recommendation for critical review; or
- information has been brought to WHO's attention that a substance is manufactured clandestinely, is an especially serious risk to public health and society and is of no recognized therapeutic use by any Party.

A critical review provides an overview of a substance using peer-reviewed published and unpublished data to allow the Expert Committee to make a recommendation on its scheduling status.

2.4.1 Hexahydrocannabinol

Substance identification

Hexahydrocannabinol (IUPAC name: 6,6,9-Trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol), also known as HHC, has three stereogenic centres, indicating that eight stereoisomers are possible. As a semi-synthetic cannabinoid, however, it is usually found as a mixture of (6aR,9S,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol (9S epimer) and (6aR,9R,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol (9R epimer).

Hexahydrocannabinol has been described as a colourless viscous oil or resin that changes to dark orange after exposure to oxygen. Hexahydrocannabinol-containing products include low- tetrahydrocannabinol (THC) cannabis flowers and resins infused or sprayed with the substance, e-liquids and cartridges for electronic cigarettes, edible products such as gummies and marshmallows, tinctures resembling dietary supplements and distillate oils. The routes of administration include inhalation, oral and sublingual.

WHO review history

Hexahydrocannabinol has not previously been reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

The (9R)-hexahydrocannabinol epimer has CB1 and CB2 receptor binding affinity similar to that of delta-9-THC. Hexahydrocannabinol acts as a partial agonist at the CB1 receptor, as does delta-9-THC, and produces psychoactive effects, including adverse effects, similar to those produced by delta-9-THC. In animals, it has been shown to produce behavioural effects consistent with delta-9-THC. In humans, sleepiness, euphoria, anxiety, agitation, psychosis, tremors and disorientation were reported, in addition to respiratory, cardiovascular and gastrointestinal effects. Hexahydrocannabinol is found in trace amounts as a phytocannabinoid in cannabis plants but is usually synthesized from cannabidiol.

Dependence potential

No studies of the dependence potential of hexahydrocannabinol in animals or

humans have been reported. Its effects at CB1 receptors suggest that it would produce dependence similar to that produced by other cannabinoid partial agonists such as delta-9-THC. Withdrawal effects have been reported in humans, and multiple countries have reported that people who use hexahydrocannabinol have presented for treatment of drug dependence.

Actual abuse and/or evidence of likelihood of abuse

No studies have been reported in animals or humans on the likelihood of abuse of hexahydrocannabinol; however, CB1 receptor agonists have known abuse potential.

Adverse effects including emergency departments presentations for non-fatal intoxications, with symptoms such as dizziness, confusion, unconsciousness, psychosis (hallucinations, delusions and paranoia), anxiety, panic attack, depression, hypertension, nausea and vomiting, similar to those seen with delta-9-THC.

Hexahydrocannabinol has been analytically confirmed in people driving under the influence of drugs and in clinical admissions for drug intoxication in adults and children in multiple countries, including cases in which hexahydrocannabinol was confirmed to be the only substance involved. Seizures of hexahydrocannabinol have been reported in many countries in a number of regions.

Therapeutic usefulness

Hexahydrocannabinol is not known to have any therapeutic use.

Rationale and recommendation

Hexahydrocannabinol [IUPAC name: 6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol], also known as HHC, is a semi-synthetic cannabinoid receptor agonist with a mechanism of action and effects similar to those of delta-9-tetrahydrocannabinol, which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. There is sufficient evidence that hexahydrocannabinol is used in such a way as to constitute a public health and social problem, warranting placement under international control.

The Committee recommended that hexahydrocannabinol [IUPAC name: 6,6,9-Trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol], be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.4.2 *N*-Pyrrolidino protonitazene

Substance identification

N-Pyrrolidino protonitazene (IUPAC name: 2-[(4-Propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole), also known as protonitazepyne, is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

N-Pyrrolidino protonitazene has been described as a beige powder or a white colourless or crystalline solid. *N*-Pyrrolidino protonitazene has been identified in falsified pharmaceutical opioid tablets.

WHO review history

N-Pyrrolidino protonitazene has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that the substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

The chemical structure and pharmacological effects of *N*-pyrrolidino protonitazene closely resemble those of protonitazene, which is controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961.

Studies in animals have demonstrated that *N*-pyrrolidino protonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine and fentanyl. Its effects are blocked by the opioid antagonist naltrexone.

Its adverse effects, documented in clinical presentations, are also consistent with opioid effects, including dizziness, bradycardia, hypotension and respiratory depression.

Dependence potential

No controlled studies of the dependence potential of *N*-pyrrolidino protonitazene in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence in a manner similar to that of other opioids, such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

In animals, *N*-pyrrolidino protonitazene showed opioid effects and abuse potential, with greater potency than fentanyl. Its abuse potential has not been studied in humans. Online self-reports describe typical opioid effects, including relaxation, euphoria and sedation.

Its presence has been analytically confirmed in many deaths and hospital admissions, including as the only substance detected. *N*-Pyrrolidino protonitazene is reported to be administered by various routes, including smoking, snorting and by injection. *N*-Pyrrolidino protonitazene has been available for sale online by Internet retailers.

Seizures of *N*-pyrrolidino protonitazene have been reported in multiple countries in three regions.

Therapeutic usefulness

N-Pyrrolidino protonitazene is not known to have any therapeutic use.

Recommendation

N-Pyrrolidino protonitazene (IUPAC name: 2-[(4-Propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole), also referred to as protonitazepyne, is a synthetic opioid that is liable to abuse and produces ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use causes substantial harm, including death. It has no known therapeutic use.

The Committee recommended that *N*-pyrrolidino protonitazene (IUPAC name: 2-[(4-Propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole), also referred to as protonitazepyne, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.4.3 *N*-Pyrrolidino metonitazene

Substance identification

N-Pyrrolidino metonitazene (IUPAC name: 2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole), also known as metonitazepyne), is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

N-Pyrrolidino metonitazene has been described as a beige powder.

WHO review history

N-Pyrrolidino metonitazene has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

The chemical structure and pharmacological effects of *N*-pyrrolidino metonitazene closely resemble those of metonitazene, which is controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961.

Studies in animals have demonstrated that *N*-pyrrolidino metonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine. Its potency varies from less than to greater than that of fentanyl, depending on the study model. Its effects are blocked by the opioid antagonist, naltrexone.

Dependence potential

No controlled studies of the dependence potential of *N*-pyrrolidino metonitazene in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similar to those of other opioids, such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

In animals, *N*-pyrrolidino metonitazene showed potent opioid effects and abuse potential, similar to those of morphine and fentanyl.

Multiple deaths have been reported in which *N*-pyrrolidino metonitazene was analytically confirmed, including one death in which no other opioids were involved. Other substances were detected in all cases. *N*-Pyrrolidino metonitazene is reported to be administered by injection.

Seizures of *N*-pyrrolidino metonitazene have been reported in multiple countries in two regions.

Therapeutic usefulness

N-Pyrrolidino metonitazene is not known to have any therapeutic use.

Rationale and recommendation

N-Pyrrolidino metonitazene (IUPAC name: 2-[(4-Methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole, also referred to as metonitazepyne, is a synthetic opioid that is liable to abuse and produces ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. There is evidence that its use causes substantial harm, including death. It has no known therapeutic use.

The Committee recommended that *N*-pyrrolidino metonitazene (IUPAC name: 2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole, also referred to as metonitazepyne, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.4.4 Etonitazepipne

Substance identification

Etonitazepipne (IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1H-benzoimidazole), also known as *N*-piperidinyl etonitazene, is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

Etonitazepipne has been described as a crystalline solid and a white-yellowish or yellow powder. It has been identified in falsified pharmaceutical opioid tablets.

WHO review history

Etonitazepipne has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

The chemical structure and pharmacological effects of etonitazepipne closely resemble those of etonitazepyne, which is controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961.

Studies in animals have demonstrated that etonitazepipne is a full agonist at μ-opioid receptors, with greater potency than morphine. Its potency varies from less than to similar to that of fentanyl, depending on the study model. Its effects are blocked by the opioid antagonist, naltrexone. In humans, adverse effects

include respiratory depression and reduced consciousness, which were reversed by naloxone.

Dependence potential

No controlled studies of the dependence potential of etonitazepipne in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similar to that of other opioids such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

In animals, etonitazepipne showed potent opioid effects and abuse potential, similar to those of morphine and fentanyl. These effects were blocked by the opioid antagonist naltrexone.

Non-fatal intoxications requiring hospitalization have been reported. Multiple deaths in which etonitazepipne use was analytically confirmed have been reported in at least two regions, including some in which etonitazepipne was considered the primary cause of death or no other substances were involved. Online self-reports indicate typical opioid effects, including relaxation, euphoria and sedation.

Seizures of etonitazepipne have been reported in multiple countries and regions.

Therapeutic usefulness

Etonitazepipne is not known to have any therapeutic use.

Recommendation

Etonitazepipne (IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1H-benzoimidazole), also referred to as *N*-piperidinyl etonitazene, is a synthetic opioid that is liable to abuse and produces ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. There is evidence that its use causes substantial harm, including death. It has no known therapeutic use.

The Committee recommended that etonitazepipne (IUPAC name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1H-benzoimidazole), also referred to as *N*-piperidinyl etonitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.4.5 *N*-Desethyl isotonitazene

Substance identification

N-Desethyl isotonitazene (IUPAC name: *N*-Ethyl-2-[[4-(1-methylethoxy) phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine), also known as norisotonitazene, is a 5-nitro-2-benzylbenzimidazole synthetic opioid.

N-Desethyl isotonitazene hydrochloride has been described as a crystalline solid. It has also been identified in falsified pharmaceuticals, in the form of round blue tablets.

WHO review history

N-Desethyl isotonitazene has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

N-Desethyl isotonitazene is a major metabolite of and has a similar chemical structure and effects to isotonitazene, which is controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961.

Studies in animals have demonstrated that *N*-desethyl isotonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine. Its potency varies from similar to to greater than that of fentanyl, depending on the study model.

Its effects are blocked by the opioid antagonists naltrexone and naloxone.

Adverse effects, including analgesia, euphoria, miosis, muscle rigidity, unconsciousness, sedation, respiratory depression, coma and hypercapnia, are consistent with opioid toxicity.

Dependence potential

No controlled studies of the dependence potential of *N*-desethyl isotonitazene in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similar to that produced by other opioids, such as morphine and fentanyl.

Actual abuse and/or evidence of likelihood of abuse

In animals, *N*-desethyl isotonitazene showed potent opioid effects and abuse potential. Its potency was greater than that of morphine and varied from similar to to greater than that of fentanyl, depending on the study model. These effects were blocked by the opioid antagonist naltrexone.

Many deaths and hospital admissions associated with *N*-desethyl isotonitazene have been reported in at least two regions, including deaths in which it was considered contributory.

Seizures of *N*-desethyl isotonitazene have been reported in many countries in three regions.

Therapeutic usefulness

N-desethyl isotonitazene is not known to have any therapeutic use.

Recommendation

N-Desethyl isotonitazene (IUPAC name: *N*-Ethyl-2-[[4-(1-methylethoxy) phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine), also referred to as norisotonitazene, is a synthetic opioid that is liable to abuse and produces ill effects similar to those of other opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs.

There is evidence that its use causes substantial harm, including death. It has no known therapeutic use.

The Committee recommended that *N*-desethyl isotonitazene (IUPAC name: *N*-ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1H-benzimidazole-1-ethanamine), also referred to as norisotonitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.4.6 3-Hydroxyphencyclidine

Substance identification

3-Hydroxyphencyclidine (IUPAC name: 3-[1-(1-Piperidinyl)cyclohexyl]phenol) or 3-OH-PCP is an analogue of the dissociative anaesthetic PCP. It has been described as a crystalline solid and white crystalline powder. It has also been found in food products (chocolates).

WHO review history

3-Hydroxyphencyclidine has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

3-Hydroxyphencyclidine is an *N*-methyl-D-aspartate receptor antagonist with a mechanism of action and effects similar to those of PCP, which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Its effects include hallucinations and dissociation.

Dependence potential

No controlled studies in animals or humans were found on the dependence potential of 3-hydroxyphencyclidine.

Actual abuse and/or evidence of likelihood of abuse

Studies in animals suggest that 3-hydroxyphencyclidine has abuse potential similar to that of PCP. No studies to determine the abuse liability of 3-hydroxyphencyclidine in humans have been reported.

It is reported to be administered by various routes, including intranasally and orally. A limited number of cases of fatal and nonfatal intoxication that involved 3-hydroxyphencyclidine in combination with other psychoactive substances have been reported. In most cases, use of 3-hydroxyphencyclidine was not analytically confirmed, and there was limited evidence that it played a causative role.

Limited seizures have been reported in several countries.

Therapeutic usefulness

3-Hydroxyphencyclidine is not known to have any therapeutic use.

Rationale and recommendation

3-Hydroxyphencyclidine (IUPAC name: 3-[1-(1-Piperidinyl)cyclohexyl]phenol) or 3-OH-PCP, is an analogue of and has similar effects to PCP, which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances. Its mode

of action suggests the likelihood of abuse, but there is insufficient evidence that it constitutes a public health and social problem to warrant its placement under international control.

The Committee recommended that 3-hydroxyphencyclidine (IUPAC name: 3-[1-(1-Piperidinyl)cyclohexyl]phenol) or 3-OH-PCP be kept under surveillance by the WHO secretariat.

2.4.7 *N*-Ethylheptedrone

Substance identification

N-Ethylheptedrone (IUPAC name: 2-(Ethylamino)-1-phenylheptan-1-one), also known as *N*-ethylnorheptedrone, ethyl heptedrone or HEP, is a synthetic cathinone. It has been described as a crystalline solid.

WHO review history

N-Ethylheptedrone has not previously been reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on central nervous system

N-Ethylheptedrone is a synthetic cathinone with a chemical structure and pharmacological properties similar to those of other synthetic cathinones (e.g. *N*-ethylhexedrone, pentedrone) that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971.

In common with other cathinone psychostimulants, *N*-ethylheptedrone has been shown to act via dopamine, serotonin and norepinephrine transporters in the central nervous system to increase the concentrations of these neurotransmitters.

Adverse effects documented in a limited number of clinical presentations include agitation and tachycardia.

Dependence potential

No controlled studies of the dependence potential of *N*-ethylheptedrone have been reported in animals or humans.

Actual abuse and/or evidence of likelihood of abuse

Studies in animals demonstrate that *N*-ethylheptedrone has an abuse potential similar to that of methamphetamine and cocaine. No controlled studies on the abuse potential of *N*-ethylheptedrone in humans have been reported.

A single death was reported to have involved *N*-ethylheptedrone and other substances. Several clinical admissions were reported in two countries.

Seizures of *N*-ethylheptedrone have been reported in two regions.

Therapeutic usefulness

N-Ethylheptedrone is not known to have any therapeutic use.

Recommendation

N-Ethylheptedrone (IUPAC name: 2-(Ethylamino)-1-phenylheptan-1-one) is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants. There was, however, insufficient evidence of its use to constitute a public health and social problem to warrant its placement under international control.

The Committee recommended that *N*-ethylheptedrone (IUPAC name: 2-(Ethylamino)-1-phenylheptan-1-one), also known as *N*-ethylnorheptedrone, be kept under surveillance by the WHO secretariat.

2.4.8 Carisoprodol

Substance identification

Carisoprodol (IUPAC name: 2-[(carbamoyloxy)methyl]-2-methylpentyl(1-ethylethyl)carbamate) is a centrally acting skeletal muscle relaxant sold as a single-ingredient preparation and in combination products. Carisoprodol is available as a pharmaceutical product in tablet form, has been detected in falsified pharmaceuticals and is also found as a white powder.

WHO review history

Carisoprodol was pre-reviewed at the 32nd ECDD meeting in 2000. At that time, the Committee did not recommend critical review, noting that sporadic nonmedical use of carisoprodol was not a new phenomenon and there was

no indication of significantly increasing nonmedical use. A new pre-review was initiated in 2023 after an international agency provided information that suggested a significant increase in the reported number of trafficking cases and seizures involving carisoprodol. At the 46th ECDD meeting, increasing evidence of nonmedical use and public health harm led the Committee to recommend that carisoprodol be subject to a critical review.

Similarity to known substances and effects on the central nervous system

Carisoprodol is metabolized to meprobamate and has effects similar to those of other central nervous system depressants, such as meprobamate, phenobarbital, diazepam and chlordiazepoxide, which are listed under schedule IV of the Convention on Psychotropic Substances of 1971. Meprobamate is also a metabolite of carisoprodol. Although its exact mechanism of action is not known, its therapeutic effects appear to be due to modulation of γ-aminobutyric acid (GABA)-A, similar to the action of barbiturates. The sedative effects of carisoprodol can be potentiated when it is combined with benzodiazepines, opioids or alcohol.

Dependence potential

Tolerance and withdrawal have been documented in experimental animals, and potential dependence on carisoprodol is considered to be similar to that of barbiturates and benzodiazepines. In humans in the context of prolonged use, tolerance, withdrawal symptoms and craving have been documented. Increasing numbers of cases of carisoprodol dependence have been recorded in pharmacovigilance reporting systems and clinical settings.

Actual abuse and/or evidence of likelihood of abuse

In animal models of abuse liability, the effects of carisoprodol were similar to those of pentobarbital, chlordiazepoxide and meprobamate and were dose-dependent. In humans, in the context of its nonmedical use at high doses, carisoprodol produces central nervous system depressant effects, including drowsiness, sedation, confusion and coma.

Public health harm, including cases of driving under the influence of the drug and nonfatal and fatal intoxications, due to carisoprodol alone or in combination with other substances have been observed.

Nonmedical use of carisoprodol is widely documented in multiple countries and regions, including in combination with opioids and/or benzodiazepines. Increased

restrictions on carisoprodol prescription or removal of the drug from the market in several countries have led to decreased incidences of poisoning and other types of public health harm. Seizures of carisoprodol have been reported in many countries in several regions.

Therapeutic use

Carisoprodol is a centrally acting muscle relaxant used in some countries in the short term as an adjunct in symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasms. It is not on the 2023 WHO Essential Medicines List or the WHO Essential Medicines List for Children. It has been withdrawn from therapeutic use in some countries because of concern about increased rates of diversion, nonmedical use, dependence, intoxication and psychomotor impairment.

Recommendation

There is increasing evidence that nonmedical use of carisoprodol in a number of countries constitutes a significant risk to public health. Carisoprodol is a medicine that has been shown to produce a state of dependence, central nervous system depression, and ill effects similar to those of other substances that are listed under Schedule IV of the Convention on Psychotropic Substances of 1971.

The Committee recommended that carisoprodol be added to Schedule IV of the Convention on Psychotropic Substances of 1971.

References

1. Single Convention on Narcotic Drugs, 1961. Vienna: United Nations Office on Drugs and Crime; 1961 (https://www.unodc.org/pdf/convention_1961_en.pdf).

2. Convention on Psychotropic Substances, 1971. Vienna: United Nations Office on Drugs and Crime; 1971 (https://www.unodc.org/pdf/convention_1971_en.pdf).

3. Regulations for expert advisory panels and committees: Report by the secretariat. Geneva: World Health Organization; 1998 (http://apps.who.int/iris/bitstream/handle/10665/79146/ee21.pdf ?sequence=1&isAllowed=y).

4. Guidance on the WHO review of psychoactive substances for international control. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/bitstream/handle/10665/44454/9789241500555_eng. pdf ?sequence=1&isAllowed=y).

3. Critical review reports

3.1 Hexahydrocannabinol

1. Substance identification

A International Nonproprietary Name (INN)

Not assigned.

B Chemical Abstracts Service (CAS) Registry Number

6692-85-9; 1972-09-4 (unspecified stereochemistry)

36403-90-4 (6a*R*,9*R*,10a*R*) isomer (9*R*-isomer)

36403-91-5 (6a*R*,9*S*,10a*R*) isomer (9*S*-isomer)

59042-47-6 [6a*S*-(6aα,9β,10aα)]- isomer

69855-11-4 [6a*R*-(6aα,9α,10aα)]-isomer

69855-12-5 [6a*R*-(6aα,9β,10aα)]-isomer

69880-65-5 [6a*S*-(6aα,9β,10aβ)]-isomer

103476-58-0 (6a*S*,9*S*,10a*S*)-isomer

69855-14-7 *rel*-(6a*R*,9*R*,10a*R*)-isomer

23050-51-3 *rel*-(6a*R*,9*R*,10a*S*)-isomer

58617-32-6 (6aα,9β,10aα)-isomer

146338-70-7 *rel*-(6a*R*,9*S*,10a*R*)-isomer

946512-74-9 *rel*-(6a*R*,10a*R*)-isomer

2891843-77-7 (6a*R*,10a*R*)-isomer

C Other chemical names

Unspecified stereochemistry

HHC (also used for 9-nor-9-hydroxyhexahydrocannabinol and for hexahydrocurcumin) *(1)*

Hexahydrocannabinol

Hexahydro-CBN

HXC

9R-isomer

(6a*R*,9*R*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol (ACI)

6H-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, [6a*R*-(6aα,9α,10aβ)]- (ZCI)

6H-Dibenzo[*b,d*]pyran-1-ol, 6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, stereoisomer (8CI)

(–)-HHC

(–)-*trans*-HHC

trans-(6a*R*,9*R*,10a*R*)-HHC

9β-HHC

11β-HHC

9β-HHC

9(R)-HHC

11β-HHC

(–) NL-105

(9S)-isomer

(6a*R*,9*S*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol (ACI)

6H-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, [6a*R*-(6aα,9β,10aβ)] (9CI)

6H-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, stereoisomer (8CI)

9α-HHC

11α-HHC

9α-HHC

9(S)-HHC

trans-(6a*R*,9*S*,10a*R*)-HHC

11α-HHC

(–) NL-106

D Trade names

Currently marketed hexahydrocannabinol is semi-synthetic and is typically a mixture of the 9*S* and 9*R* epimers. It is sold under the trade names HHC, Hexahydrocannabinol, Hexahydro-CBN and HXC. As an analytical standard, it is sold under the trade names 9(*S*)-Hexahydrocannabinol (9*S*-HHC) and 9(*R*)-Hexahydrocannabinol (9*R*-HHC) *(2,3)*.

E Street names

Hexahydrocannabinol products are currently available on the market in various forms, including low-THC cannabis flowers and resins infused or sprayed with hexahydrocannabinol, disposable vape pens, e-liquids and cartridges for electronic cigarettes, edibles such as gummies and marshmallows, tinctures resembling dietary supplements and HHC distillate oils *(1,4)*.

Hexahydrocannabinol-containing products are packaged in attractive, brightly coloured, sophisticated designs. Low-THC cannabis flowers with hexahydrocannabinol are marketed under popular cannabis strain names such as Afghan Kush, Amnesia, BubbleGum Kush, Strawberry Kush, Pineapple Express and Purple Haze, suggesting effects similar to those of the strains *(1,4)*.

F Physical appearance

Hexahydrocannabinol has been described as a colourless viscous oil or resin *(5,6)* that tends to dark orange after exposure to oxygen, with a slightly floral odour *(4)*.

G WHO review history

Hexahydrocannabinol has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC names:

6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol (unspecified stereochemistry)

(6a*R*,9*S*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol (9*S* isomer)

(6a*R*,9*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[*c*]chromen-1-ol (9*R* isomer)

Chemical Abstracts (CA) Index names:

6*H*-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-(7CI, 8CI, 9CI, ACI) (unspecified stereochemistry)

6*H*-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, (6a*R*,9*S*,10a*R*) (ACI) (9S isomer)

6*H*-Dibenzo[*b,d*]pyran-1-ol,6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-, (6a*R*,9*R*,10a*R*) (9CI, ACI) (9*R* isomer)

Canonical simplified molecular input line entry system (SMILES):

OC=1C=C(C=C2OC(C)(C)C3CCC(C)CC3C12)CCCCC (unspecified stereochemistry)

OC1=C2[C@]3([C@](C(C)(C)OC2=CC(CCCCC)=C1)(CC[C@H](C)C3)[H])[H] (9*S* isomer)

OC1=C2[C@]3([C@](C(C)(C)OC2=CC(CCCCC)=C1)(CC[C@@H](C)C3)[H])[H] (9*R* isomer)

Imternational Chemical Identifier (InChI):

InChI=1S/C21H32O2/c1-5-6-7-8-15-12-18(22)20-16-11-14(2)9-10-17(16)21(3,4)23-19(20)13-15/h12-14,16-17,22H,5-11H2,1-4H3 (unspecified stereochemistry)

InChI=1S/C21H32O2/c1-5-6-7-8-15-12-18(22)20-16-11-14(2)9-10-17(16)21(3,4)23-19(20)13-15/h12-14,16-17,22H,5-11H2,1-4H3/t14-,16+,17+/m0/s1 (9S isomer)

InChI=1S/C21H32O2/c1-5-6-7-8-15-12-18(22)20-16-11-14(2)9-10-17(16)21(3,4)23-19(20)13-15/h12-14,16-17,22H,5-11H2,1-4H3/t14-,16-,17-/m1/s1 (9R isomer)

InChI key:

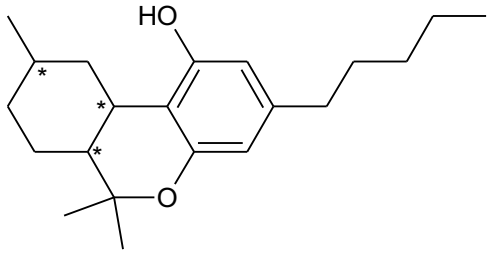
XKRHRBJLCLXSGE-UHFFFAOYSA-N (unspecified stereochemistry)

XKRHRBJLCLXSGE-USXIJHARSA-N (9*S* isomer)

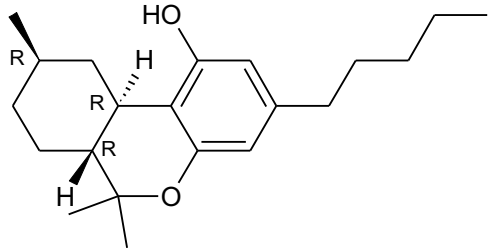
XKRHRBJLCLXSGE-DJIMGWMZSA-N (9*R* isomer)

B Chemical structure

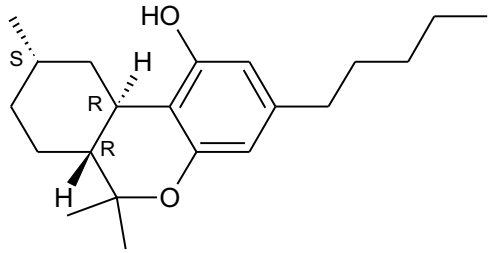
Free base:



Unspecified stereochemistry



(6a*R*,9*R*,10a*R*)-isomer (9*R*-HHC)

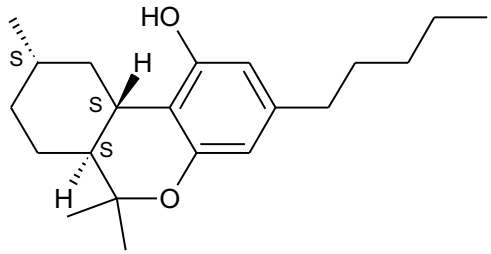


(6a*R*,9*S*,10a*R*)-isomer (9*S*-HHC)

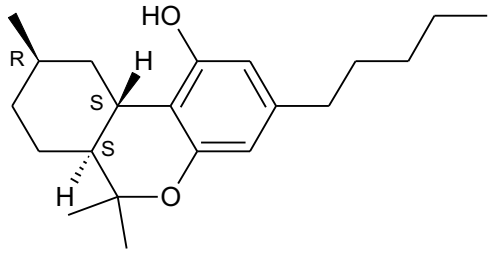
Molecular formula: $C_{21}H_{32}O_2$
Molecular weight: 316.48 g/mol

C Stereoisomers

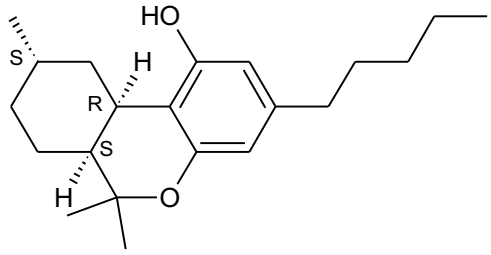
As hexahydrocannabinol has three stereogenic carbon atoms (6a, 9 and 10a), eight stereoisomers with four pairs of enantiomers are possible. The structures shown above depict HHC of unspecified stereochemistry and the two diastereomers (epimers), in which the configurations of the 6a and 10a carbon atoms are identical to those of (–)-*trans*-Δ^9-THC (6a*R*,7,8,10a*R*-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol). These two epimers (9*R*-HHC and 9*S*-HHC) are the expected main components of hexahydrocannabinol-containing products manufactured from cannabidiol. The chemical structures of the other stereoisomers are shown below.



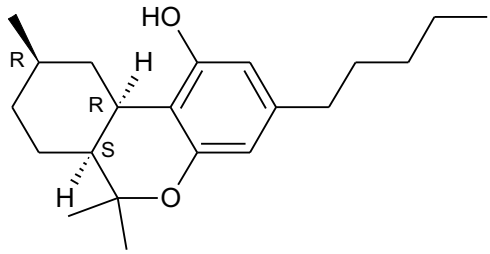
(6a*S*,9*S*,10a*S*)-isomer



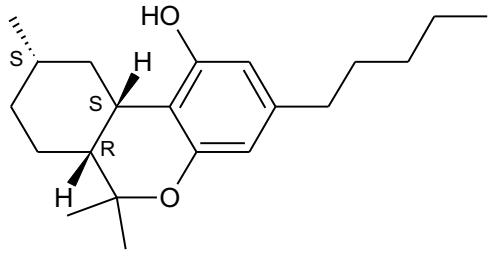
(6a*S*,9*R*,10a*S*)-isomer



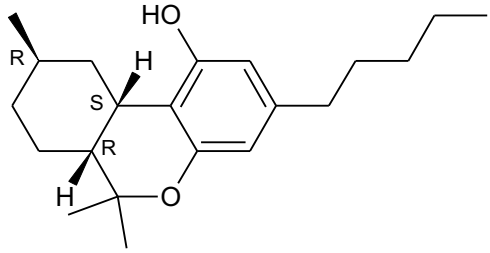
(6a*S*,9*S*,10a*R*)-isomer



(6a*S*,9*R*,10a*R*)-isomer



(6a*R*,9*S*,10a*S*)-isomer



(6a*R*,9*R*,10a*S*)-isomer

D Methods and ease of illicit manufacture

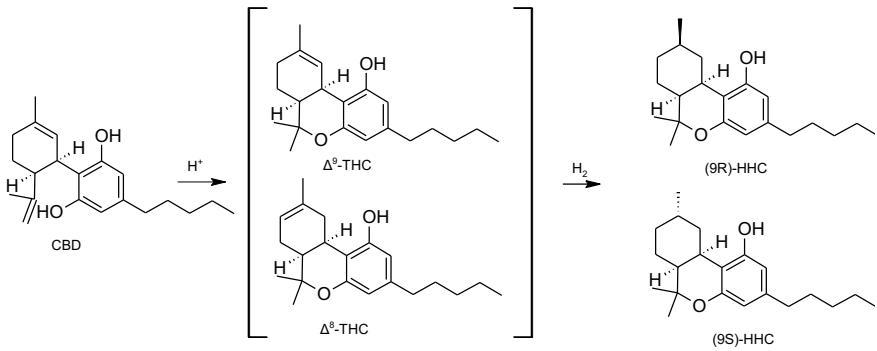
Although the technical methods of large-scale production of hexahydrocannabinol are not well known, it is suggested to be derived from (–)-*trans*-CBD through a two-step synthesis *(1,4)*.

The first step involves acid-catalysed cyclization of CBD, which leads to either Δ^9-THC, Δ8-THC or a mixture of the two isomers, with various by-products *(1)*. The ratio of the two THC isomers and the amount and chemical nature of the byproducts depend on the reaction conditions *(7)*. Gaoni & Mechoulam *(8)* obtained Δ^9-THC by treating CBD with

hydrochloric acid as a catalyst for a short time, while Δ^8-THC was obtained when CBD was treated with *p*-toluenesulfonic acid for longer. More recently, an in-depth study of the product composition of the cyclization of CBD was conducted with various protic and Lewis acids in different solvents *(9)*.

In the second step, reduction of the double bond on the terpene group of Δ^9-THC/Δ^8-THC results in a mixture of the two (9*R*)- and (9*S*)-hexahydrocannabinol epimers. The ratio of the two epimers depends mainly on the starting reactant (Δ^9-THC or Δ^8-THC) and the catalyst used *(1,4,7)*. Catalytic hydrogenation of Δ^9-THC with a platinum catalyst leads to an excess of the 9*R*-hexahydrocannabinol isomer over the 9*S* isomer, while use of a palladium catalyst reverses the ratio, resulting in an excess of the 9*S* epimer over the 9*R* epimer *(7,10)*. In contrast, hydrogenation of Δ^8-THC with a platinum catalyst favours production of the 9*S*-hexahydrocannabinol isomer over the 9*R*-hexahydrocannabinol isomer in a 3:1 ratio *(7,8,11)*. Recently, tri(acetylacetonato)iron(III) was reported as the hydrogen atom donor catalyst for radical reduction reactions in combination with thiophenol and sylilbenzene to reduce Δ^8-THC, resulting in an epimeric ratio of 11:1 ((9*R*)-hexahydrocannabinol:(9*S*)-hexahydrocannabinol) *(12)*.

The presence of both (9*R*)- and (9*S*)- hexahydrocannabinol epimers in various commercial hexahydrocannabinol products and of impurities of Δ^9-THC and Δ^8-THC has led some authors to suggest that the synthetic pathway used to manufacture commercial hexahydrocannabinol starts from CBD, a process that is relatively simple and does not require sophisticated equipment or highly trained personnel *(4,7)*.



Scheme 1. Synthesis of HHC

Step 1: Cyclization of CBD • Step 2: Hydrogenation of Δ^9-THC/Δ^8-THC

A second approach for the synthesis of hexahydrocannabinol is total synthesis, with small molecules of both natural and synthetic origin as starting materials *(4)*. This approach has the advantage over synthesis with CBD as the starting material that it allows for production of single stereoisomers or hexahydrocannabinol analogues "language":"eng","publisher":"Publications Office","publisher-place":"LU","source":"DOI.org (CSL JSON*(1,4,13)*. The first total synthesis of hexahydrocannabinol was proposed by Adams et al. in 1940 *(5)* through hydrogenation of $\Delta^{6a,7}$-THC. The first total stereoselective synthesis of (9*R*)-hexahydrocannabinol and its 9*S* isomer was performed by Tietze et al. *(14)*, starting with 5-pentylcyclohexane-1,3-dione and optically pure citronellal via an intramolecular Diels-Alder reaction and aldol condensation, followed by aromatization and elimination. The reaction was later modified by using olivetol, which eliminates the use of toxic selenium reagents in the aromatization step. Specifically, the one-step condensation reaction of (*R*)-citronellal with olivetol in the presence of diethylaluminium chloride *(15,16)* or ethylenediamine diacetate/triethylamine *(17)* leads to (9R)-hexahydrocannabinol in good yields and with stereochemical purity > 76% *(1,4)*. This synthetic method has the advantage that it is applicable for the production of hexahydrocannabinol analogues such as hexahydrocannabiphorol (heptyl hexahydrocannabinol, HHCP) or hexahydrocannabihexol (hexyl hexahydrocannabinol, HHCH), with olivetol homologues with seven- or six-carbon chains, respectively *(1,4,13)*. The total synthesis of hexahydrocannabinol is, however, a more complex method than the semi-synthetic process starting from CBD. Moreover, it requires more sophisticated equipment and more specialized personnel.

E Chemical properties

Melting-point

No information was found.

Boiling-point

153–155 °C (0.1 mm Hg) (unspecified stereochemistry) *(1,4,5)*
174–177 °C (0.1 mm Hg) (unspecified stereochemistry) *(8)*

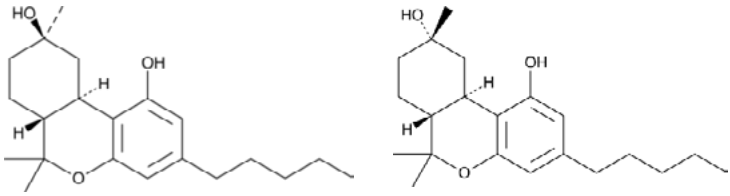
Solubility

Little information was found on the solubility of HHC, but data on structurally related phytocannabinoids suggest high lipid solubility and poor water solubility *(1,4)*. A solubility of 10 mg/mL in acetonitrile has been reported for both 9*R* and 9*S* epimers *(2,3)*.

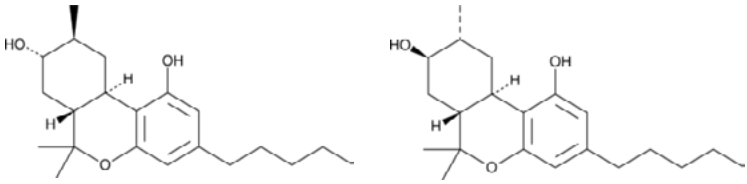
Optical rotation
$[\alpha]_D$ −85.4 (c. 0.30, $CHCl_3$) (9*R*-HHC) *(17)*
$[\alpha]_D$ −107 ($CHCl_3$) (9*R*-HHC) *(8)*
[α]D −109 ($CHCl_3$) (9*S*-HHC) *(8)*

F Identification and analysis

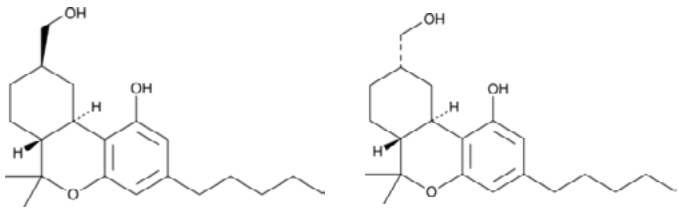
Synthetic (9*R*)-hexahydrocannabinol and (9*S*)-hexahydrocannabinol were both characterized, and optical rotatory properties *(8,17)*, ultraviolet (UV) properties *(7)*, proton magnetic resonance (^{1}H-nuclear magnetic resonance [NMR]) properties *(7,10,11)*, ^{13}C-NMR properties *(7,10,18)*, infrared (IR) properties *(8,16,17)* and mass spectrometry (MS) properties *(2,3,7)* have been reported. UV–visible spectroscopy reveals the hexahydrocannabinol spectrum, with primary absorption peaks at wavelengths of 272 and 282 nm (4,7,13). ^{1}H-NMR spectroscopy can differentiate the two epimers by analysing the chemical shifts of protons near the phenolic group, which are affected by solvent interactions *(1,4,7,10,13)*. ^{13}C-NMR spectroscopy distinguishes the 9*S*- and 9*R*- stereoisomers from the chemical shifts of carbon atoms in the cycloalkane segment, the 9*R* epimer displaying a downfield shift for all carbon atoms except C6a *(1,4,7,10,13)*. Hence, this technique is essential for structural identification. As the MS fragmentation patterns of the 9*S*- and 9*R*- hexahydrocannabinol epimers are almost identical, the stereochemical composition of samples is determined by coupling MS with a chromatographic technique such as gas chromatography (GC) or liquid chromatography (LC), followed by confirmation with a standard of known epimeric purity *(1,4,13)*. Pure 9*R*-hexahydrocannabinol and its labelled version ((9*R*)-hexahydrocannabinol-d_9), 9*S*-HHC, and eight metabolites ((±)-9(*S*)-hydroxy-HHC, (±)-9(*R*)-hydroxy-hexahydrocannabinol, 8(*S*)-hydroxy-9(*S*)-hexahydrocannabinol, 8(*R*)-hydroxy-9(*R*)-hexahydrocannabinol, 11-hydroxy-9(*R*)-hexahydrocannabinol, 11-hydroxy-9(*S*)-hexahydrocannabinol, 11-nor-9(*R*)-carboxy-hexahydrocannabinol and 11-nor-9(*S*)-carboxy-hexahydrocannabinol), are available as reference materials from commercial suppliers for use in routine methods of analysis in forensic and clinical investigations *(2,3)*.



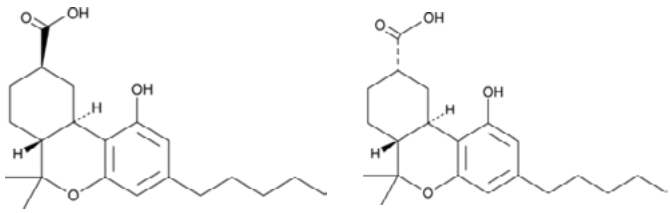
(±)-9(*S*)-Hydroxy-Hexahydrocannabinol and (±)9(*R*)-hydroxy-Hexahydrocannabinol



8(*S*)-Hydroxy-9(*S*)-hexahydrocannabinol and 8(*R*)-hydroxy-9(*R*)-hexahydrocannabinol



11-Hydroxy-9(*R*)-hexahydrocannabinol and 11-hydroxy-9(*S*)-hexahydrocannabinol



11-nor-9(*R*)-carboxy-Hexahydrocannabinol and 11-nor-9(*S*)-carboxy-Hexahydrocannabinol

Fig. 1. Commercially available HHC metabolites

Source: Cayman Chemical *(2,3)*.

Several thin-layer chromatography (TLC) *(8,10,14)*, GC *(10,18,19)* and LC *(7,10,18,20–24)* analytical methods coupled with detectors such as UV and MS have been published. These methods can readily separate the 9*S*- and 9*R*-hexahydrocannabinol epimers *(1,4,7,13)*. Early research was conducted to explore the relations between chemical structure and GC retention times for different cannabis constituents and synthetic cannabinoids, including hexahydrocannabinol, with both unmodified and trimethylsilyl-derivatized analytes *(10,18,19)*. LC has also proven effective in separating these cannabinoids and the hexahydrocannabinol epimers *(1,4,7,13)*.

Recently, LC-MS/MS bioanalytical methods with reversed-phase or chiral stationary phases have been developed to detect (9*R*)-hexahydrocannabinol and (9*S*)-hexahydrocannabinol and their metabolites in human blood, oral fluid and urine *(20,21,23–25)*. Several radioimmunoassay methods designed mainly for detection of cannabis cross-react with other phytocannabinoids and their metabolites, including hexahydrocannabinol, regardless of epimeric purity *(1,4,13)*. Derne et al. *(26)* suggested that, in the absence of concomitant THC, the vast majority of hexahydrocannabinol in users may not be detected by immunoassays; only comprehensive instrumental analytical techniques will accurately assess the spread of recreational use of hexahydrocannabinol.

3. Ease of conversion into controlled substances

The published literature does not indicate whether hexahydrocannabinol can be converted into a controlled substance.

4. General pharmacology

A Routes of administration and dosage

Several routes of administration have been used for hexahydrocannabinol, including inhalation, oral and sublingual *(1,25,27–29)*. Formulations for oral consumption include tinctures and edibles. Hexahydrocannabinol has been detected in electronic cigarette cartridges and sprayed on hemp plant material for smoking. This information was derived from self-reports by people who use hexahydrocannabinol and from reports on the formulation of marketed products and seized material.

No reliable information on standard doses was identified. Websites that advertise hexahydrocannabinol products for sale recommend different doses according to the experience of the person who intends to use the product (e.g. 5–12 mg for "beginners", 12–30 mg for "intermediate" and 30–≥ 60 mg for "pros" *(30,31)*. Doses of 50–100 mg were self-reported in a study of cases referred to poisoning centres in France, the onset of symptoms occurring 10–240 min (mean, 101 min) after consumption *(29)*. While the amount of HHC per unit (e.g. liquid cartridge, edible) is often listed on branded products, the accuracy of this information is uncertain, as analytical verification of these amounts is not usually provided.

B Pharmacokinetics

Like many cannabinoids, hexahydrocannabinol has a low topological polar surface area (calculated to be 29.46, a value that is identical to that of

Δ^9- and Δ^8-tetrahydrocannabinol). This value suggests high lipophilicity, which facilitates absorption and distribution through cellular membranes, including penetration of the blood–brain barrier *(1)*. No other information on the absorption and distribution of hexahydrocannabinol was found.

The results of recent studies on the metabolism of hexahydrocannabinol in humans have shown that the compound undergoes extensive hepatic metabolism. While the relative proportions of different metabolites reported differ between studies, analysis of blood and urine samples in all the studies revealed phase-I reactions of oxidation and hydroxylation, primarily at C11 and at the pentyl side-chain positions on the molecule *(20,24,32,33)*. The major metabolites identified were 11-hydroxy-9*R*-hexahydrocannabinol and 11-nor-carboxy-9*R*-hexahydrocannabinol (9*R*-HHC-COOH). The corresponding epimers of these metabolites were not identified as frequently or were detected at lower concentrations *(20,24,34)*. As studies have reported higher amounts of 9*R*-hexahydrocannabinol than of 9*S*-hexahydrocannabinol in sampled products purchased on the drug market *(7,12)*, the findings may have been due to less 9S-hexahydrocannabinol in the consumed product. In addition, faster elimination of 9S-hexahydrocannabinol than of 9*R*-hexahydrocannabinol has been reported after consumption of a 50:50 racemic mixture of the two epimers *(20)*. In urine, 4′-OH-hexahydrocannabinol was identified as a potentially unique and abundant phase-I metabolite that could serve as a marker of exposure *(33)*. Phase-II metabolites resulting from glucuronidation of the C1 hydroxyl group have also been reported *(34)*.

Analysis of absorption and elimination after smoking of a 50:50 mix of (9*R*)- and (9*S*)-hexahydrocannabinol showed different time courses for the two epimers, (9*R*)-hexahydrocannabinol being absorbed more efficiently *(20)*. At every time point during the 3-h measurement period, the serum concentrations of (9*R*)-hexahydrocannabinol exceeded those of (9*S*)-hexahydrocannabinol, with mean maximum concentrations (C_{max}) of 7.9 ng/mL and 2.3 ng/mL, respectively. The apparent half-lives of the epimers were similar (1.3 and 1.6 h for 9*R*- and 9*S*-hexahydrocannabinol, respectively).

Analysis by non-targeted immunoassays of blood samples from people with suspected cannabis exposure showed cross-reactivity of hexahydrocannabinol metabolites with 11-nor-carboxy-tetrahydrocannabinol (THC-COOH), a major Δ^9-tetrahydrocannabinol metabolite *(24,34,35)*. The results suggest that exposure to HHC could cause a positive reading for THC-COOH without consumption of Δ^9-tetrahydrocannabinol.

C Pharmacodynamics

Hexahydrocannabinol is a semi-synthetic cannabinoid that may also be present naturally in the cannabis plant in trace amounts. The most likely epimers contained in unapproved marketed products are (9*R*)-hexahydrocannabinol and (9*S*)-hexahydrocannabinol, with an average (9*R*):(9*S*) ratio of 1.4:1 *(12)*. Although hexahydrocannabinol was discovered in 1940 *(5)*, it has not been studied extensively, especially as compared with well-known cannabinoids such as Δ^9-tetrahydrocannabinol (Δ^9 -THC) and cannabidiol. Further, interpretation of early pharmacological studies is complicated by the unknown purity or composition of the substance and lack of procedures to measure cannabinoid receptor binding and functioning *(4,13)*. Hence, this review focuses on the results of more recent studies of pharmacodynamics.

Recent in-vitro and in-vivo studies suggest that the psychoactivity of the substance is due primarily to the (9*R*)-hexahydrocannabinol configuration. In vivo, a single dose (10 mg/kg) of each epimer of hexahydrocannabinol was assessed in a tetrad of tests in which psychoactive cannabinoids produce characteristic effects. Whereas the (9*R*)-hexahydrocannabinol decreased locomotion, increased antinoception and showed trends to producing catalepsy and hypothermia, (9*S*)-hexahydrocannabinol had no effect in any of the tests *(7)*.

In-vitro binding affinity (K_i) for (9*R*)-hexahydrocannabinol for human CB1 and CB2 receptors expressed in Chinese hamster ovary cells was 15 ± 0.8 nM and 13 ± 0.4 nM, respectively. In comparison, the CB1 and CB2 binding affinities of Δ^9-THC in the same study were 15 ± 4.4 nM and 9.1 ± 3.6 nM, respectively. In contrast, the affinities for (9*S*)-HHC were substantially lower than those of both the (9*R*)-epimer and Δ^9-THC (Ki = 176 ± 3.3 nM for CB1 receptors and 105 ± 26 nM for CB2 receptors) *(12)*. In a functional assay of inhibition of forskolin-stimulated cyclic adenosine monophosphate (cAMP), both hexahydrocannabinol epimers were partial agonists (as is Δ^9-THC), but (9*R*)-hexahydrocannabinol was 17 times more potent than (9*S*)-hexahydrocannabinol in activating CB1 receptors (half maximum concentration (EC_{50}) = 3.4 ± 1.5 nM and 57 ± 19 nM, respectively) and nine times more potent in activating CB2 receptors (EC_{50} = 6.2 ± 2.1 nM and 56 ± 10 nM, respectively) *(12)*. The results of other functional assays showed that (9*R*)-hexahydrocannabinol directly activated CB1 receptor G-proteins, stimulated GPK3 and *β*-arrestin2 pathways, enhanced internalization of activated CB1 receptors and produced low levels of ERK1/2 phosphorylation *(36)*. The effectiveness varied among the assays in a pattern different from

that produced by Δ^9-THC, suggesting biased intracellular signalling in CB1 receptor pathways. Like Δ^9-THC, hexahydrocannabinol has been shown to activate transient receptor potential ankyrin 1 receptors *(15)*.

5. Toxicology

The preclinical toxicology of hexahydrocannabinol (racemic mixture of *R*- and *S*-epimers) was examined in a single study *(37)*. In the systems evaluated, hexahydrocannabinol showed little toxicity in vitro. It was not mutagenic in an Ames test, it did not block *hERG*-encoded channels in HEK293 cells, and it was not cytotoxicity in human hepatocytes. Potential cytotoxicity was observed in human lung fibroblasts but only at high concentrations (> 10 μM) and was comparable to the effect reported with the control, chlorpromazine.

6. Adverse reactions in humans

Between January 2022 and May 2023, three patients with analytically confirmed exposure only to hexahydrocannabinol were hospitalized in France *(29)*. The patients had moderate to severe symptoms involving several physiological systems, including cardiovascular (palpitations, chest pain, tachycardia), gastrointestinal (nausea, vomiting), neurological (dizziness, tremors, spatiotemporal disorientation, dyskinesia, convulsions), psychiatric (anxiety, agitation) and respiratory (respiratory pause and discomfort) systems *(29,38)*. Hexahydrocannabinol was also suspected of precipitating the onset of psychosis in two individuals in Ireland *(39)*.

People who used hexahydrocannabinol have described effects such as relaxation, euphoria, calming, sleepiness and hunger *(40)*. While some people reported that they used hexahydrocannabinol specifically for its euphoric effects, others reported using the substance as self-medication for anxiety, pain relief, sleep difficulty or to treat symptoms of withdrawal from cannabis or benzodiazepines *(13,29)*. Undesired effects such as withdrawal effects (e.g. sleep difficulty, depressed mood), psychosis and uncontrolled tremors have also been noted *(13,35,40)*. Self-reported experiences of the psychological effects of hexahydrocannabinol should be considered anecdotal, as no analytical confirmation of sole use was obtained.

7. Dependence potential

A Studies in experimental animals

No information was found.

B Studies in humans

No information was found.

8. Abuse potential

A Studies in experimental animals

No information was found.

B Studies in humans

No information was found.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

There are no known therapeutic uses of hexahydrocannabinol.

10. Listing on the WHO Model List of Essential Medicines

Hexahydrocannabinol is not listed on the 23rd WHO Model List of Essential Medicines or on the 9th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Hexahydrocannabinol has no known marketing authorizations.

12. Industrial use

Hexahydrocannabinol has no known industrial use.

13. Non-medical use, abuse and dependence

Hexahydrocannabinol is a semi-synthetic cannabinoid that is most commonly synthesized from cannabidiol as a precursor. It was first detected in the United States in 2021, but its use quickly spread to other countries. Reports on online forums by people who use drugs provide evidence that hexahydrocannabinol has been used intentionally for its intoxicating effects (see section 6). The presence of this substance had been reported in at least 31 countries (see section 16 for listing). The prevalence of chronic use and dependence of hexahydrocannabinol has not been reported.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

In Europe, hexahydrocannabinol has been associated with cases of hospitalization and driving under the influence of drugs. Between January 2022 and May 2023, 37 cases of self-reported use of hexahydrocannabinol presented to French poison centres *(29)*. A wide variety of symptoms were reported, including neurological (e.g. dizziness, headache, paresthesia), cardiovascular (e.g. palpitations, sinus tachycardia, chest pain), gastrointestinal (e.g. nausea/vomiting, abdominal pain) and psychiatric (e.g. anxiety, hallucinations/delirium) *(29)*; however, analytical confirmation of hexahydrocannabinol consumption was obtained in only six cases, and hexahydrocannabinol was the sole substance in three of these individuals *(29,38)*. These three patients showed moderate to severe symptoms, leading to admission to an emergency department. Other cases of hospitalization have occurred in Czechia, where 12 children who consumed hexahydrocannabinol-containing sweets were admitted *(41)*. Hexahydrocannabinol has also been suspected of precipitating the onset of psychosis in two individuals in Ireland *(39)*.

Hexahydrocannabinol has been confirmed analytically in blood samples from drivers suspected of driving under the influence of cannabis in Germany and Sweden *(24,33)*, although neither report provided details of the effects of the substance on the drivers' behaviour. In early 2023, the rate of hexahydrocannabinol detection among Swedish drivers who were stopped on suspicion of cannabis use increased sharply, from 5% in January to 14% in February–March and to 50% in April–May *(24)*. In addition, Helander et al. *(35)* reported that the percentage of Swedish drivers who had false positive tests for Δ^9-THC increased from < 2% before the spring of 2023 to > 10% by June 2023. The presumed reason for the false positives is the cross-reactivity of immunoassays used for detection of metabolites of Δ^9-THC and hexahydrocannabinol (see section 4B). This reported increase is consistent with the dramatic rise in the number of posts mentioning HHC on a Swedish Internet chat site during 2023 *(35)*. The posts primarily addressed online dealers and products intended for smoking or vaping and on the likelihood of testing positive for Δ^9-THC after ingestion or inhalation of hexahydrocannabinol.

15. Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

Hexahydrocannabinol emerged on the drug market in the United States in September 2021, followed by its appearance and rapid increase in Europe in May 2022 *(1)*. By December 2022, hexahydrocannabinol had been detected in 70% of the European Union Member States. Countries in which hexahydrocannabinol has been identified are Austria, Belgium, Bulgaria, Colombia, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Latvia, Lithuania, Netherlands, Norway, Poland, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, the United Kingdom and the United States *(1,25,40,42)*.

The 2023 technical report of the EMCDDA on hexahydrocannabinol *(1)* cited reports of 50 seizures by customs and law enforcement personnel, comprising a total of 70.7 kg of material. The formulations included low-THC cannabis flower, resin, liquid and HHC-containing food products. While most of the seizures were of small amounts, at least three involved larger quantities, suggesting more extensive trafficking.

17. Current international controls and their impact

Hexahydrocannabinol is not currently under international control.

18. Current and past national controls

Hexahydrocannabinol is regulated under psychoactive drug control regulations in Austria, Belgium, Czechia, Denmark, France, Italy, Japan, Lithuania, Luxembourg, Sweden and the United Kingdom *(25,41,43)*.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

No other matters were identified.

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3.2 *N*-Pyrrolidino protonitazene

1. Substance identification

A INN

Not available.

B CAS Registry Number

3038401-95-2

C Other chemical names

2-[(4-Propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl) benzimidazole

5-Nitro-2-[(4-propoxyphenyl)methyl]-1-(2-pyrrolidin-1-ylethyl) benzimidazole

2-(4-propoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d] imidazole

D Trade names

Sold as an analytical standard under the name "*N*-Pyrrolidino protonitazene".

E Street names

N-Pyrrolidino protonitazene is known under its own name or as "protonitazepyne".

F Physical appearance

N-Pyrrolidino protonitazene as a reference material has been described as a crystalline solid *(1)*. It was found as a light brown (beige) powder in samples sold as heroin in Dublin and Cork, Ireland, in late 2023 *(2)*. Another sample containing *N*-pyrrolidino protonitazene was reported as a white, colourless solid *(3)*. Counterfeit pharmaceutical pills in Canada that appeared to be blue oxycodone M30s were found to contain *N*-pyrrolidino protonitazene *(4)*. *N*-Pyrrolidino protonitazene was found in a brown powder in Australia *(5)*.

G WHO review history

N-Pyrrolidino protonitazene has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC name

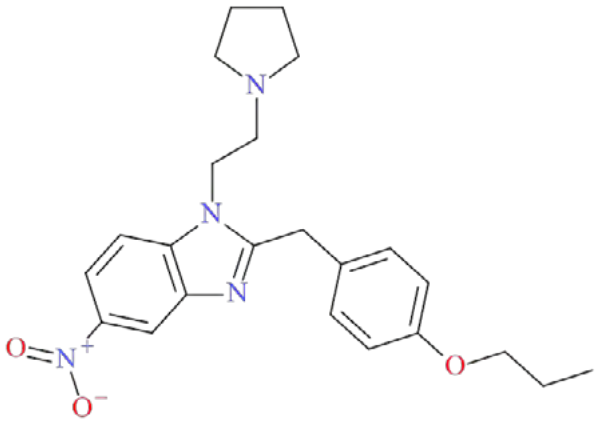
2-[(4-Propoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole

CA Index name

Not assigned.

B Chemical structure

Free base:



Molecular formula: $C_{23}H_{28}O_3$

Molecular weight: 408.49 g/mol

C Stereoisomers

No stereoisomers of *N*-pyrrolidino protonitazene have been described.

D Methods and ease of illicit manufacture

N-Pyrrolidino protonitazene belongs to the opioid 2-benzylbenzimidazole group, also known as "nitazenes" or "nitazene analogues", which were initially developed as opioid analgesics in the late 1950s *(2)*. *N*-Pyrrolidino protonitazene closely resembles protonitazene but has a pyrrolidino ring instead of a diethylaminoethyl group at the 1-position of the benzimidazole ring *(2)*.

Although its synthesis has not been documented, *N*-pyrrolidino protonitazene can be synthesized with the methods established for 5-nitro-2-benzylbenzimidazole analogues such as etonitazene, with appropriate modifications to the reagents *(6–9)*.

While details of the production method and scale for the recently identified *N*-pyrrolidino protonitazene are not available, application of the synthesis techniques used for its nitazene analogues suggests that the process is straightforward, cost-effective and does not require regulated precursors.

E Chemical properties

Melting-point
No information was found.

Boiling-point
No information was found.

Solubility
N-Pyrrolidino protonitazene is soluble in dimethylformamide and in dimethyl sulfoxide at 5 mg/mL and 3 mg/mL, respectively. In ethanol, it is soluble at 2 mg/mL *(1)*.

F Identification and analysis

N-Pyrrolidino protonitazene is available as reference material from commercial suppliers for use in routine analysis in forensic and clinical investigations *(1)*.

Analytical methods for identification of *N*-pyrrolidino protonitazene in seized sample matrices include spectroscopy, ^{1}NMR, GC coupled to MS and LC coupled to quadrupole ion trap *(2)*.

Only one method has been reported for quantification of *N*-pyrrolidino protonitazene in post-mortem blood *(10,11)*.

3. Ease of conversion into controlled substances

It is not known from the literature whether *N*-pyrrolidino protonitazene can be converted into a controlled substance.

4. General pharmacology

A Routes of administration and dosage

No clinical studies on *N*-pyrrolidino protonitazene were identified.

Information obtained from Internet discussion forums mentioned doses of *N*-pyrrolidino protonitazene of 20–25 mg, yet as little at 6 mg was associated with adverse effects *(12)*. Routes of administration of *N*-pyrrolidino protonitazene reported on drug user forums included snorting, smoking and ingestion, while the most common route associated with fatal intoxication was injection.

B Pharmacokinetics

No information was available on the absorption and distribution of *N*-pyrrolidino protonitazene, and its metabolism has not been reported in the peer-reviewed literature. Researchers have suggested that the metabolites of *N*-pyrrolidino protonitazene would be similar to those of *N*-pyrrolidino etonitazene and isotonitazene (Fig. 2) *(13,14)*.

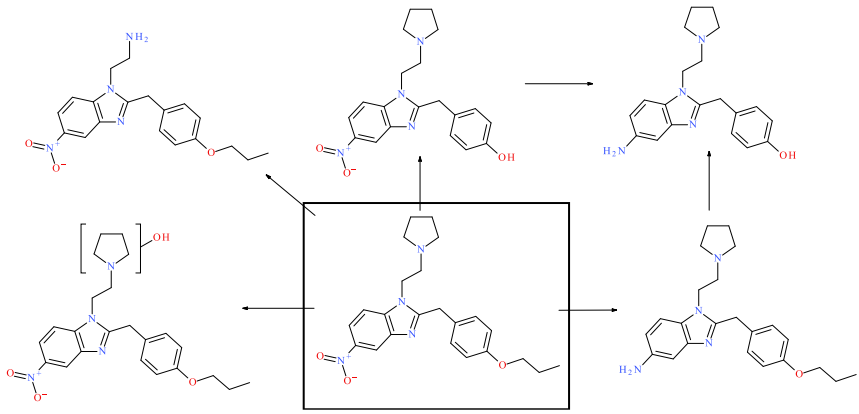


Fig. 2. Proposed metabolism of *N*-pyrrolidino protonitazene

C Pharmacodynamics

N-Pyrrolidino protonitazene had psychoactive effects in in-vitro cell models and in-vivo animal models.

In an in-vitro study, De Vrieze et al. *(11)* showed that *N*-pyrrolidino protonitazene was a μ opioid receptor agonist, with a maximum effect [E_{max}] 198% greater than that of hydromorphone. Comparison of approximate median effective concentration ratios of *N*-pyrrolidino protonitazene (EC_{50} 0.942 nM) with those of other opioids indicated that it is 25 times more potent than fentanyl (EC_{50} 25.7 nM), 300 times more potent than morphine (EC_{50} 327 nM), twice as potent as protonitazene (EC_{50} 7.19 nM) and about

two times less potent than *N*-pyrrolidino etonitazene (EC_{50} 0.548 nM). *N*-Pyrrolidino 4′-OH nitazene (EC_{50} 222 nM) was significantly less active than the parent drug.

In an in-vitro study *(12)*, *N*-pyrrolidino protonitazene was described as a full agonist at the μ opioid receptor (E_{max} 102% as compared with fentanyl). *N*-Pyrrolidino protonitazene (EC_{50} 0.293 nM) was approximately three times more potent than fentanyl (EC_{50} 1.01 nM).

A receptor-based assay of opioid receptor binding and functional activity showed that *N*-pyrrolidino protonitazene had higher binding affinity and markedly greater potency than fentanyl and morphine. In a tail-flick assay, *N*-pyrrolidino protonitazene had considerably greater analgesic potency than fentanyl and morphine. The analgesic effects were reversed by naltrexone. This study also showed *N*-pyrrolidino protonitazene to be selective for the μ opioid receptor (see Annex 3).

5. Toxicology

No information was found on the acute or chronic preclinical toxicology of *N*-pyrrolidino protonitazene.

6. Adverse reactions in humans

In 2023, 39 medicolegal deaths were reported from the United Kingdom and the United States that involved *N*-pyrrolidino protonitazene *(11,15)*. Blood specimens from the cases contained other nitazene analogues, as well as other synthetic opioids and new psychoactive benzodiazepines. The median blood concentration of *N*-pyrrolidino protonitazene in the cases, which was confirmed quantitatively, was 1.2 ng/mL (range: 0.3–55 ng/mL).

Many of the 39 post-mortem case reports mentioned prior drug use (e.g. opioids) and/or suspicion of drug overdose; however, the cause and manner of death were not formally verified at the time of reporting. Five post-mortem cases contained *N*-pyrrolidino protonitazene with no other opioids, at concentrations of 55, 15, 1.1, 0.3 and < 0.1 ng/mL. In one case, a 26-year-old male was found on a farm, lying fully clothed on a towel that had been carefully placed on the ground. No signs of trauma or injury were noted. No additional details were available. *N*-Pyrrolidino protonitazene was found in his blood at 15 ng/mL; the other substances found were clonazepam (35 ng/mL), 7-aminoclonazepam (750 ng/mL), caffeine and cotinine.

In November 2023, more than 50 overdoses of a novel drug were reported in Dublin, Ireland *(2,16)*. Confirmatory analytical testing showed it to be *N*-pyrrolidino protonitazene.

7. Dependence potential

A Studies in experimental animals

No studies were identified.

B Studies in humans

No studies were identified.

8. Abuse potential

A Studies in experimental animals

A drug discrimination study was conducted in rats, which were trained to discriminate morphine from saline. *N*-Pyrrolidino protonitazene substituted fully for a training dose of morphine and was more potent than fentanyl. Naltrexone blocked the morphine-like discriminative stimulus effects of *N*-pyrrolidino protonitazene (see Annex 3).

B Studies in humans

No studies were identified.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

No information was found.

10. Listing on the WHO Model Lists of Essential Medicines

N-Pyrrolidino protonitazene is not listed on the 23rd WHO Essential Medicines List or on the 9th WHO Essential Medicines List for Children updated in 2023.

11. Marketing authorizations (as a medicinal product)

No information was found.

12. Industrial use

No information was found.

13. Non-medical use, abuse and dependence

N-Pyrrolidino protonitazene was first found on the US drug market in January 2023 by testing at the Center for Forensic Science Research and Education *(10)*. Since then, detections of *N*-pyrrolidino protonitazene have increased throughout the country's drug supply. Detections of *N*-pyrrolidino protonitazene were reported in the first (n=6), second (n=11), third (n=22) and fourth quarters of 2023 (n=9) and in the first (n=5) and second quarters of 2024 (n=8) *(17)*.

N-Pyrrolidino protonitazene was first reported on the European drug market in May 2023 and notified to the European Drugs Agency by Slovenia *(2)*. Since then, detections of *N*-pyrrolidino protonitazene have been reported in several other European countries, including a large outbreak of overdoses associated with the drug in Ireland *(16)*.

According to the UNODC EWA on New Psychoactive Substances *(18)*, *N*-pyrrolidino protonitazene was detected in Austria (n=1), Canada (n=77), Slovenia (n=1), Switzerland (n=1), the United Kingdom (n=2) and the United States (n=2) in 2023 and 2024. *N*-Pyrrolidino protonitazene has also been detected in Australia and Canada *(4,5)*.

According to the Drug Query System of the National Forensic Laboratory Information System (NFLIS) in the US Drug Enforcement Administration, *N*-pyrrolidino protonitazene was reported 27 times in 2023 by participating crime laboratories in six states.

In January 2024, a sample submitted to the Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) programme tested positive for *N*-pyrrolidino protonitazene, with minor amounts of diazepam and etomidate *(3)*. The sample was purchased online as "China White" heroin. The reported effects included euphoria, empathy and relaxation after intravenous use.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

N-Pyrrolidino protonitazene has been offered for sale by numerous Internet retailers. As people who use drugs are likely to obtain *N*-pyrrolidino protonitazene through unregulated sources, its purity and quantity are not assured, thus presenting an additional risk of adverse reactions. As a potent opioid, *N*-pyrrolidino protonitazene could have a large impact on public health; however, its presence on the global drug market appears to be minimal at

this time. Given its pharmacological profile and associated literature reports, *N*-pyrrolidino protonitazene appears to pose a high risk for recreational use, physiological dependence and overdose.

N-Pyrrolidino protonitazene has been misrepresented and sold as "heroin" and falsified oxycodone pills.

15. Licit production, consumption and international trade

N-Pyrrolidino protonitazene is used as reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic uses. Some Internet retailers have advertised it for sale as a "research chemical" or similar type of substance.

16. Illicit manufacture and traffic and related information

No information was available on seizures of *N*-pyrrolidino metonitazene.

Man et al. analysed the availability of nitazene analogues for purchase on cryptomarkets between February 2023 and January 2024 and found that *N*-pyrrolidino protonitazene was listed for sale, accounting for approximately 7% of the market share for this family of opioids *(20)*.

17. Current international controls and their impact

N-Pyrrolidino protonitazene is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

N-Pyrrolidino protonitazene controlled as a Class A drug under the United Kingdom Misuse of Drugs Act 1971. In September 2024, the US Drug Enforcement Agency issued a notice of intent to temporarily place *N*-pyrrolidino protonitazene under Schedule I of the Controlled Substances Act.

19. Other medical and scientific matters relevant to a recommendation on scheduling of the substance

Detections of *N*-pyrrolidino protonitazene may be under-reported if this substance is not routinely screened for in all laboratories that receive samples for analysis.

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3.3 *N*-Pyrrolidino metonitazene

1. Substance identification

A INN

Not available.

B CAS Registry Number

Not assigned.

C Other chemical names

2-[(4-Methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl) benzimidazole

2-(4-Methoxybenzyl)-5-nitro-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d] imidazole

D Trade names

Sold as an analytical standard under the name *N*-pyrrolidino metonitazene

E Street names

N-Pyrrolidino metonitazene is known under its own name or as "metonitazepyne".

F Physical appearance

N-Pyrrolidino metonitazene has been described as a beige powder *(1)*.

G WHO review history

N-Pyrrolidino metonitazene has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC name

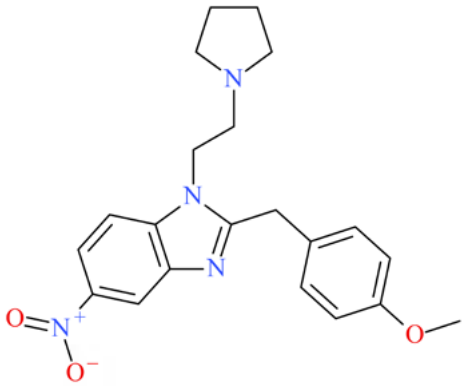
2-[(4-methoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole

CA Index name

Not assigned

B Chemical structure

Free base



Molecular formula: $C_{21}H_{24}N_4O_3$

Molecular weight: 380.44 g/mol

C Stereoisomers

No stereoisomers of *N*-pyrrolidino metonitazene have been described.

D Methods and ease of illicit manufacture

N-Pyrrolidino metonitazene is in the opioid 2-benzylbenzimidazole group, also known as "nitazenes" or "nitazene analogues", which were initially developed as opioid analgesics in the late 1950s *(2)*. *N*-Pyrrolidino metonitazene closely resembles metonitazene but has a pyrrolidino ring instead of a diethylaminoethyl group at the 1-position of the benzimidazole ring *(2)*.

Although its synthesis has not been reported in the literature, *N*-pyrrolidino metonitazene can be synthesized by methods established for other 5-nitro-2-benzylbenzimidazole analogues, such as etonitazene, with appropriate modifications to the reagents *(3–6)*.

While details of the production method and scale for recently identified *N*-pyrrolidino metonitazene are not available, application of the synthesis techniques used for its nitazene analogues suggests that the process is straightforward, cost-effective and does not require regulated precursors.

E Chemical properties

Melting-point
No information was found.

Boiling-point
No information was found.

Solubility
N-Pyrrolidino metonitazene (citrate) is soluble in dimethylformamide and in dimethyl sulfoxide at 3 mg/mL *(7)*.

F Identification and analysis

N-Pyrrolidino metonitazene (citrate) is available as a reference material from commercial suppliers for use in routine methods of analysis in forensic and clinical investigations *(7)*.

Analytical methods for identification of *N*-pyrrolidino metonitazene in seized sample matrices include GC–MS and LC coupled to high-resolution MS *(1,8)*.

3. Ease of conversion into controlled substances

It is not known from the literature whether *N*-pyrrolidino metonitazene can be converted into a controlled substance.

4. General pharmacology

A Routes of administration and dosage

No clinical studies on *N*-pyrrolidino metonitazene were identified. Internet discussion forums mentioned doses of *N*-pyrrolidino metonitazene of 150–200 mg intravenously and 5–100 mg nasally *(9)*. The most commonly reported routes of administration of nitazene analogues were injection, inhalation, insufflation and ingestion.

B Pharmacokinetics

No information was available on the absorption or distribution of *N*-pyrrolidino metonitazene, and its metabolism has not been described in the peer-reviewed literature. It has been proposed that the metabolites of *N*-pyrrolidino metonitazene are similar to those of *N*-pyrrolidino etonitazene and metonitazene (Fig. 3) *(10, 11)*.

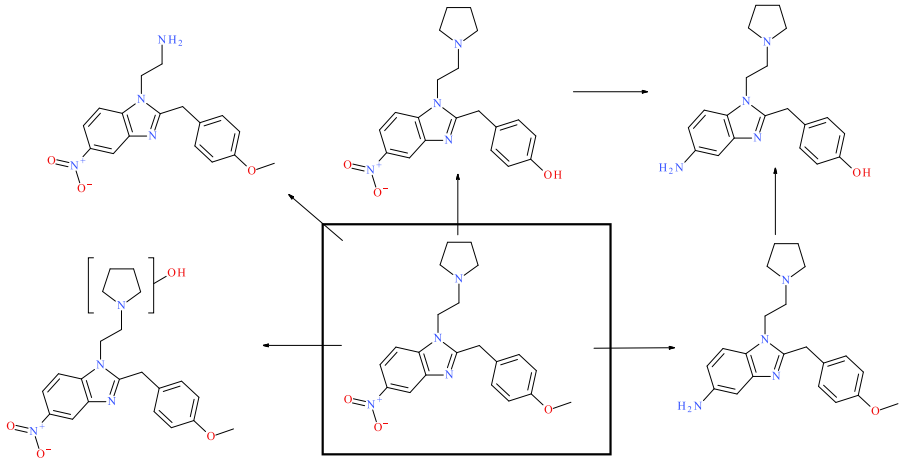


Fig. 3. Proposed metabolic scheme for *N*-pyrrolidino metonitazene

C Pharmacodynamics

Information has become available on the pharmacodynamics of *N*-pyrrolidino metonitazene, which show that it has psychoactive effects in in-vitro cell models and in-vivo animal models.

In an in-vitro study by De Vrieze et al. *(8)*, *N*-pyrrolidino metonitazene was shown to be a μ opioid receptor agonist (E_{max} 174% higher than hydromorphone). The potency ratio of *N*-pyrrolidino metonitazene (EC_{50} 12.0 nM) was approximately twice that of fentanyl (EC_{50} 25.7 nM) and 25 times that of morphine (EC_{50} 327 nM). *N*-Pyrrolidino metonitazene was nearly half as potent as metonitazene (EC_{50} 7.19 nM) and approximately 25 times less potent than *N*-pyrrolidino etonitazene (EC_{50} 0.548 nM). *N*-Pyrrolidino 4′-OH nitazene (EC_{50} 222 nM) was significantly less active than the parent drug.

In an in-vitro study *(9)*, *N*-pyrrolidino metonitazene was a full agonist at the μ opioid receptor (Emax 103% times that of fentanyl). The approximate potency ratio of *N*-pyrrolidino metonitazene (EC_{50} 1.98 nM) to fentanyl (EC_{50} 1.01 nM) was 2:1 (i.e. half as potent).

A receptor-based assay of opioid receptor binding and functional activity showed that *N*-pyrrolidino metonitazene had similar binding affinity and greater potency than fentanyl and morphine. In a tail-flick assay, the analgesic potency of *N*-pyrrolidino metonitazene was similar to that of fentanyl and greater than that of morphine. The analgesic effects were

blocked by naltrexone. This study also showed *N*-pyrrolidino metonitazene to be selective for the μ opioid receptor (MOR) (see Annex 3).

5. Toxicology

No information was found on the acute or chronic preclinical toxicity of *N*-pyrrolidino metonitazene.

6. Adverse reactions in humans

In 2023, 15 medicolegal death investigations were reported in the United States that involved *N*-pyrrolidino metonitazene *(8)*. Blood specimens from these cases commonly contained other nitazene analogues (14 of 15 cases) and other synthetic opioids and new psychoactive benzodiazepines. The median blood concentration of *N*-pyrrolidino metonitazene confirmed quantitatively was 0.47 ng/mL, with a range of 0.2–26 ng/mL.

In many of the 15 post-mortem cases, drug use (e.g. opioids) and/or suspicion of drug overdose were mentioned; however, the cause and manner of death were not formally known at the time of reporting. Only one post-mortem case contained only *N*-pyrrolidino metonitazene (26 ng/mL) and no other opioids. Amphetamine, bromazolam, tianeptine and naloxone were also found in some other cases. Detailed case information was not available.

7. Dependence potential

A Studies in experimental animals

No studies of the dependence potential of *N*-pyrrolidino metonitazene in experimental animals were identified.

B Studies in humans

No studies of the dependence potential of *N*-pyrrolidino metonitazene in humans were identified.

8. Abuse potential

A Studies in experimental animals

A study was conducted in rats trained to discriminate morphine from saline. *N*-Pyrrolidino metonitazene substituted fully for a training dose of morphine. *N*-Pyrrolidino metonitazene had similar efficacy to fentanyl but

was less potent than fentanyl and more potent than morphine. Naltrexone blocked the morphine-like discriminative stimulus effects of *N*-pyrrolidino metonitazene (see Annex 3).

B Studies in humans

No studies of the dependence potential of *N*-pyrrolidino metonitazene in humans were identified.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

No information was found on therapeutic use of *N*-pyrrolidino metonitazene.

10. Listing on the WHO Model Lists of Essential Medicines

N-Pyrrolidino metonitazene is not listed on the 23rd WHO Essential Medicines List or the 9th WHO Essential Medicines List for Children, updated in 2023.

11. Marketing authorizations (as a medicinal product)

No information was found on marketing authorization of *N*-pyrrolidino metonitazene as a medicinal product.

12. Industrial use

No information was found on any industrial use of *N*-pyrrolidino metonitazene.

13. Non-medical use, abuse and dependence

N-Pyrrolidino metonitazene was first reported on the European drug market in June 2023, and seizure of a powder by a customs agency was notified to the European Drugs Agency by Sweden *(9)*. According to the UNODC EWA on NPS, *N*-pyrrolidino metonitazene was detected in Sweden in 2023 and in Austria in 2024. Because of the novelty of this nitazene analogue, data are still being collected by the UNODC.

N-Pyrrolidino metonitazene was first reported on the US drug market in February 2023, by the Center for Forensic Science Research and Education *(1)*. Since then, detection of *N*-pyrrolidino metonitazene has been less common than of other nitazene analogues in the US drug supply, although it continued to be detected in the first (n=3), second (n=6), third (n=4) and fourth quarters of 2023 (n=3) and the first (n=1) and second quarters of 2024 (n=3) *(12)*.

According to the US Drug Enforcement Administration NFLIS Drug Query System, *N*-pyrrolidino metonitazene was reported eight times in 2023 by participating crime laboratories *(13)*. Five identifications originated from Ohio and two from Missouri. No additional information was available.

Information on use of *N*-pyrrolidino metonitazene is limited; however, drug use forum posts suggest that the drug produces euphoric effects and has a long half-life *(9)*. This anecdotal information also notes that *N*-pyrrolidino metonitazene "feels toxic" and gives rise to severe withdrawal symptoms.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

N-Pyrrolidino metonitazene has been offered for sale by numerous Internet retailers. As people who use drugs are likely to obtain *N*-pyrrolidino metonitazene from unregulated sources, its purity and quantity are not assured, presenting an additional risk of adverse reactions. As a potent opioid, *N*-pyrrolidino metonitazene could have a large impact on public health; however, its presence on the drug market globally appears to be minimal at this time, although the exact prevalence cannot be stated due to lack of testing for this novel drug. Given its pharmacological profile and associated literature reports, *N*-pyrrolidino metonitazene appears to pose a high risk for recreational use, physiological dependence and overdose.

15. Licit production, consumption and international trade

N-Pyrrolidino metonitazene is used as reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic uses. Some Internet retailers have advertised it for sale as a "research chemical" or similar type of substance.

16. Illicit manufacture and traffic and related information

No information was found on seizures of *N*-pyrrolidino metonitazene.

Man et al. *(14)* described the availability of nitazene analogues for purchase on cryptomarkets between February 2023 and January 2024. *N*-Pyrrolidino metonitazene was included, accounting for approximately 5% of the market share for this family of opioids *(14)*.

17. Current international controls and their impact

N-Pyrrolidino metonitazene is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

Limited information on national controls for *N*-pyrrolidino metonitazene was found. The substance is a Schedule 1 drug in the state of Ohio, United States. In September 2024, the US Drug Enforcement Agency issued a notice of intent to temporarily place *N*-pyrrolidino metonitazene under Schedule I of the Controlled Substances Act.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

Detection of *N*-pyrrolidino metonitazene may be under-reported if this substance is not routinely screened for in all laboratories that receive samples for analysis.

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3.4 Etonitazepipne

1. Substance identification

A INN

Not available.

B CAS Registry Number

734496-28-7

C Other chemical names

2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl) benzimidazole

2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-[2-(1-piperidinyl)ethyl]-1*H*-benzimidazole

1*H*-Benzimidazole, 2-((4-ethoxyphenyl)methyl)-5-nitro-1-(2-(1-piperidinyl)ethyl)-

2-((4-Ethoxybenzyl)-5-nitro-1-(2-(1-piperidinyl)ethyl)-1*H*-benzimidazole

D Trade names

Etonitazepipne is sold as an analytical standard as citrate salt under the name "*N*-piperidinyl etonitazene (citrate)" *(1)*.

E Street names

Etonitazepipne is known under its own name or as *N*-piperidinyl etonitazene.

F Physical appearance

Etonitazepipne citrate as a reference material has been described as a crystalline solid *(1)*. Etonitazepipne hydrochloride has been described as a white-yellowish powder *(2)*.

G. WHO review history

Etonitazepipne has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC name

2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-piperidin-1-ylethyl)-1*H*-benzoimidazole

CA Index name

1*H*-Benzimidazole,2-[(4-ethoxyphenyl)methyl]-5-nitro-1-[2-(1-piperidinyl)ethyl]

Canonical SMILES

O=N(=O)C=1C=CC2=C(N=C(N2CCN3CCCCC3)CC4=CC=C(OCC)C=C4)C1

InChI

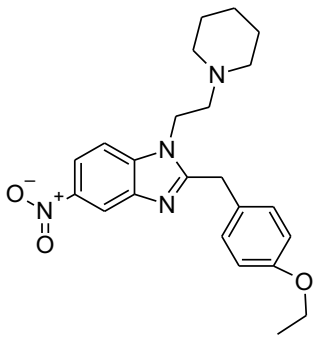
1S/C23H28N4O3/c1-2-30-20-9-6-18(7-10-20)16-23-24-21-17-19(27(28)29)8-11-22(21)26(23)15-14-25-12-4-3-5-13-25/h6-11,17H,2-5,12-16H2,1H3

InChI key

UMGXRAISFRUVKD-UHFFFAOYSA-N

B Chemical structure

Free base



Molecular formula: $C_{23}H_{28}N_4O_3$

Molecular weight: 408.49 g/mol

C Stereoisomers

No stereoisomers of etonitazepipne have been described.

D Methods and ease of illicit manufacture

Etonitazepipne belongs to the opioid 2-benzylbenzimidazoles group, also known as "nitazenes", which were initially developed as opioid analgesics in the late 1950s *(3)*. Etonitazepipne closely resembles etonitazepyne but has a piperidino ring instead of a pyrrolidino ring at the 1-position of the benzimidazole ring *(2,4)*.

Synthesis of etonitazepipne was reported by Hunger et al. *(5)*. The activated chloro atom of 1-chloro-2,4-dinitrobenzene can easily be substituted by 1-(2-aminoethyl)piperidine. Then, regioselective reduction of the nitro group in the ortho position to the resulting amino function and condensation of the ortho-phenylenediamine species with ethoxyphenyl imidate (obtained from ethoxyphenylacetonitrile derivative) results in the 5-nitro-substituted final product etonitazepipne. It is possible to obtain etonitazepipne through other synthetic routes with the methods established for 5-nitro-2-benzylbenzimidazole analogues, with appropriate modifications to the reagents *(4, 6–9)*.

While no details of the production method or the scale of the recently identified etonitazepipne are available, the synthesis techniques used for its nitazene analogues suggest that the process is straightforward, cost-effective and does not require regulated precursors.

E Chemical properties

Melting-point

181–184 °C (Etonitazepipne hydrochloride) *(5)*.

Boiling-point

No information could be identified.

Solubility

Etonitazepipne is soluble in dimethylformamide and in dimethyl sulfoxide at 10 mg/mL. In phosphate-buffered saline (pH 7.2), it is soluble at 1 mg/mL *(1)*.

F Identification and analysis

Etonitazepipne citrate is available as reference material from commercial suppliers for use in routine methods of analysis in forensic and clinical investigations *(1)*.

Analytical methods for the identification of etonitazepipne in seized sample matrices include LC high-resolution MS (HRMS), GC–MS, LC-diode array detector and Fourier-transform infrared (FTIR) spectroscopy *(2)*.

LC-HRMS analytical methods were developed to quantify etonitazepipne in serum *(2, 10)* and urine *(2)* and to identify its principal urinary metabolites *(2)* in patients suspected of opioid overdose.

Another LC-HRMS method was developed to identify and quantify etonitazepipne in post-mortem biological matrices such as urine, gastric content and vitreous humour *(11)*. An LC–tandem MS (LC-MS/MS) method was developed to quantify etonitazepipne in post-mortem blood and urine *(12)*.

3. Ease of conversion into controlled substances

No information was available in the literature about whether etonitazepipne can be converted into a controlled substance.

4. General pharmacology

A Routes of administration and dosage

The literature and user reports suggest that etonitazepipne is most commonly administered by insufflation after solubilization into a nasal spray *(2,13,14)*. Intravenous administration may also be used, as syringes containing etonitazepipne were found near two decedents in cases of overdose *(15)*. Less commonly mentioned routes of administration include oral and inhalation of vapour after heating *(14,16)*.

Dosage estimates are based entirely on self-reports from people who use it. The reported doses delivered in intranasal sprays are 75–100 µg per spray, with three to six sprays per usage *(2, 13, 14)*. These anecdotal data should be interpreted with caution.

B Pharmacokinetics

No studies were identified on the absorption, distribution or elimination of etonitazepipne. Its metabolism was studied in vitro (in pooled human liver microsomes) *(2)* and in vivo (in biological samples) *(12)*. The parent compound was found in serum and urine samples at levels of 1.21–7.4 ng/mL and 0.51–6.9 ng/mL, respectively. Phase-I metabolic transformation included O-dealkylation, hydroxylation, oxidation and combinations of these processes. Whether these metabolites are psychoactive has not been assessed in vivo; however, *N*-piperidinyl 4′-OH nitazene (the hypothetical

primary metabolite) was 11 and 21 times less potent than etonitazepipne in β-arrestin 2 recruitment (EC_{50} = 56.9 nM) and cAMP (EC_{50} = 4.75 nM) functional assays *(17)*. These results suggest that the metabolites of etonitazepipne could retain psychoactivity, albeit at reduced potency than the parent compound (see also comment in 2) *(2)*.

C Pharmacodynamics

Etonitazepipne binds with high affinity to the MOR. The Ki for displacement of [3H] [D-Ala2, N-MePhe4, Gly-ol]-enkephalin ranged from 0.51 ± 0.10 nM (19) to 14.3 ± 2.5 nM *(2)*. In comparison, the MOR Ki for fentanyl was 1.255 ± 0.084 nM to 6.17 ± 0.82 nM in the same two studies, respectively. Etonitazepipne showed over 1000 times more selectivity for the MOR than for the k opioid (Ki = 1290 ± 110 nM) and Δ (Ki = 607 ± 63 nM) opioid receptors *(19)*.

Like fentanyl, etonitazepipne is a full, potent agonist at MOR, as measured in a [35S]GTPγS assay (EC_{50} = 8.47 ± 0.81 nM; E_{max} = 98.4 ± 6.7%) *(19)*. In contrast, it had low potency for activation of the κ and Δ opioid receptors (EC_{50} = 1610 ± 370 nM and 2370 ± 3.1 nM, respectively). Replicate in-vitro assays verified that etonitazepipne is a full agonist for enhancement of β-arrestin 2 recruitment, with EC_{50} values ranging from 3.06 nM (95% confidence interval: 2.19 ; 4.26 nM) *(2)* to 5.12 nM (95% confidence interval: 3.5 ; 7.4 nM) *(18)* and inhibition of forskolin-stimulated cAMP, with EC_{50} = 0.222 nM (95% confidence interval: 0.157 ; 0.319 nM) *(18)*.

In rats treated subcutaneously, etonitazepipne had potent analgesic effects in a hot-plate assay (median effective dose (ED_{50}) = 0.0205 mg/kg) *(2)*. In this assay, it was approximately equipotent with fentanyl (fentanyl ED_{50} = 0.0209 mg/kg). The peak effect occurred at a dose of 0.1 mg/kg 15 min after administration. Etonitazepipne also produced analgesic effects in mice, which were reversible with naltrexone. In rats treated subcutaneously, etonitazepipne also induced catalepsy (ED_{50} = 0.0354 mg/kg) and a pronounced, sustained drop in body temperature at a dose of 0.10 mg/kg *(2)*.

5. Toxicology

No studies of the preclinical toxicology of etonitazepipne were found.

6. Adverse reactions in humans

The presence of measurable concentrations of etonitazepipne in 14 post-mortem biological samples was reported in Germany (n=1), Italy (n=3) and the United

States (n=10) *(11,12,15,19,20)*; however, the presence of other drugs, including other opioids, was also reported in many of these cases. The extent to which etonitazepipne was casual to or contributed to the deaths was not specified in most instances. In two cases (one in Germany and one in Italy), etonitazepipne was considered to be the primary cause of death *(11,12,19)*. In 2021, three patients admitted to the emergency department of a New Jersey (United States) hospital tested positive for etonitazepipne *(10,21)*. All three patients were found unresponsive before admission and showed respiratory depression upon arrival at hospital. Treatment with naloxone resolved the clinical signs of opioid intoxication. Analysis of biological samples from two patients showed the presence of other opioids, whereas only etonitazepipne was reported in the third.

The predominant effects of etonitazepipne described by people who have used it include euphoria, relaxation, itchiness, energetic feelings and slight nodding or sedation *(13,14)*. Posts on online forums on self-reported experience of use of etonitazepipne should be considered anecdotal, as no analytical confirmation of sole use was obtained.

7. Dependence potential

A Studies in experimental animals

No information was found.

B Studies in humans

No information was found.

8. Abuse potential

A Studies in animals

Drug discrimination is a pharmacologically selective animal model of the subjective effects of psychoactive drugs in humans. Etonitazepipne produced full dose-dependent substitution in rats trained to discriminate morphine from vehicle. These effects were reversed by naltrexone.

B Studies in humans

No information was found.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

There are no known therapeutic uses of etonitazepipne.

10. Listing on the WHO Model List of Essential Medicines

Etonitazepipne is not listed on the 23rd WHO Model List of Essential Medicines or on the 9th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Etonitazepipne has no known marketing authorization.

12. Industrial use

Etonitazepine has no known industrial use.

13. Non-medical use, abuse and dependence

Etonitazepipne was first synthesized in the 1950s during development of a medication by CIBA Aktiengesellschaft in Switzerland; however, it was not submitted for regulatory approval or brought to the legal drug market. In 2021, etonitazepipne emerged on the illicit synthetic drug market in Europe and the United States *(22)*. Reports on online forums by people who use drugs provide evidence that etonitazepipne has been used intentionally for its intoxicating effects (see section 6). By the end of 2022, the presence of this substance had been reported in at least six countries (see section 16 for listing). The prevalence of chronic use and dependence of etonitazepipne has not been reported.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Since its emergence as a novel psychoactive substance in 2021, etonitazepipne has been analytically confirmed in post-mortem samples and in samples collected from patients admitted to emergency departments in several countries, including Germany, Italy and the United States. Between 2021 and 2023, 10 deaths from analytically confirmed etonitazepipne were found in the United States *(15,23)*. In each case, other psychoactive substances (including other opioids) were present in the biological samples, and some decedents had comorbid conditions that may have compromised their health. Hence, a definitive statement about the extent to which etonitazepipne caused or contributed to death could not made in any of the cases. Three additional fatalities occurred in Italy between July and September 2022 *(11,19)*. Whereas the cause of death in two of the cases could not be attributed definitively to etonitazepipne due to the presence of cocaine and other opioids in biological samples, etonitazepipne was considered to be the primary cause of death in the third fatality *(11,19)*. Etonitazepipne overdose was also identified as the primary cause of death of an individual in Germany

in 2022 *(12)*. In this case, the concentration of etonitazepipne in femoral blood was 8.3 ng/mL.

Nonfatal cases of etonitazepipne use have also been reported. Etonitazepipne was analytically confirmed in the serum of three patients who presented to the emergency department of a hospital in New Jersey (United States) *(10,21)*. In all three cases, the individuals had been found nonresponsive and had respiratory depression or low oxygen saturation upon admission. The symptoms of all the patient resolved with administration of naloxone *(21)*. As biological samples from two of the patients also contained other psychoactive substances, including other opioids, the clinical symptoms could not be attributed solely to etonitazepipne. The third patient tested positive only for etonitazepipne, suggesting that the clinical signs were related to overdose of this compound.

15. Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

Countries in which the presence of etonitazepipne has been reported are Austria, Canada, Italy, Germany, the United Kingdom and the United States *(12,19,23,24)*. While etonitazepipne is banned and/or under increased surveillance in the European Union and in several countries (e.g. Canada, the United Kingdom and the United States), accurate estimates of its prevalence and traffic have been complicated by its rapid appearance on the illicit market, its high potency (requiring measurement of minute amounts in forensic samples) and underreporting due to an initial lack of reference standards *(22)*.

17. Current international controls and their impact

Etonitazepipne is not currently under international control.

18. Current and past national controls

In 2023, an order for temporary placement of etonitazepipne under Schedule 1 of the US Controlled Substances Act was published *(22)*. Benzimidazoles and their derivatives are also classified under Schedule 1 under Canadian law. In the United Kingdom, etonitazepipne was included in the list of new Class A substances issued in 2023 *(24)*. In 2022, etonitazepipne was placed under intensive monitoring in the European Union *(12)*, and it was included in Table 1 of narcotic drugs issued by the Italian Ministry of Health *(19)*.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

None.

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3.5 *N*-Desethyl isotonitazene

1. Substance identification

A INN

Not available.

B CAS Registry Number

2732926-24-6

C Other chemical names

N-Ethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine (ACI)

D Trade names

N-Desethyl isotonitazene is sold under its name or as the hydrochloride salt, *N*-desethyl isotonitazene (hydrochloride) *(1)*.

E Street names

N-Desethyl isotonitazene is known under its name or as "Des-Iso", "Norisotonitazene" or "NDI" *(2,3)*.

F Physical appearance

N-Desethyl isotonitazene hydrochloride as a synthetic standard is a crystalline solid *(1)*. It has also been detected in falsified pharmaceuticals, in round blue pills *(4)*.

G WHO review history

N-Desethyl isotonitazene has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC name

N-Ethyl-2-[(4-(1-methylethoxy)phenyl]methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine

CA Index name

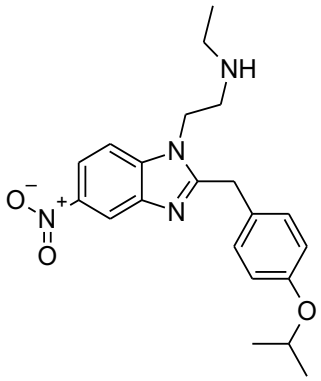
1*H*-Benzimidazole-1-ethanamine, *N*-ethyl-2-[(4-(1-methylethoxy)phenyl] methyl]-5-nitro- (ACI)

Canonical SMILES

O=N(=O)C=1C=CC2=C(N=C(N2CCNCC)CC3=CC=C(OC(C)C) C=C3)C1

B Chemical structure

Free base



Molecular formula: $C_{21}H_{26}N_4O$

Molecular weight: 382.46 g/mol

C Stereoisomers

No stereoisomers of *N*-desethyl isotonitazene have been described.

D Methods and ease of illicit manufacture

N-Desethyl isotonitazene was identified in vivo as an isotonitazene urinary metabolite by Krotulski et al. in 2020 *(4)*.

Synthesis of *N*-desethyl isotonitazene was reported by Vandeputte et al. *(5)*. The activated halogen atom of 1-halo-2,4-dinitrobenzene (halo = F, Cl, or Br) can easily be substituted by *N*-boc-*N*-ethylethylenediamine. Then, regioselective reduction of the nitro group in the ortho position to the resulting amino function is followed by condensation with 4-isopropoxyphenylacetic acid in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. Removal of the *tert*-butoxycarbonyl protecting group with trifluoroacetic acid affords the final product, *N*-desethyl isotonitazene, as the free base.

N-Desethyl isotonitazene can also be obtained through other synthetic routes with the methods established for the 5-nitro-2-benzylbenzimidazole analogues, with appropriate modifications to the reagents *(5–7)*.

While details of the production method and scale of recently identified *N*-desethyl isotonitazene are not available, the synthesis techniques for its nitazene analogues suggests that the process is straightforward, cost-effective and does not require regulated precursors *(5,6)*.

E Chemical properties

Melting-point

No information was identified.

Boiling-point

No information was identified.

Solubility

N-Desethyl isotonitazene hydrochloride salt is soluble in dimethylformamide and in dimethyl sulfoxide at 30 mg/mL. It is soluble at 5 mg/mL in phosphate-buffered saline (pH 7.2) and at 30 mg/mL in ethanol *(1)*.

F Identification and analysis

Synthetic *N*-desethyl isotonitazene was characterized by NMR spectroscopy, high-performance LC coupled to diode-array detection, GC-MS and LC–MS *(5)*.

N-Desethyl isotonitazene hydrochloride is available as reference material from commercial suppliers and used for routine analysis in forensic and clinical investigations *(1)*. It was detected in round blue pills by GC-MS, LC–quadrupole time-of-flight MS (LC–QTOF-MS) and GC with IR spectroscopy *(8)*.

N-Desethyl isotonitazene was detected as metabolite of isotonitazene in human post-mortem plasma and urine with LC–QTOF-MS *(4)*. It was detected in the plasma of rats after administration of isotonitazene by LC with tandem quadrupole MS *(9)*. Recently, *N*-desethyl isotonitazene was detected and quantified in whole blood and urine from polydrug users admitted to a hospital in the United Kingdom by LC-MS/MS *(10)*.

3. Ease of conversion into controlled substances

It is not clear from the literature whether *N*-desethyl isotonitazene can be converted into a controlled substance.

4. General pharmacology

A Routes of administration and dosage

Two reports from WEDINOS (W049751 and 000037166) *(11)* provided results for samples that were smoked. No reports from participants in online discussion forums were found that provided information on the preferred routes of administration or dosage of *N*-desethyl isotonitazene.

B Pharmacokinetics

No data on the absorption, distribution, metabolism or excretion of *N*-desethyl isotonitazene were found. Although data on the metabolism of nitazenes are limited, in a recent study on quantification of isotonitazene and identification of its metabolites in animals, the four main metabolites found after ingestion of isotonitazene included *N*-desethyl isotonitazene *(4)*. Isotonitazene is probably metabolized by *N*-dealkylation and *O*-dealkylation, like other benzimidazole opioids (a class of opioids that includes isotonitazene), which usually undergo *N*-dealkylation at the *N*-ethylamine chain and *O*-dealkylation at the phenylalkyl chain *(12)*.

N-Desethyl isotonitazene has been identified by toxicological analysis as a major metabolite of isotonitazene *(9,12,13)*. In a recent study, *N*-desethyl isotonitazene was the main metabolite found, with isotonitazene, being detected in 96% of 64 samples from people driving under the influence of drugs and 47 post-mortem samples containing isotonitazene *(13)*. In all the cases analysed, the presence of *N*-desethyl isotonitazene was evaluated only qualitatively, as its concentration was below the limit of quantification (0.5 ng/mL), further indicating that its presence was probably due to the metabolism of isotonitazene.

N-Desethyl isotonitazene was detected in the plasma of male Sprague-Dawley rats administered 10 or 30 μg/kg isotonitazene subcutaneously, at concentrations below the limit of quantification (0.5 ng/mL) *(9)*.

C Pharmacodynamics

Unpublished studies on the binding and functional activity of *N*-desethyl isotonitazene showed that it had a higher binding affinity to m-opioid receptors than morphine and fentanyl and was more potent at μ-opioid receptors than at Δ- and κ-opioid receptors.

Vandeputte et al. *(5)* analysed the biological m-opioid receptor activity in vitro of 14 nitazenes, including *N*-desethyl isotonitazene, in two cell-based

assays based on stable expression by HEK293T cells of either the human m-opioid receptor-β-arrestin2-G protein-coupled receptor kinase 2 (MOR-βarr2-GRK2) or the human m-opioid receptor-GTPase domain of the Gαi subunit (MOR-mini Gi). Both recruitment assays showed that *N*-desethyl isotonitazene was more potent at m-opioid receptors (EC_{50} = 0.614 and 1.16 nM for β-arrestin-2 and mini-Gi systems, respectively) than any other benzimidazole opioid tested, morphine or fentanyl *(5)*.

Walton et al. *(9)* determined the binding affinity of *N*-desethyl isotonitazene for opioid receptors in rat brain membranes and compared it with that of its parent compound (isotonitazene) with the radioligands [3H]DAMGO, [3H]DADLE and [3H]U69,593 used to label m, D and k opioid receptors, respectively. The authors observed that *N*-desethyl isotonitazene (Ki = 2.2 ± 0.4 nM) had seven and two times greater affinity for the m-opioid receptor than isotonitazene (Ki = 15.8 ± 3.1 nM) and fentanyl (Ki = 4.4 ± 1.0 nM) but was similar to that of morphine (Ki = 2.1 ± 0.4 nM). In these assays, *N*-desethyl isotonitazene also showed slightly higher affinity to the Δ-opioid receptor (Ki = 610.2 ± 108.0 nM) than isotonitazene (Ki = 745.8 ± 265.0 nM) and fentanyl (Ki = 932.1 ± 292.0 nM) and slightly lower than morphine (Ki = 442.1 ± 150.0 nM). Moreover, *N*-desethyl isotonitazene had less affinity to the k-opioid receptor (Ki = 838.9 ± 120.0 nM) than isotonitazene (Ki = 691.0 ± 220.0 nM), fentanyl (Ki = 365.0 ± 113.0 nM) and morphine (Ki = 146.1 ± 61.9 nM).

Malcolm et al. (14) used optimized bioluminescence resonance energy transfer (BRET) G protein and β-arrestin2 recruitment assays and found that *N*-desethyl isotonitazene had sub-nanomolar potency and superagonism in both assays, similar to isotonitazene. In the BRET assay, *N*-desethyl isotonitazene was less potent (EC_{50} = 252 pM) than isotonitazene (EC_{50} = 107 pM). The authors correlated the potencies observed in the BRET assays with the high affinity of isotonitazene and *N*-desethyl isotonitazene at m-opioid receptors.

In an unpublished study, *N*-desethyl isotonitazene was tested for its ability to produce analgesic effects in a warm-water tail-flick assay. *N*-Desethyl isotonitazene increased the latency of tail-flick in a dose-dependent manner. The results indicated *N*-desethyl isotonitazene was more potent than morphine and fentanyl and as efficacious as morphine and fentanyl. Subcutaneous injection of naltrexone before administration of *N*-desethyl isotonitazene blocked its analgesic effect, indicating involvement of opioid receptors in its action.

The results of unpublished tail-flick assays in C57BL/6J mice demonstrated that *N*-desethyl isotonitazene has significant analgesic effects. A comparison

of molar mass showed that the substance (ED_{50} = 40.1 µg/kg) was equipotent to fentanyl, whereas its parent compound, isotonitazene (ED_{50} = 11.3 µg/kg), had an analgesic potency almost four times higher than that of fentanyl (ED_{50} = 55.7 µg/kg) *(15)*. The same authors compared the respiratory depressant effects of *N*-desethyl isotonitazene and fentanyl by measuring phrenic nerve activity in a well-established decerebrate rabbit model in which partial pressure of oxygen (pO_2) and partial pressure of carbon dioxide (pCO_2) were maintained constant throughout drug administration. *N*-Desethyl isotonitazene required less than half (3.5 ± 0.3 µg/kg, n = 6) of the dose required by fentanyl to cause complete apnoea (9.0 ± 0.5 µg/kg, n = 4, $P < 0.001$), indicating a doubling of the potency when given intravenously. A single equal dose (1 µg/kg) of *N*-desethyl isotonitazene induced greater respiratory depression (59 ± 2% of baseline respiratory rate, n = 6) than fentanyl (75 ± 3%, n = 3, $P < 0.001$). The time to the maximal effect for this dose was nearly four times longer for *N*-desethyl isotonitazene (10.5 ± 1 min) than for fentanyl (2.5 ± 0.5 min, $P < 0.001$). The time for recovery from apnoea to baseline respiratory rate was approximately three times longer with *N*-desethyl isotonitazene (208 ± 38 min) than with fentanyl (67 ± 9 min, $P = 0.018$). Injection of naloxone completely reversed apnoea induced by 3 µg/kg *N*-desethyl isotonitazene within 5.5 ± 0.6 min (n = 6), suggesting the involvement of opioid receptors in these processes.

5. Toxicology

According to a UNODC EWA, *N*-desethyl isotonitazene was found in a total of 14 post-mortem cases (4 males, 10 females), with two in the United Kingdom and 12 in the United States in 2023 *(15)*. The blood concentrations of *N*-desethyl isotonitazene ranged between 0.7 and 290 ng/mL, but its contribution to the cause of death was unknown in all cases. Other substances found in six cases were bromazolam *(3)*, flubromazepam *(1)*, metonitazene *(3)* and *N,N*-dimethylamphetamine *(1)*.

In an observational case series of patients admitted to hospitals in the Sandwell and West Birmingham National Health Service Trust, United Kingdom, between July and October 2023 with suspected or declared substance use, 19 tested positive for *N*-desethyl isotonitazene, at a median concentration of 1.53 µg/L (range, 0.59–5.48, n = 14) in whole blood and 27.75 µg/L (range 0.51–91.53, n = 16) in urine. Other substances (which included cocaine, morphine, xylazine, gabapentinoids, methadone, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine, benzodiazepines and the synthetic cannabinoid MDMB-4en-PINACA) were detected in 18 of those patients. *N*-Desethyl isotonitazene

was the only substance detected in one patient, who was admitted in coma and showed signs of miosis, bradypnoea and hypercapnia *(10)*.

The toxic dose of *N*-desethyl isotonitazene for humans has not been reported.

6. Adverse reactions in humans

N-Desethyl isotonitazene belongs to the opioid chemical subgroup 2-benzylbenzimidazoles, the most common effects of which include analgesia, euphoria, miosis, muscle rigidity, unconsciousness, sedation, and respiratory depression. A single report on adverse reactions to *N*-desethyl isotonitazene in humans was found, in which a patient was admitted to hospital in coma, with miosis, bradypnoea and hypercapnia *(10)*.

Unverified information from a participant in an online forum *(16)* referred to stimulant-like effects after taking *N*-desethyl isotonitazene intravenously. Self-reported effects from one report in WEDINOS (W049751) *(11)* included euphoria, nausea and vomiting.

Because of its high potency, *N*-desethyl isotonitazene poses a higher risk of overdose than other opioids, such as fentanyl *(17,18)*. *N*-Desethyl isotonitazene was confirmed analytically in 14 post-mortem cases reported to the UNODC EWA, but the contribution of this substance to the death was unknown *(15)*. A recent publication also mentioned identification of *N*-desethyl isotonitazene in 37 deaths between 2019 and 2021 in the United States. In all cases, *N*-desethyl isotonitazene was detected with isotonitazene, at lower blood concentrations, suggesting that the presence of *N*-desethyl isotonitazene was probably due to metabolism of isotonitazene *(9)*.

7. Dependence potential

A Studies in experimental animals

No studies were identified.

B Studies in humans

No studies were identified.

8. Abuse potential

A Studies in experimental animals

In unpublished drug discrimination studies, *N*-desethyl isotonitazene fully

substituted for morphine. It was more potent than morphine and slightly less potent than fentanyl, with similar efficacy to that of morphine and fentanyl.

Subcutaneous injection of naltrexone blocked the morphine-like discriminative stimulus effects of *N*-desethyl isotonitazene, indicating the involvement of opioid receptors in its discriminative stimulus effects.

B Studies in humans

No studies of the human abuse potential of *N*-desethyl isotonitazene were identified.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Synthesis of a group of benzimidazole derivatives with analgesic properties was described in 1957 by the Swiss chemical company CIBA Aktiengesellschaft *(19)*, but none of the derivatives was medically approved. *N*-Desethyl isotonitazene is not known to have any medical use.

10. Listing on the WHO Model List of Essential Medicines

N-Desethyl isotonitazene is not listed on the 23rd WHO List of Essential Medicines or the 9th WHO List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

N-desethyl isotonitazene is not known to be authorized for marketing.

12. Industrial use

N-Desethyl isotonitazene is not known to have any industrial use.

13. Non-medical use, abuse and dependence

The Toronto (Canada) Drug Checking Service reported identification of *N*-desethyl isotonitazene by the Centre for Addiction and Mental Health (Clinical Laboratory and Diagnostic Services) on 23 February 2024 in a sample collected in Toronto's west end. The sample was bought as fentanyl but consisted of *N*-desethyl isotonitazene and caffeine, with no fentanyl *(17)*.

A recent report from the Public Health Agency of Sweden indicated that *N*-desethyl isotonitazene is present in the country *(18)*.

Detection of *N*-desethyl isotonitazene has been cited in 10 reports of the US NFLIS Drug since 2022 *(20)*, suggesting its use.

N-Desethyl isotonitazene was detected in 19 people who had used several substances and were admitted to hospitals in Birmingham, United Kingdom, between July and October 2023 *(10)*.

N-Desethyl isotonitazene was identified by WEDINOS in two samples received by purchaser(s) who intended to buy heroin *(11)*, suggesting its unintentional use.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

No information was found on the nature or magnitude of health problems associated with use of *N*-desethyl isotonitazene. *N*-Desethyl isotonitazene has been confirmed in at least nine fatal and one non-fatal overdose events in the United States *(20)*.

According to the UNODC EWA, *N*-desethyl isotonitazene was reported in 14 post-mortem cases during 2023 in the United Kingdom *(2)* and the United States *(12) (15)*.

In 2022, *N*-desethyl isotonitazene was identified in falsified pharmaceutical tablets in the United Kingdom and the United States. Data from law enforcement agencies suggest that it is used as a recreational drug in the United States. The Center for Forensic Science Research and Education in the United States recently reported identification of *N*-desethyl isotonitazene in falsified oxycodone round blue tablets in Florida. In December 2022, *N*-desethyl isotonitazene was identified in samples referred to as "dope", with other substances (e.g. xylazine, fentanyl, parafluorofentanyl and designer benzodiazepines such as flubromazepam and bromazolam) in the drug supply in Philadelphia (PA) *(21)*.

15. Licit production, consumption and international trade

N-Desethyl isotonitazene is used as reference material in scientific research and forensic applications.

16. Illicit manufacture and traffic and related information

Reports from NFLIS Drug indicate that *N*-desethyl isotonitazene was first detected in the United States in 2022 in Florida and in Kansas. Since 2022, there

have been a total of 10 reports to NFLIS-Drug from four US states: Pennsylvania *(5)*, Florida *(3)*, Kansas *(1)* and Texas *(1)*. Of those reports, 9 were of fatal overdoses and one of a non-fatal overdose. In 2023, six reports were made to NFLIS-Drug, only five of which reported weights, totaling 2.58 g *(20)*.

17. Current international controls and their impact

N-Desethyl isotonitazene is not currently controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

In Germany, *N*-desethyl isotonitazene is classified as "Anlage II" (authorized trade only, not prescriptible).

Because of the negative effects of *N*-desethyl isotonitazene, the Public Health Agency of Sweden has recommended that it be included in Ordinance (1992:1554) on the Control of Narcotic Drugs *(18)*.

In the United Kingdom, *N*-desethyl isotonitazene is controlled under the Psychoactive Substances Act.

A notice of intent to control *N*-desethyl isotonitazene as a Schedule I substance was published in the US Federal Register on 25 October 2023 *(21)*.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

N-Desethyl isotonitazene remains a cause for concern due to its greater potency than the parent drug, the possibility that it aggravates the risks of isotonitazene use and its potential acquisition directly rather than isotonitazene.

As people who use *N*-desethyl isotonitazene are likely to obtain it from unregulated sources, its identity, purity and quantity are uncertain and inconsistent. This, combined with its high potency, may pose significant adverse health risks to people who use it *(21)*.

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3.6 3-Hydroxyphencyclidine

1. Substance identification

A INN

Not available

B CAS registry number

79787-43-2 (free base)

79295-51-5 (hydrochloride)

80770-71-4 (hydrobromide)

C Other chemical names

3-[1-(Piperidin-1-yl)cyclohexyl]phenol

1-[1-(3-Hydroxyphenyl)cyclohexyl]piperidine

N-[1-(3-Hydroxyphenyl)cyclohexyl]piperidine

3-Hydroxyphencyclidine

3-HO-PCP

Pcp-3-OH

3-OH-PCP

3-Hyydroxy PCP

D Trade names

3-Hydroxyphencyclidine is sold as an analytical standard as the hydrochloride salt under the name 3-hydroxy PCP (hydrochloride) *(1)*. It is sold as powder under its own chemical names *(2,3)*.

E Street names

3-Hydroxyphencyclidine, 3-HO-PCP, 3-OH-PCP *(4)*

F Physical appearance

As a pure standard, 3-hydroxyphencyclidine hydrochloride has been described as a crystalline solid *(1)*. One vendor described it as a white crystalline powder *(3)*.

G WHO review history

3-Hydroxyphencyclidine has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC name

3-[1-(1-Piperidinyl)cyclohexyl]phenol

CA Index name

Phenol, 3-[1-(1-piperidinyl)cyclohexyl]- (9CI, ACI)

3-Hydroxyphencyclidine (free base)

Canonical SMILES

OC1=CC=CC(=C1)C2(N3CCCCC3)CCCCC2

InChI

1S/C17H25NO/c19-16-9-7-8-15(14-16)17(10-3-1-4-11-17)18-12-5-2-6-13-18/h7-9,14,19H,1-6,10-13H2

InChI key

AMSXTZUCNOKUEN-UHFFFAOYSA-N

3-Hydroxyphencyclidine (hydrochloride)

Canonical SMILES

Cl.OC1=CC=CC(=C1)C2(N3CCCCC3)CCCCC2

InChI

InChI=1S/C17H25NO.ClH/c19-16-9-7-8-15(14-16)17(10-3-1-4-11-17)18-12-5-2-6-13-18;/h7-9,14,19H,1-6,10-13H2;1H

InChI key

XLHLAXXFXAYRJS-UHFFFAOYSA-N

3-Hydroxyphencyclidine (hydrobromide)

Canonical SMILES

Br.OC1=CC=CC(=C1)C2(N3CCCCC3)CCCCC2

InChI

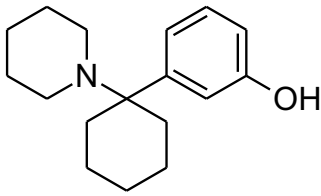
InChI=1S/C17H25NO.BrH/c19-16-9-7-8-15(14-16)17(10-3-1-4-11-17)18-12-5-2-6-13-18;/h7-9,14,19H,1-6,10-13H2;1H

InChI key

ZXSOICVUBMZDIC-UHFFFAOYSA-N

B Chemical structure

Free base:



Molecular formula: $C_{17}H_{25}NO$

Molecular weight: 259.39 g/mol

C Stereoisomers

No stereoisomers of 3-hydroxyphencyclidine have been described.

D Methods and ease of illicit manufacture

3-Hydroxyphencyclidine is a hydroxy derivative of phencyclidine. Its synthesis was described in 1982 by Kamenka et al. *(5)*, who obtained 3-hydroxyphencyclidine by dealkylation of 3-methoxyphencyclidine (Schedule II of the 1971 Convention on Psychotropic Substances) with boron tribromide at low temperature. The same dealkylation procedure was described with boron tribromide by Zarantonello et al. *(6)*, while Haradahira et al. *(7)* used bromic acid in acetic acid for demethylation of 3-methoxyphencyclidine. Synthesis of the precursor 3-methoxyphencyclidine was first described in the literature by Geneste et al. in 1979 *(8)*, and the method was subsequently used by Kamenka et al. *(5)* and Haradahira et al. *(7)* for preparation of 3-hydroxyphencyclidine by demethylation. Zarantonello et al. *(6)* described a two-step synthesis of 3-methoxyphencyclidine involving the reaction of cyclohexanone and pyridine in the presence of triazole in the first step. The resulting triazolyl intermediate was not isolated but was added directly to a solution of 3-methoxyphenylmagnesium bromide to obtain 3-methoxyphencyclidine. The preparation described by Zarantonello et al. is very straightforward and easily applicable to clandestine production *(9)*.

E Chemical properties

Melting-point

192–195 °C (3-Hydroxyphencyclidine hydrobromide) *(5)*

Boiling-point

No information was found.

Solubility

3-Hydroxyphencyclidine is soluble at 16 mg/mL in dimethylformamide, 11 mg/mL in dimethyl sulfoxide and 20 mg/mL in ethanol. It is also soluble in phosphate-buffered saline (pH 7.2) at 10 mg/mL *(1)*.

F Identification and analysis

3-Hydroxyphencyclidine (hydrochloride) and its deuterated form, 3-hydroxyphencyclidine-d_{10} (hydrochloride), are available as reference materials from commercial suppliers for use in routine analytical methods in forensic and clinical investigations *(1)*.

Synthetic 3-hydroxyphencyclidine was characterized by GC-MS, LC-TOF-MS, FTIR spectroscopy-attenuated total reflectance, proton (^{1}H) NMR and ^{13}C-NMR *(10)*.

Seized powder of 3-hydroxyphencyclidine was characterized by ^{1}H-NMR and ^{13}C-NMR *(11)*.

Use of LC-HRMS or to MS/MS has been described in the literature for quantitative determination of 3-hydroxyphencyclidine and for identification of its metabolites in biological specimens such as blood, urine and hair of intoxicated subjects, and in the blood and brain of post-mortem forensic cases *(11–13)*.

3. Ease of conversion into controlled substances

3-Hydroxyphencyclidine is easily methylated on the phenolic hydroxyl group to yield the controlled substance 3-methoxyphencyclidine, which is under Schedule II of the 1971 Convention on Psychotropic Substances *(7)*.

4. General pharmacology

A Routes of administration and dosage

The available data, including reports from people who use 3-hydroxyphencyclidine and law enforcement seizures, indicate that 3-hydroxyphencyclidine is usually purchased in the form of liquid, crystals

or powder *(4,14,15)*. After purchase, crystals may be crushed, or powder may be placed in capsules. The powder or crushed crystals can be solubilized. Common routes of administration include insufflation (direct snorting of powder or crushed crystals or solubilization into a nasal spray) and oral; intravenous injection is less commonly mentioned as a route of administration *(4,14,15)*.

No studies were found that describe human dosages; however, one informational website categorized doses according to their intoxicating effects after oral administration as "light" (2–4 mg), "common" (4–5 mg) and "strong" (≥ 5 mg) *(16)*. For comparison, the website lists the following doses of oral PCP: "light" (2–5 mg), "common" (5–10 mg) and "strong" (8–≥ 15 mg) *(17)*. People who have insufflated 3-hydroxyphencyclidine report use of doses of 1–20 mg *(15)*. The onset of effects of 3-hydroxyphencyclidine is estimated to occur 20–40 min after insufflation, the duration of action is 3–4 h, and the after-effects last 0–2 h *(16)*. The basis for this information is unclear, and, given its anecdotal nature, caution is suggested in interpreting it.

B Pharmacokinetics

No information was available on the absorption, distribution or elimination of 3-hydroxyphencyclidine. A single study of its metabolism in vitro (human liver hepatocytes) and in vivo (analysis of biological samples) identified two phase-I metabolites and two phase-II metabolites *(12)*. Phase-I metabolic processes included (i) mono-hydroxylation on the piperidine ring and (ii) *N*-dealkylation and double oxidation (ω-carboxylation); phase-II processes were (i) O-glucuronidation and (ii) sulfate conjugation. Analysis of blood and brain samples found significant amounts of the parent compound, with a brain:blood ratio > 1.5, indicating high lipophilicity and penetration of the central nervous system.

C Pharmacodynamics

Like phencyclidine, 3-hydroxyphencyclidine showed high affinity for the phencyclidine receptor site *(5,18)*. At *N*-methyl-D-aspartate receptors, it displaced [3H]MK-801 (see Annex 3 for details). Although 3-hydroxyphencyclidine had higher affinity for μ and s opioid receptors than phencyclidine, it was approximately equipotent in inhibiting electrically stimulated guinea-pig ileum, and the effect was reversed by naloxone *(18,19)*. Autoradiographic analysis showed that the regional distribution of the binding site labelled with [3H]3-hydroxyphencyclidine and with [3H] MK-801 were similar *(20,21)*.

5. Toxicology

No studies of the preclinical toxicology of 3-hydroxyphencyclidine were available.

6. Adverse reactions in humans

Isolated cases of morbidity or mortality associated with exposure to analytically confirmed 3-hydroxyphencyclidine have been reported in the literature. As other substances were detected in all cases, the degree to which the substance contributed to clinical effects or mortality cannot be determined conclusively. (For additional details, see section 14.) One patient (a 56-year-old male) who presented to an emergency department in the United Kingdom reported phencyclidine-like symptoms, including visual hallucinations, reduced consciousness, diaphoresis, tachycardia, hypertension and vertical nystagmus *(13)*. Although the patient had taken a cathinone (*N*-ethylhexedrone) the previous night (as analytically confirmed), he claimed sole use of 3-hydroxyphencyclidine on the morning before admission. These results suggest that the clinical profile produced by 3-hydroxyphencyclidine probably resembles that of phencyclidine.

People who used 3-hydroxyphencyclidine have described effects such as euphoria, relaxation, dissociation, distorted perception (including visual hallucinations), sociability confusion and mental stimulation *(14,15)*. Self-reported experience of the psychological effects of 3-hydroxyphencyclidine should be considered anecdotal, as no analytical confirmation of sole use was obtained.

7. Dependence potential

A Studies in experimental animals

No information was found.

B Studies in humans

No information was found.

8. Abuse potential

A Studies in experimental animals

3-Hydroxyphencyclidine injected intraperitoneally resulted in full dose-dependent substitution for phencyclidine in male rats trained to discriminate phencyclidine from vehicle.

B Studies in humans

No information was found.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

There are no known therapeutic uses for 3-hydroxyphencyclidine.

10. Listing on the WHO Model List of Essential Medicines

3-Hydroxyphencyclidine is not listed on the 23rd WHO Model List of Essential Medicines or on the 9th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

3-Hydroxyphencyclidine has no known marketing authorization.

12. Industrial use

3-Hydroxyphencyclidine has no known industrial use.

13. Non-medical use, abuse and dependence

3-Hydroxyphencyclidine is an analogue of the dissociative anaesthetic phencyclidine. It was synthesized in 1982 as part of an investigation on the structure–activity relations of phencyclidine analogues *(5)*, and the first reports of its use as a new psychoactive substance appeared on the online forum Bluelight in 2009 *(4,13)*. Reports on online forums by people who use drugs provide evidence that 3-hydroxyphencyclidine has been used intentionally for its intoxicating effects (see section 6). The presence of this substance has been reported in at least 25 countries. (See section 16 for listing.) The prevalence of chronic use and dependence of 3-hydroxyphencyclidine have not been reported.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

The presence of 3-hydroxyphencyclidine was analytically confirmed in three fatalities and in six emergency department admissions. Fatalities were reported in Denmark, France and Germany *(11,12,22)*. In France, the post-mortem concentration of 3-hydroxyphencyclidine was 524 ng/mL in one death *(11)* and 25 and 95 ng/mL in the other two. The high 3-hydroxyphencyclidine concentration in one death led the authors to conclude that this substance

had contributed substantially. The nonfatal cases included four emergency department admissions in Australia in 2023 *(23)*, one in the United Kingdom *(13)* and one in France *(24)*. In none of the fatal and nonfatal cases was 3-hydroxyphencyclidine the only substance detected; the other identified substances included benzodiazepines, opioids and stimulants. Hence, the degree to which 3-hydroxyphencyclidine contributed to any clinical effects or fatality cannot be determined conclusively.

15. Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

The first reported use of 3-hydroxyphencyclidine as a psychoactive substance was recorded on the online forum Bluelight in 2009 *(4,13)*. The countries in which the presence of 3-hydroxyphencyclidine has been reported are Austria, Australia, Bulgaria, Canada, China, Croatia, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Japan, Lithuania, Netherlands (Kingdom of the), New Zealand, Norway, Poland, Slovenia, Spain, Sweden, Switzerland, Türkiye, the United Kingdom and the United States *(13,23,25)*. No additional information was available on its manufacture or trafficking.

17. Current international controls and their impact

3-Hydroxyphencyclidine is not currently under international control.

18. Current and past national controls

3-Hydroxyphencyclidine is regulated under psychoactive drug control regulations in Canada *(26)* and the United Kingdom *(27)*.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

Sixty-five chocolate samples submitted to the National Anti-drug Laboratory of China for analysis were found to contain novel psychoactive substances *(28)*, of which 15 contained 3-hydroxyphencyclidine. Information on the source of the chocolate samples was not provided, nor were data on the prevalence. The presence of 3-hydroxyphencyclidine and other novel psychoactive substances in food could increase the risk of unintentional (including paediatric) exposure.

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3.7 *N*-Ethylheptedrone

1. Substance identification

A INN

Not assigned.

B CAS Registry Number

2514784-72-4

C Other chemical names

2-(Ethylamino)-1-phenyl-1-heptanone (ACI)

NEHP

N-ethylnorheptedrone

2-(Ethylamino)-1-phenyl-1-heptanone (ACI)

NE-HpP *(1)*

NE-heptanophenone *(1)*

D Trade names

N-Ethylheptedrone hydrochloride is sold under the name *N*-ethyl heptedrone (hydrochloride) as an analytical reference standard *(2)*.

E Street names

N-Ethylheptedrone is sold under its name, as ethyl heptedrone or as HEP *(3)*.

F Physical appearance

N-Ethylheptedrone hydrochloride as a reference material has been described as a crystalline solid *(2)*.

G WHO review history

N-Ethylheptedrone has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A Chemical name

IUPAC name

2-(Ethylamino)-1-phenylheptan-1-one

CA index name

1-Heptanone, 2-(ethylamino)-1-phenyl- (ACI)

Canonical SMILES

O=C(C=1C=CC=CC1)C(NCC)CCCCC

InChI

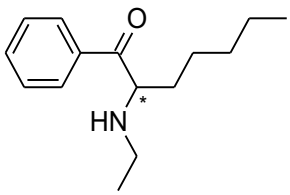
1S/C15H23NO/c1-3-5-7-12-14(16-4-2)15(17)13-10-8-6-9-11-13/h6,8-11,14,16H,3-5,7,12H2,1-2H3

InChI key

KCDBNUUMBCYCQC-UHFFFAOYSA-N

B Chemical structure

Free base:

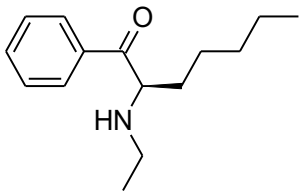


Molecular formula: $C_{15}H_{23}NO$

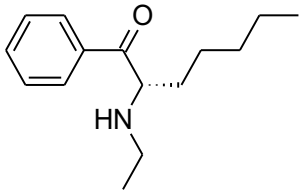
Molecular weight: 233.35 g/mol

C Stereoisomers

N-Ethylheptedrone contains a chiral centre; therefore, two enantiomers may exist: (*R*)-*N*-ethylheptedrone and (*S*)-*N*-ethylheptedrone. No information was available on the enantiomeric composition of *N*-ethylheptedrone on the drug market, but it is probably available as a racemic mixture of the (*R*)- and (*S*)- enantiomers, although the appearance of individual stereoisomers cannot be excluded.



(*R*)-*N*-ethylheptedrone



(*S*)-*N*-ethylheptedrone

D Methods and ease of illicit manufacture

No information was available on the routes of synthesis used for the *N*-ethylheptedrone products circulating on the market; however, chemical synthesis of cathinones is straightforward. Nadal-Gratacós et al. reported the synthesis of *N*-ethylheptedrone *(4)*. Benzonitrile was reacted with heptylmagnesium bromide Grignard reagent, then, acidic hydrolysis resulted in the intermediate ketone, which was α-halogenated by the addition of bromine. Reaction with ethylamine gave the synthetic cathinone *N*-ethylheptedrone, which was crystallized as a hydrochloride salt.

The synthesis reported in the literature, although simple, requires the equipment of a chemical synthetic laboratory and qualified personnel.

E Chemical properties

Melting-point

No information was identified

Boiling-point

No information was identified.

Solubility

N-Ethylheptedrone is soluble in dimethylformamide and in dimethyl sulfoxide at 15 mg/mL. Its solubility is 20 mg/mL in ethanol and 10 mg/mL in phosphate-buffered saline (pH 7.2) *(2)*.

F Identification and analysis

N-Ethylheptedrone (hydrochloride) is available as a reference material from commercial suppliers for use in routine methods of analysis in forensic and clinical investigations *(2)*.

Synthetic *N*-ethylheptedrone hydrochloride was characterized by TLC, ^{1}H-NMR and ^{13}C-NMR, IR spectroscopy and LC-MS. Seized *N*-ethylheptedrone (hydrochloride) was characterized by GC-MS, direct infusion electrospray ionization MS (ESI-MS), high-resolution MS (HRMS), IR spectroscopy, X-ray crystallography, thermogravimetric analysis, differential scanning calorimetry and ^{1}H-NMR and ^{13}C-NMR *(5)*.

Enatioseparation of racemic *N*-ethylheptedrone was reported by capillary electrophoresis, with single-isomeric cyclodextrin derivatives as chiral selectors *(6)*.

An LC triple quadrupole MS method was validated for quantification of *N*-ethylheptedrone in wastewater *(7)*. A method for the quantification of synthetic cathinones, including *N*-ethylheptedrone, in urine was recently developed and validated, which comprised magnetic dispersive solid-phase extraction in combination with direct analysis in real time coupled to HRMS *(8)*.

3. Ease of conversion into controlled substances

No information was found the literature that *N*-ethylheptedrone can be converted into a controlled substance.

4. General pharmacology

A Routes of administration and dosage

Reports from WEDINOS indicate that *N*-ethylheptedrone may be smoked, snorted or sniffed or taken orally *(2,9)*.

The Public Health Agency of Sweden indicated that participants on online drug forums self-reported taking doses of ≥ 50 mg *(10)*.

B Pharmacokinetics

No data were available on the absorption, distribution, metabolism or excretion of *N*-ethylheptedrone.

C Pharmacodynamics

The Public Health Agency of Sweden reported an in vitro study with transfected cells expressing human dopamine, serotonin and noradrenaline

transporters (DAT, SERT and NET), which showed that *N*-ethylheptedrone completely inhibited DAT and NET but had slightly less activity on SERT (> 93% maximum inhibition of the receptor). *N*-Ethylheptedrone inhibited DAT and NET at significantly lower concentrations than cocaine in the test system, the concentration causing 50% inhibition of the receptor being 24.8 nM vs 94.5 nM for DAT and 155 nM vs 588 nM for NET. SERT was inhibited at significantly higher concentrations by both substances: 1430 nM and 300 nM for *N*-ethylheptedrone and cocaine, respectively. The inhibition ratio for DAT/SERT was 57.7 for *N*-ethylheptedrone and 3.17 for cocaine. The ratio indicates that *N*-ethylheptedrone is associated with psychostimulant effects and a high abuse potential *(10)*.

N-Ethylheptedrone has also been tested for its effects on the release of preloaded [^{3}H]dopamine, [^{3}H]serotonin and [^{3}H]norepinephrine from HEK cells expressing cDNA for the human dopamine (HEK-hDAT cells), serotonin (HEK-hSERT cells) and norepinephrine (HEK-hNET cells) transporters, respectively. These studies showed that release of [^{3}H]dopamine, [^{3}H]serotonin and [^{3}H]norepinephrine was barely detectable in HEK-hDAT, HEK-hSERT and HEK-hNET cells treated with *N*-ethylheptedrone, supporting its ability to inhibit all three monoamine transporters. Moreover, this substance was much less able to induce the release of all three [^{3}H] neurotransmitters than methamphetamine and methcathinone.

Unpublished data indicate that administration of *N*-ethylheptedrone to mice stimulated locomotor activity in a time- and dose-dependent manner. The maximal stimulant effect of *N*-ethylheptedrone was considered to be similar to the maximal stimulant effect of cocaine and methamphetamine.

5. Toxicology

A single occurrence involving *N*-ethylheptedrone was reported to the UNODC EWA. The substance was detected with diclazepam, etizolam and *N*-ethylhexedrone in the femoral blood of a post-mortem case reported in 2020 in Australia *(11)*. The dose was unknown, and *N*-ethylheptedrone was considered to have made a medium contribution to the death.

No reports were found on the toxic doses of *N*-ethylheptedrone for humans.

6. Adverse reactions in humans

Information provided by the Swedish Poison Information Centre and posted by the Public Health Agency of Sweden in the Network for the Current Drug Situation in Sweden indicated that *N*-ethylheptedrone is sold as a stimulant,

having been reported to have greater psychoactive effects than other cathinones. The same source noted that no deaths are known to have been linked to *N*-ethylheptedrone, although the patients in two hospital cases presented with symptoms such as seizures, tachycardia, hypertension, motor agitation, profuse sweating, nausea and vomiting *(10)*.

Three entries in WEDINOS (W011119, W017185, W018181) indicated self-reports of increased energy. One (W011119) also included self-reports of increased confidence, irregular heartbeat and agitation. One (W019656) noted a self-report of no effect *(9)*.

7. Dependence potential

A Studies in experimental animals

No studies were identified.

B Studies in humans

No studies were identified.

8. Abuse potential

A Studies in experimental animals

In unpublished studies of drug discrimination in rats trained to discriminate methamphetamine or cocaine from saline, *N*-ethylheptedrone fully substituted for methamphetamine or cocaine, demonstrating abuse potential.

B Studies in humans

No studies were identified on the abuse potential of *N*-ethylheptedrone in humans.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

N-Ethylheptedrone is not known to have any medical use.

10. Listing on the WHO Model List of Essential Medicines

N-Ethylheptedrone is not listed on the 23rd WHO List of Essential Medicines or on the 9th WHO List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

N-Ethylheptedrone is not known to be authorized for marketing.

12. Industrial use

N-Ethylheptedrone is not known to have any industrial use.

13. Non-medical use, abuse and dependence

In a recent study, temporal trends were measured in NPS detected and quantified in wastewater collected from up to 57 wastewater treatment plants across Australia between February 2022 and February 2023 (avoiding public holidays and unusual events to determine trends in NPS use across the year) by LC–MS *(12)*. The authors detected *N*-ethylheptedrone in one (5%) of 20 capital city wastewater sites analysed in February 2022.

In May 2021, intensive monitoring of *N*-ethylheptedrone began in the European Union because of an increased number of seizures between 2019 and 2020 and the potential risk to public health posed by this substance *(13)*.

N-Ethylheptedrone has been detected frequently in products mislabelled and/or thought to be sold as other substances (e.g. *N*-ethylpentedrone, methamphetamine, MDMA, cocaine, imitation columbian, clonazolam, alprazolam, diclazepam, Vicodin/Norco, cannabidiol or *O*-desmethyltramadol), suggesting that most people who use *N*-ethylheptedrone may be unaware that they are using it *(9,14)*.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

No information on the nature or magnitude of public health problems associated with the use of *N*-ethylheptedrone was identified, other than that described in section 6 (Adverse reactions in humans).

15. Licit production, consumption and international trade

N-Ethylheptedrone is used as reference material in scientific research and forensic applications.

16. Illicit manufacture and traffic and related information

N-Ethylheptedrone was first identified in seizures in Sweden in May 2019, and a total of 23 incidents were reported up to November 2022 *(10)*. It was identified in Hungary in 2019 and has since been identified in 22 biological samples in that country *(15,16)*.

N-Ethylheptedrone was formally listed with the EMCDDA in February 2019, having been identified in seizures in 15 European countries: Austria, Cyprus, Czechia, Denmark, Finland, France, Germany, Hungary, Latvia, Luxembourg, Netherlands (Kingdom of the), Romania, Slovakia, Spain and Sweden *(17)*.

N-Ethylheptedrone was first identified in New Zealand in 2020 (18). According to the UNODC EWA, *N*-ethylheptedrone was first identified in Australia in 2020 *(11)*.

The DrugsData forum reported 17 entries involving *N*-ethylheptedrone in Austria, China, Switzerland the United States *(14)*.

17. Current international controls and their impact

N-Ethylheptedrone is not currently controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

N-Ethylheptedrone was regulated in Sweden under Act 1999:42 on the Prohibition of Certain Health Hazardous Products on 28 April 2020. The Public Health Agency of Sweden recommended that the substance be included in Ordinance 1992:1554 on the Control of Narcotic Drugs, to prevent any negative consequences *(10)*.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

As *N*-ethylheptedrone has been identified in products labelled as other substances, it is reasonable to expect that the prevalence of *N*-ethylheptedrone and *N*-ethylheptedrone-related intoxications is underreported. Moreover, as individuals are likely to obtain substances from unregulated sources, they may be unaware of the presence, purity and quantity of *N*-ethylheptedrone, posing significant risks of adverse health effects to users.

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3.8 Carisoprodol

1. Substance identification

A INN

Carisoprodol

B CAS registry number

78-44-4

C Other chemical names

Carbamic acid, (1-methylethyl)-, 2-[[(aminocarbonyl)oxy]methyl]-2-methylpentyl ester (9CI), carbamic acid, isopropyl-, 2-(hydroxymethyl)-2-methylpentyl ester carbamate (ester) (8CI). carbamic acid, isopropyl-, 2-(hydroxymethyl)-2-methylpentyl ester, carbamate (6CI), 2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate

Apesan, Arusal, Atonalyt, Calenfa, Caprodat, Carisol, Carisoma, Carisoprodate, Carisoprodatum, Carisoprodol, Domarax, Flexal, Flexartal, Isobamate, Isomeprobamate, Isopropyl meprobamate, Isoprotan, Isoprotane, Isoprothane, Izoprotan, Miolisodal, Mioril, *N*-Isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate, NIH 10966, NSC 172124, Rela (carbamic acid), Relasom, Sanoma, Skutamil, Soma, Somadril, Somalgit, Stialgin

Canonical SMILES

O=C(OCC(C)(COC(=O)NC(C)C)CCC)N

InChI

InChI=1S/C12H24N2O4/c1-5-6-12(4,7-17-10(13)15)8-18-11(16)14-9(2)3/h9H,5-8H2,1-4H3(H2,13,15)(H,14,16)

InChI Key

OFZCIYFFPZCNJE-UHFFFAOYSA-N

D Trade names

Carisoprodol is sold as single-ingredient preparation under names including *(2)*: Artifar, Caridolin, Carisoma, Chinchen, Dolaren, Flexartal, Listaflex, Mio Relax, Mioxom, Muslax, Myolax, Neotica, Rela, Rotalin, Sanoma, Scutamil-C, Soma, Somacid, Somadril and Somalgit.

It is also an ingredient of: Algiseda, Algiseda Plus, Algi-Tanderil, Beserol, Blocacid, Caridoxen, Carisoma Compound, Caritasone, Contraxen

Diclofetamol, Dolaren, Dorsal, Duoflex, Dorilax Empatil Flectomas, Flexalgin, Flexicamin A, Flexicamin B12, Flexidone, Flogiatrin, Flogiatrin B12, Infralax, Lagaflex, Listaflex Forte, Mio-Citalgan, Mioflex A, Mioflex, Mionevrix, Naprontag Flex, Naprux Disten, Naxodol New Skelant Praxona Relaxibys, Rumisedan Fuerte, Sedilax, Sodol, Sodol Compound Solocam Plus, Solocam-Flex Compound, Soma Compound, Somadril Compound Somaflam Somalgesic Tandene, Tanderalgin, Tandriflan, Tandrilax, Tandrotamol, Torsilax, Trilax and Teknadone. It is further known as 2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate *(1)*. The US Pharmacopoeia *(2)* lists carisoprodol pharmacopoeial preparations under the names Carisoprodol and Aspirin Tablets, Carisoprodol Tablets, Carisoprodol, Aspirin and Codeine Phosphate Tablets.

E Street names

The combination of an opioid, benzodiazepine and carisoprodol is commonly known by the street name of "Holy Trinity" *(3)* or "Houston cocktail" *(4)*. Other street names include Ds, Dance, Las Vegas Cocktail (referring to the mixture of Soma and Vicodin) and Soma Coma (indicating the combination of Soma and codeine) *(5)*. A further street name is PCC (paracetamol–caffeine–carisoprodol). Nicknames include "Lousiana trio" and "red apple" (e.g. for tapentadol + carisoprodol).

F Physical appearance

Carisoprodol is a white or almost white, fine powder *(6)* and is found as a white crystalline powder with a mild characteristic odour *(7)*. It has also been described as a crystalline solid with a slightly bitter taste *(8)*.

G WHO review history

Carisoprodol was pre-reviewed in 2001 at the 32nd ECDD meeting. The Committee did not recommend a critical review at that time. Carisoprodol was further presented, discussed and pre-reviewed in 2023 at the 46th ECDD meeting, where a critical review was recommended.

2. Chemistry

A Chemical name

IUPAC Name

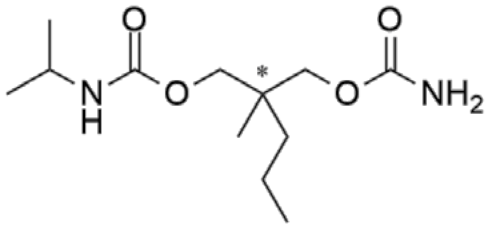
(2*RS*)-2-[(Carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl) carbamate

CA index name

Carbamic acid, *N*-(1-methylethyl)-, 2-[[(aminocarbonyl)oxy]methyl]-2-methylpentyl ester (ACI)

B Chemical structure

Free base

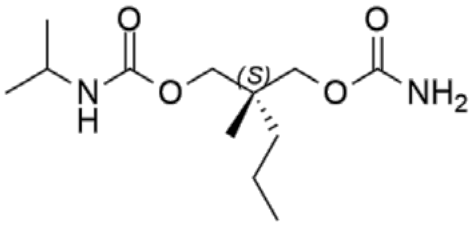


Molecular formula: $C_{12}H_{24}N_2O_4$

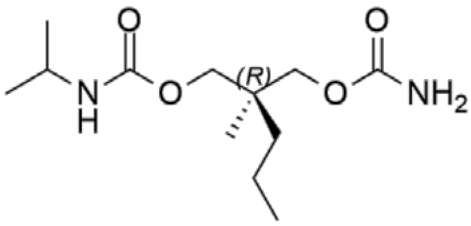
Molecular weight: 260.33 g/mol

C Stereoisomers

Carisoprodol is a racemic mixture of the enantiomers (*R*)-carisoprodol and (*S*)-carisoprodol.



[(2*S*)-2-(carbamoyloxymethyl)-2-methylpentyl] *N*-propan-2-ylcarbamate



[(2*R*)-2-(carbamoyloxymethyl)-2-methylpentyl] *N*-propan-2-ylcarbamate

D Methods and ease of illicit manufacture

Carisoprodol is an analogue of meprobamate in which one hydrogen atom is replaced by an isopropyl group on one of the carbamyl nitrogens. As the substitution makes carbon 2 a chiral centre, carisoprodol can exist as two enantiomers, (*S*)-carisoprodol and (*R*)-carisoprodol.

Carisoprodol is readily synthesized by reacting 2-methyl-2-propylpropanediol, 1, with phosgene , 2. The resulting chloroformate, 3, is reacted with isopropylamine, 4, to form 2-(hydroxymethyl)-2-methylpentyl *N*-(1-methylethyl)carbamate), 5. The last step consists of reaction of 5 with either urethane, 6, sodium cyanate, 7, or trichloroacetyl isocyanate, 8 *(9,10)*.

The synthesis method reported in the literature, albeit simple, requires the equipment of a chemical synthetic laboratory and qualified personnel.

E Chemical properties

Melting-point

160–170 °C (2 Torr) *(11)*

Boiling-point

92 °C (12); 423.412 °C at 760 mm Hg *(13)*

Solubility

In water: very slightly soluble (6); one volume of carisoprodol in 2083 volumes of water according to USP31-NF26 *(1)*.

30 mg/mL at 25 °C, 140 mg/mL at 50 °C *(8)*

Feely soluble in acetone, in ethanol 96% and in methylene chloride *(6)*

One volume of carisoprodol is soluble in 2.5 volumes of alcohol and acetone and 2.3 volumes of chloroform *(7)*.

Carisoprodol is also soluble in dimethyl formamide at 20 mg/mL, in dimethyl sulfoxide at 10 mg/mL, in ethanol at 20 mg/mL, in ethanol:phosphate-buffered saline 1:1 mixture (pH 7.2) at 0.5 mg/mL *(14)*. Carisoprodol has a logP of 2.1 *(15)*.

F Identification and analysis

Carisoprodol as a pure compound was fully characterized by NMR, IR spectroscopy and MS *(16)*.

Identification and analysis of carisoprodol as a pharmaceutical ingredient is reported in the *US Pharmacopoeia (3)* and in the *European Pharmacopoeia (17)*. The latter reports tests for identification and analysis, including

comparison of the IR spectrum with that of a reference standard, TLC for identification of impurities, a chemical colorimetric assay with cobalt nitrate and quantitative determination by titration *(17)*.

Several spectroscopic and chromatographic methods have been published for determination of carisoprodol in pharmaceutical formulations *(18–21)*. As carisoprodol does not have a UV chromophore with significant absorbance, the *US Pharmacopeia* assay for carisoprodol tablets is based on LC coupled to a refractive index detector *(2)*.

Numerous chromatographic methods have been reported for identification and quantification of carisoprodol in whole blood, urine, bile, muscle, liver, hair, vitreous fluid, plasma and serum. As carisoprodol is highly susceptible to thermal decomposition, methods based on GC coupled with either flame ionization detection or MS require derivatization to improve thermal stability and to form more characteristic mass spectral fragment ions, which can be used for compound identification *(22)*. Derivatization is, however, difficult and time-consuming, and alternative, sensitive methods have been developed *(23,24)*.

Currently, methods based on LC coupled with either MS/MS or HRMS are the choice for quantitative determination of carisoprodol in biological fluids *(25–29)*. Qualitative and quantitative determination of carisoprodol and its primary metabolite meprobamate in biological fluids have been achieved by LC–MS *(30,31)*. The commercial availability of the deuterated reference standards of both carisoprodol and meprobamate for use as internal standards has generally facilitated development and validation of LC–MS methods *(32)*.

As carisoprodol is extensively metabolized and has a short half-life, its concentration in biological samples may be below the limit of detection. Depending on the time of sample collection, detection may be possible only of meprobamate *(33)*, which is also a prescription drug and a controlled substance in some countries (e.g. schedule IV of the Controlled Substances Act in the United States) *(34)*. Carisoprodol is metabolized to a lesser extent to hydroxy-carisoprodol *(35)*. Meprobamate and hydroxy-carisoprodol are both metabolized to hydroxy-meprobamate, then partially conjugated *(36)*. To date, no analytical method has been published on the detection of either hydroxy-carisoprodol or hydroxy-meprobamate in humans.

Enzyme-linked immunosorbent assay (ELISA) kits are commercially available for the detection of carisoprodol and its major metabolite, meprobamate, in urine and blood samples. When a positive response is obtained in this assay, the result must be confirmed by LC–MS (36,37).

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

A Routes of administration and dosage

Carisoprodol is typically taken orally, and it is available in tablet form. The usual recommended dosage of carisoprodol for adults is 250–350 mg taken three times a day and at bedtime. Dosages may differ according to individual factors and the instructions of the prescribing health-care professional *(1,17)*.

B Pharmacokinetics

Carisoprodol was authorized in 1959 before full characterization of its pharmacokinetics and pharmacodynamics *(38,39)*. The pharmacokinetics of carisoprodol are summarized below.

Absorption

Carisoprodol is well absorbed after oral administration, with a rapid onset of action (0.5–1 h) and a time to maximum plasma concentration of 1.5 h for a 250-mg tablet and 1.7 h for a 350-mg tablet. Its duration of action is generally 4–6 h. Simon et al. *(40)* quantified the bioavailability of carisoprodol and its conversion to the metabolite meprobamate. They provided single 250-mg and 350-mg carisoprodol tablets to 24 healthy subjects in a randomized, open-label, crossover study. The dose-adjusted area under the dose–concentration curve (AUC)0–∞ values for carisoprodol were 5.29–5.75 µg/mL per h, depending on the dose, and the relative bioavailability was 92%. The mean maximal concentration (C_{max}) values for carisoprodol were 1.24–1.78 µg/mL, depending on the dose, and the apparent terminal phase half-life (t1/2) was 1.74–1.96 h. For the metabolite meprobamate, the corresponding C_{max} values were 1.84 and 2.46 µg/mL. Calvo et al. *(38)* conducted a double-blind, placebo-controlled, randomized clinical trial to define the pharmacokinetics of carisoprodol and its metabolite meprobamate in 13 healthy volunteers in a crossover design. Following a single 350-mg carisoprodol dose, the values for carisoprodol were: C_{max}, 2580 ± 1214 ng/mL, AUC0–∞, 8072 ± 6303 h·ng/mL and $t_{1/2}$, 2 ± 0.8 h. For meprobamate, the parameters were C_{max}: 2181 ± 605 ng/mL and 34 529 ± 7747 h·ng/mL and $t_{1/2}$, 9 ± 1.9 h. After 14 days of treatment (350 mg/8 h), the results were C_{max}, 2504 ± 730 ng/mL, AUC0-∞, 7451 ± 3615 h·ng/mL and $t_{1/2}$, 2 ± 0.7 h. For meprobamate (a steady state was reached), the parameters were C_{max}:5758 ± 1255 ng/mL and 79,699 ± 17 978 h·ng/mL

and $t_{1/2}$, 8.7 ± 1.4 h. Accumulation of meprobamate, but not of carisoprodol, was seen after 14 days of treatment.

Distribution

Carisoprodol shows a moderate distribution capacity, signifying its presence throughout body tissues. It can cross the placenta and is also eliminated in breast milk. A proposed two-compartment pharmacokinetics model describes the metabolism of both carisoprodol and meprobamate. Lewandowski *(41)* analysed four distinct datasets and found a potential range of 0.93–1.3 L/kg for the volume of distribution of carisoprodol and 1.4–1.6 L/kg for meprobamate.

Metabolism

Olsen et al. *(42)* investigated the pharmacokinetics of carisoprodol in 10 healthy volunteers, who received 700 mg orally. Nine participants eliminated carisoprodol rapidly, with an average half-life of 99 ± 46 min, and it was extensively converted into meprobamate, the serum concentrations of meprobamate surpassing those of carisoprodol within 2.5 h of carisoprodol intake. One person, who was found to be a poor metabolizer of mephenytoin (indicative of low cytochrome P450 (CYP)2C19 activity), eliminated carisoprodol with an overall half-life of 376 min, and only small amounts of meprobamate were found. Protein binding of carisoprodol was 41–67%, whereas meprobamate was bound to a lesser extent, 14–24%.

Carisoprodol undergoes extensive metabolism in the liver, primarily by the liver enzyme CYP2C19, to form its main metabolite, meprobamate. According to Dean et al. *(43)*, standard doses of carisoprodol in individuals who have little or no CYP2C19 activity can lead to four times greater exposure to carisoprodol and a concomitant 50% reduction in exposure to meprobamate. Approximately 3–5% of Whites and of Africans and 15–20% of Asians are CYP2C19 poor metabolizers. To better understand the issue, Bramness et al. *(44)* enrolled 37 healthy White volunteers, of whom 2 were poor metabolizers, 11 intermediate metabolizers and 12 extensive metabolizers; the remaining 12 participants were 6 extensive metabolizers and 6 intermediate metabolizers who used oral contraceptives. A single oral dose of 700 mg of carisoprodol was given. Intermediate metabolizers had a longer elimination half-life (127 min) than extensive metabolizers (96 min) and a larger AUC for carisoprodol (16.3 µg.h/mL) than extensive metabolizers (11.3 µg.h/mL). Overall, the authors concluded that, after a single dose of carisoprodol, the AUC was approximately 45% larger in CYP2C19 intermediate metabolizers than in extensive metabolizers. Use of oral contraceptives increased the AUC by approximately 60% in

both extensive and intermediate metabolizers. Other common CYP2C19 inhibitors include omeprazole, ticlopidine, fluoxetine, fluvoxamine, topiramate, sertraline and tricyclic antidepressants. Co-administration of CYP2C19 inducers (e.g. rifampicin, carbamazepine, phenobarbital, aspirin and St John's wort) decreased the levels of carisoprodol and increased those of meprobamate.

Elimination

The half-life for elimination of carisoprodol is 1.7–2 h, and that of meprobamate is approximately 10 h. The kidneys are the primary route of excretion of both carisoprodol and its metabolites. Therefore, individuals with impaired kidney function might experience prolonged elimination of carisoprodol. Carisoprodol can be removed by haemodialysis and peritoneal dialysis.

C Pharmacodynamics

The muscle relaxant properties of carisoprodol are probably associated with its sedative effect. In experimental animals, the muscle relaxant properties are associated with altered interneuronal activity in the spinal cord and the descending reticular formation of the brain. Meprobamate is thought to contribute to the therapeutic effects of carisoprodol. Its subjective effects are similar to those of other central nervous system depressants, such as meprobamate, pentobarbital and chlordiazepoxide. They act primarily by enhancing the inhibitory effects of GABA *(45,46)*.

To assess these issues, Kumar et al. *(47)* used whole-cell patch clamp recordings to reveal the capacity of carisoprodol to directly control and enhance GABA-gated currents. The β1 subunit was more efficient than maximal GABA currents in direct activation, whereas the β2 subunit was most effective in augmenting the GABA response through allosteric modulation. Kumar & Dillon *(48)*, in a sequence of investigations with recombinant GABA-A receptors, showed amplification of GABA-induced current in all α subunit variations, the most significant impact being found in receptors expressing α5. Direct modulation was evident in receptors containing all α subunits, although it was diminished in receptors expressing α3.

More recently, Kumar et al. *(49)* investigated the influence of amino acids in transmembrane domain 4 of the GABA-A receptor α subunit on the effects of carisoprodol on direct gating and allosteric modulation. By analysing various mutations at the 415 position, they established a positive correlation between amino acid volume and the efficacy of carisoprodol in direct gating;

no such correlation was observed with its allosteric modulatory actions. This indicates that separate binding sites are responsible for the distinct effects of carisoprodol in direct gating and allosteric modulation.

In a preclinical investigation, Carbonaro et al. *(50)* investigated whether the behavioural effects of carisoprodol are direct or whether conversion to meprobamate is required. Rats were conditioned to discriminate the effects of carisoprodol (100 mg/kg). The pharmacokinetics of carisoprodol and meprobamate were evaluated in vivo by microdialysis, with LC–MS–MS of samples of blood and from the nucleus accumbens. The timeline of the discriminative-stimulus effects of carisoprodol was closely aligned to its levels in blood and the nucleus accumbens, while those of meprobamate were not, indicating that carisoprodol elicits behavioural effects directly, independently of meprobamate metabolism. Calvo et al. *(39)* conducted a double-blind, placebo-controlled, randomized clinical trial involving 13 healthy participants to assess the pharmacokinetics and pharmacodynamics of carisoprodol after single (350 mg), double (700 mg) and multiple doses (≤ 350 mg/8 h, 14 days). Muscular (electromyogram, muscular strength dynamometry) and central (sedation) effects, tolerability (psychomotor activity test, adverse events) and withdrawal symptoms were measured. No explicit indications of direct muscle relaxation were observed; however, there was evidence that some of the effects of carisoprodol may be due to sedation. Notably, the impact on psychomotor impairment peaked at 1.5 h, suggesting that it originated from carisoprodol rather than meprobamate.

5. Toxicology

Acute toxicity

The oral LD_{50} of carisoprodol was 1800 mg/kg in mice and 1320 mg/kg in rats *(51)*.

Subchronic toxicity

In rats given carisoprodol at < 100 mg/kg per day, the clinical signs observed were lethargy, diarrhoea, rough hair coat, prostration, urine staining in the vaginal area, ataxia and body weight changes *(52)*.

Human toxicity

Usually, ingestion of one to three carisoprodol tablets of 350 mg produces a general feeling of well-being, 4–10 tablets are associated with hypomania, and > 10 tablets may cause confusion, disorientation and partial amnesia *(53)*. A 4-year-old child died after ingesting 3.5 g of carisoprodol *(54)*. According to TOXBASE® *(55)*, ingestion of 21–35 g by adults has resulted in respiratory failure

and coma, and ingestion of 8–10 g caused drowsiness, dizziness and impaired coordination in some patients, although ingestion of 9 g by one person resulted in coma. Agitation, hypertonia and myoclonic encephalopathy may be seen at high doses. A 34-year-old male with a history of carisoprodol abuse developed severe central nervous system and respiratory depression after acute ingestion of 7.5 g. He required high doses of sedatives to control agitation considered to be due to withdrawal from carisoprodol *(56)*.

According to Bramness et al. *(57)*, the symptoms and signs of carisoprodol intoxication do not fully resemble those caused by its metabolite meprobamate, a GABAergic agonist. The clinical toxicity signs and symptoms of carisoprodol intoxication are not, however, readily explained only by interaction with GABA, and a serotonin syndrome was reported in four people after ingestion of carisoprodol *(57)*. As carisoprodol is metabolized substantially to meprobamate *(44)*, the concentration of meprobamate is likely to be raised after an overdose, with clinical consequences including slurred speech, ataxia, headache, weakness, hyperreflexia, clonus, convulsions, respiratory depression, hypotension, tachycardia and other dysrhythmia, hypothermia, agranulocytosis, pancreatitis, acute kidney injury, rhabdomyolysis and blisters (erythematous or haemorrhagic) *(54)*. Nevertheless, meprobamate, like benzodiazepines, acts on the GABA-A receptor *(43)*. Consequently, as the overdose progresses and meprobamate accumulates, flumazenil might counteract the effects. A case study reported reversal of central nervous system depression after intravenous administration of flumazenil *(58)*. Chegondi et al. *(59)* reported the case of an adolescent girl who had overdosed with carisoprodol. She was unresponsive and had respiratory depression but recovered immediately after intravenous emulsion therapy.

Teratogenicity

It is not known whether carisoprodol increases the risks for miscarriage or birth defects. Briggs et al. *(60)* reported only mild sedation in a near-term infant exposed to carisoprodol throughout gestation and during breast-feeding in the first month after birth. Both carisoprodol and its metabolite meprobamate are excreted into breastmilk *(61)*.

Intake of other drugs with carisoprodol

Xu et al. *(62)* developed a preclinical in-vivo model for detecting worsening respiratory depression when various psychotropics were used in combination with oxycodone as compared with use of each opioid alone. The model is based on increased arterial partial pressure of carbon dioxide. No changes were observed after co-administration of carisoprodol with oxycodone, although

carisoprodol was given only at the estimated human equivalent dose of a 250-mg tablet (a small therapeutic dose). For further information on use of other drugs with carisoprodol, see sections 13 and 14.

6. Adverse reactions in humans

At therapeutic doses, common adverse effects include drowsiness (13–17%), dizziness (7–8%), ataxia, tremor, agitation, irritability, depressive reactions, syncope, insomnia and headache (all at 3–5%) *(54)*. Cardiovascular (including tachycardia, postural hypotension and facial flushing), gastrointestinal (including nausea, vomiting, hiccup and epigastric distress) and haematological effects may occur. In post-marketing and case reports, carisoprodol has been associated with idiosyncratic reactions, including severe weakness, transient quadriplegia, euphoria, dilated pupils, disorientation and temporary vision loss *(54)*. A rare reported adverse effect is seizures.

Many drugs interact with carisoprodol, including virtually all opioids, other centrally acting analgesics and alcohol *(63)*. People affected by porphyria and renal disease may be particularly vulnerable to the effects of carisoprodol *(63)*.

7. Dependence potential

A Studies in experimental animals

Swiss-Webster mice received carisoprodol intraperitoneally at 0, 100, 200, 300 or 500 mg/kg over 4 days, and loss of righting reflex was measured 20–30 min after each dose. The initial dose caused dose-dependent impairment of the righting reflex. During the 4-day exposure, the extent of impairment decreased by 75–100%, indicating development of tolerance. Withdrawal symptoms were elicited by both bemegride and flumazenil *(64)*.

B Studies in humans

The active metabolite of carisoprodol, meprobamate, was a frequently misused drug in the 1950s and 1960s, with reported overdoses *(65,66)*.

Long-term or excessive use of carisoprodol can lead to dependence, and abrupt discontinuation or a significant reduction in dose after prolonged use can result in barbiturate- and alcohol-type withdrawal symptoms *(67–70)* such as anxiety, insomnia, tremors, muscle twitching and, in severe cases *(56)*, hallucinations and seizures. The withdrawal syndrome can be treated with benzodiazepines *(70)*, a combination of carisoprodol and phenobarbital *(56)* or oral baclofen *(71)*. As with benzodiazepines, potential craving may persist.

VigiBase, the WHO global database of reported adverse events of medicinal products, is the largest database of its kind in the world. Individual case safety reports have been submitted since 1968 *(72)*. The WHO Programme for International Drug Monitoring is a global network to ensure the safety of medicines and vaccines, with 177 members. VigiLyze, a signal detection and signal management tool that contains VigiBase data, provides additional information on dependence in humans *(72)*. A data search was conducted on 14 August 2024 of all 6015 individual case safety reports associated with carisoprodol as the suspected drug submitted to VigiBase in 1968–2024 *(72)*. When reports were classified by an international, clinically validated terminology, the search retrieved a total of 1678 entries mentioning drug abuse (643 cases, 10.7%), drug dependence (611 cases, 10.1%), drug withdrawal (201 cases, 3.3%) or intentional product misuse (223 cases, 3.7%). The peak of reporting was in 2021 (405 cases). Most patients (about 74%) were aged 18–64 years, and 57% were female; 96% of the reports were from the United States, followed by Spain (0.7%), Sweden and Norway (both at 0.5%). These data should be interpreted with caution in view of the known limitations of spontaneous adverse event reporting systems, such as underreporting, notoriety bias and missing information.

8. Abuse potential

A Studies in experimental animals

Gonzalez et al. *(46)* used both electrophysiological and behavioural methods to demonstrate that carisoprodol elicited picrotoxin-sensitive inward currents surpassing those generated by meprobamate, suggesting that carisoprodol can directly induce GABAergic effects in vivo.

In further drug discrimination studies involving rats trained with carisoprodol, Gonzalez et al. *(46)* found that the GABAergic ligands pentobarbital, chlordiazepoxide and meprobamate substituted for carisoprodol in a dose-dependent manner. The discriminative stimulus effects of carisoprodol were effectively countered by bemegride, a barbiturate antagonist, but not by flumazenil, a benzodiazepine antagonist. They concluded that the barbiturate-like effects of carisoprodol are not due solely to meprobamate. Gatch et al. *(73)* conditioned Sprague-Dawley rats to differentiate propofol (10 mg/kg intraperitoneally) from vehicle and assessed carisoprodol (100 mg/kg), chlordiazepoxide and dizocilpine. Carisoprodol produced 59% and chlordiazepoxide produced 65% propofol-appropriate responses, while propofol produced 52% carisoprodol-appropriate responses. According to Gatch et al. *(73)* propofol discriminative-stimulus

effects were similar to those of GABA-A receptor agonists. These preclinical findings may shed further light on the liability levels of carisoprodol abuse. (See also last paragraph of this section.)

B Studies in humans

Owens et al. (74) identified individuals with prolonged use of carisoprodol (n = 340) and other skeletal muscle relaxants (n = 453) in a dataset of 130 000 individuals in the Idaho Medicaid pharmacy and medical claims database in the United States in 2005. People who were prescribed carisoprodol had a higher incidence of concurrent opioid use (81.5% vs 59.8%; $P < 0.01$) and were more likely to have had previous diagnoses suggesting other substance abuse (34.1% vs 21.4%; $P < 0.01$); 80% continued to self-finance carisoprodol when third-party coverage was terminated. The researcher considered that the data support potential abuse of carisoprodol.

Zacny et al. *(75)* conducted a study of the subjective and psychomotor effects of carisoprodol in 15 healthy participants who received the drug at a dose of at 0, 350 or 700 mg. The higher dose led to increased scores on the visual analogue scale for descriptors associated with sedation rather than potential abuse. Nebinhani et al. *(53)* investigated a group of 34 individuals, most of whom described an overall sense of wellness after consuming up to three tablets. After 4–10 tablets, a hypomanic state was reported, with feelings of confusion. When more than 10 tablets were taken at once, they experienced sensations of disorientation and drowsiness. Overall, subjects who use carisoprodol nonmedically may report impairment of physical or mental capability, dizziness and nausea/vomiting *(76)*.

The available preclinical and clinical evidence indicates that carisoprodol has clear GABA-A agonist pharmacodynamics, which may be more similar to those of barbiturates and/or propofol *(73)* than benzodiazepine. Bemegride (an analeptic) has shown better antagonist activities than flumazenil *(46)*. In terms of the relative contribution of meprobamate, the main metabolite of carisoprodol, no data on the relative potency or efficacy of the two were available. The psychotropic effects of carisoprodol peak at 1.5 h *(39)*, probably before its full metabolic conversion to meprobamate, and the serum concentrations of meprobamate are higher than those of carisoprodol within 2.5 h of carisoprodol intake *(42)*. It is also possible, however, that, at least at high or very high doses of carisoprodol, pharmacodynamics different from GABA-A agonism may play a role, and evidence of a serotonergic syndrome has been reported after overdose ingestion of carisoprodol in four subjects *(57)*. Overall, one could agree with Gatch et al. *(64)*, who suggested that the potential for addiction to carisoprodol is similar to that of other long-acting benzodiazepine and barbiturate compounds.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Indications for which the substance is approved for therapeutic use

Carisoprodol is a centrally acting muscle relaxant used in the short term as an adjunct in symptomatic treatment of acute musculoskeletal disorders associated with painful muscle spasm. Carisoprodol is prescribed to relieve symptoms of muscle pain in people ≥ 16 years of age at a dosage of 250–350 mg orally three times a day and at bedtime, for a maximum duration of 2–3 weeks (55). Its main clinical and therapeutic use is therefore to relieve muscle spasms and restricted movement due to strains, sprains and injuries. Carisoprodol is intended to be used with rest, physical therapy and other measures to relax muscles. Muscle relaxants such as carisoprodol have also been used in the management of diverse clinical conditions marked by heightened skeletal muscle activity, including in multiple sclerosis *(77)*.

There is evidence of widespread nonmedical use of carisoprodol and an increased risk of opioid overdose when it is combined with opioids, whereas other skeletal muscle relaxant drugs such as tizanidine are thought to have similar efficacy without a similar risk profile *(78)*. It is recommended that carisoprodol be avoided in the elderly population due to risks for sedation and falls *(79)*.

Extent of use for related therapeutic purposes

In 2007, Bramness et al. *(80)* analysed the Norwegian Prescription Database of information on prescription drugs dispensed to the Norwegian population. They found that 53 889 Norwegian women (2.4%) and 29 824 men (1.3%) aged ≥ 18 years had received carisoprodol at least once in 2004. Prescribing of carisoprodol was, however, skewed, some 32% of the patients having received more than 15 defined daily doses of carisoprodol and > 11 000 patients (15%) received ≥ 75 defined daily doses in 2004. In England, the prescription cost analysis system for 2000–2005 *(81)* showed that prescriptions for carisoprodol increased over time, from 4100 prescriptions in 2000 to 5000 in 2005. In the United States, approximately 4.2 million carisoprodol prescriptions were dispensed in 2017 *(82)*, with a decrease to 3.2 million in 2018. When ranked according to the frequency with which a given medication is prescribed in a calendar year, carisoprodol prescriptions in the United States gradually increased over time, from 175 in 2013 to 343 in 2019 *(83)*. Despite restrictions, carisoprodol is still widely prescribed, with over 3 million prescriptions (a decrease from 10 million in 2008) written in the United States in 2016 *(84)*.

Li et al. *(85)* evaluated the prevalence and duration of treatment with skeletal muscle relaxants in commercially insured adults in the United States from the MarketScan Research Database for 2005–2018, covering approximately 49 million individuals. The prevalence of skeletal muscle relaxant treatment varied from 61.5 to 68.3 per 1000 individuals. About one third of users did not have a diagnosis of musculoskeletal disorder. When compared with other skeletal muscle relaxants, such as cyclobenzaprine, baclofen, tizanidine and methocarbamol, use of carisoprodol decreased over time. Individuals prescribed carisoprodol tended to have longer treatment than those treated with other skeletal muscle relaxants. Data from IQVIA™ reported by the US Drug Enforcement Administration in 2019 indicated that about 4.2 million carisoprodol prescriptions were dispensed in the United States in 2017, decreasing to approximately 3.2 million in 2018 *(86)*.

10. Listing on the WHO Model List of Essential Medicines

Carisoprodol is not listed on the 23rd WHO Model List of Essential Medicines or the WHO Essential Medicines List for Children *(87)*.

11. Marketing authorizations (as a medicinal product)

Carisoprodol is a prescription medication. It was introduced onto the market in 1959. At present, carisoprodol (either on its own or in combination) appears to be a licensed drug in several countries and areas, including Argentina (dispensing possible, but the drug is dispensed under the condition of an archived prescription and is subject to intensive pharmacovigilance; *(88)*, Brazil, Ecuador, Egypt, Guatemala, Indonesia, Mexico, Nicaragua, Paraguay, Uruguay, the United States *(89)*, Hong Kong (SAR China) and Taiwan, China. In Texas, United States, although carisoprodol is a prescription drug, pharmacists must access the Texas Prescription Monitoring Program for the patient's information before dispensing *(90)*. In New Zealand, carisoprodol is under part 1 of the relevant schedule (item 305) *(91)*. In Canada *(92)*, carisoprodol is a prescription drug (Schedule I) at federal level, although provincial regulations may differ; its overall use is restricted *(93)*.

12. Industrial use

No industrial use was identified.

13. Non-medical use, abuse and dependence

According to Gupta *(6)*, carisoprodol is usually ingested orally; however, snorting of the substance induces euphoria more rapidly.

Carisoprodol may be diverted from legitimate medical channels and enter the illicit market *(65)* to be sold without proper medical supervision, increasing potential abuse and adverse consequences. To mitigate potential misuse, it is recommended that health-care providers evaluate patients before prescribing carisoprodol, including their history of substance abuse, addiction or psychological disorders *(94)*. Monitoring of patients given carisoprodol is also recommended, to identify signs of misuse or escalating doses *(95)*.

Siddiqui et al. *(96)* assessed drug arrests reported to the Diversion Alert Program in Maine, United States. Of the 9216 arrests for drugs, 64% involved a single drug. Carisoprodol, amitriptyline and quetiapine were those most likely to be found in intoxications due to misuse.

Alblooshi et al. *(97)* studied 250 patients in the National Rehabilitation Centre of Abu Dhabi, United Arab Emirates. While opioid and alcohol were the most common substances used, carisoprodol (4.2 ± 0.4 tablets per day) was one of the most popular drugs reported in combinations, especially among people aged < 30 years. Hardon & Ihsan *(98)* assessed use of psychoactive prescription drugs by sex workers in Makassar, Indonesia, and particularly carisoprodol, which is available over the counter. Sex workers reportedly used most of their earnings to purchase carisoprodol, which was alleged to make them feel more confident and to make their work more acceptable to themselves. Hardon et al. *(99)* conducted a study in South Sulawesi, Indonesia, with mixed methods including interviews with 142 young people, focus group discussions and participant observation to understand how young people in the region engage with pharmaceuticals and cosmetics for sexual health. Some participants expressed interest in a blend of carisoprodol, paracetamol and caffeine, which they used to stimulate their libido and enhance their sexual confidence.

Alaryan et al. *(100)* conducted a cross-sectional study of misuse of drugs in community pharmacies in Damascus, Syrian Arab Republic, and in the surrounding countryside. Data were collected from 143 community pharmacists between December 2016 and March 2017 on a structured questionnaire. Carisoprodol and tramadol were the drugs most frequently requested for misuse.

Carisoprodol is aften misused in combination with opioids *(53)*. Elarabi et al. *(101)* analysed data from a 16-week randomized controlled trial of 141 adult outpatients with opioid use disorder in the United Arab Emirates and found that carisoprodol was used nonmedically by 30 of the 141 participants. In this study, self-reported independent use of carisoprodol predicted an increased odds for nonfatal overdose (adjusted odds ratio, 4.52; 95% CI: 1.81; 11.22). Li et al. *(102)*

compared the risk of overdose associated with concomitant use of opioids and muscle relaxants with that of opioid use alone. The risk appeared to increase for misuse of carisoprodol in combination (1.84; 95% CI: 1.34; 2.54). In a pharmaco-epidemiological investigation, Wang et al. *(103)* compared the characteristics of about 17 000 patients prescribed a combination of benzodiazepines, opioids and carisoprodol with those of a group that received opioids and benzodiazepines. The recipients were predominantly young and female, who often sought care from several providers (commonly referred to as "doctor shopping") and were given higher average daily doses of opioids. Concurrent use of hydrocodone, alprazolam and carisoprodol ("Houston cocktail" or "Holy Trinity"; *(103)*) may give users heroin-like euphoria, and combined use of these agents may be associated with a synergistic increase in dopamine in the nucleus accumbens *(3,4)*. According to some social media-based, "netnographic" *(104)* observations, carisoprodol intake is particularly popular in combination with pregabalin, GABAergics and tapentadol (nickname: "red apple"). Carisoprodol is reportedly ingested with heroin by people who have developed a tolerance to the related benzodiazepine and pregabalin. In July 2023, in a "Google trend" research, the term "carisoprodol" was searched in Latin America (Guyana, Honduras, Mexico, Nicaragua, Paraguay and the Plurinational State of Bolivia). Most searches with the brand name Soma®, which is popular in the United States, originated from India and the United States, although searches by brand names comprised only a small fraction of those for carisoprodol. No peaks in searches were identified during the past 5 years, but the number peaked in 2006. According to Google Trends in 2024, international interest in carisoprodol remained roughly the same during 2023–2024.

Reddit (a popular social media platform) included discussions on both the effects of carisoprodol at doses > 500 mg and possible alternatives to carisoprodol *(105)*. Most of the threads appeared to be older than 2 years. Some carisoprodol purchase options were also identified. Carisoprodol still appeared to be actively searched and available for online purchase from both open and deep-web sites. According to a current social media analysis, carisoprodol is typically ingested either on its own or in combination, especially with remaining GABAergics, gabapentinoids and opiates/opioids, and particulalry tapentadol.

Qualitative analysis

To enrich current knowledge of carisoprodol, three "psychonaut" websites were qualitatively analysed (106,107): Drugs-Forum (108 threads identified in 2011–2022 and 6 in 2022); Erowid (107 threads identified, most of which were quite old); and Bluelight (which contained the most recent entries, with 180 posts). The issues discussed included the following.

Carisoprodol as a recreational drug: Carisoprodol enthusiasts noted that, from the recreational point of view, the drug may be closest to both "old barbiturates" and methaqualone and may be "pretty popular" with people who are "drug nerds".

Carisoprodol potentiation techniques: According to some entries, the effects of carisoprodol can be potentiated by aspirin, while others recommended concurrent use of the *N*-methyl-D-aspartate antagonists, ketamine-like dextromethorphan of methoxetamine. Other possible combinations described as "the ultimate sedation" included concurrent use of tramadol, carisoprodol, pregabalin and methocarbamol.

Carisoprodol and opiates or opioids: According to some entries, carisoprodol is "the only thing that categorically potentiates" the opiate high. All opiates and opioids were described as appropriate, although tramadol was noted specifically.

"Coming off" carisoprodol: Possible anecdotal suggestions for self-detoxification included tapering off use and taking further GABAergics, such as benzodiazepines and phenibut.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

The National Drug Intelligence Center in the United States *(108)* cited the findings of the National Survey on Drug Use and Health, which suggest that about 2 276 000 US residents aged ≥ 12 years had used carisoprodol or Soma® nonmedically at least once in their lifetime. The prevalence increased over time; according to the 2012 National Survey on Drug Use and Health, 3.69 million people aged ≥ 12 years reported non-medical use of Soma® at some time in their life, representing a notable rise from 3.06 million in 2011 *(109,110)*.

According to the Laboratory Information System, a database managed by the Drug Enforcement Administration in the United States, federal, state and local forensic laboratories identified 3847 drug items (i.e. exhibits that have been analysed) identified as carisoprodol in 2013 and 1735 in 2017, with a preliminary count of 1305 in 2018 *(82)*.

Between 1996 and 2005, the number of emergency department visits due to carisoprodol in the United States increased from 6569 to 19 513, the drug being listed at that time as one of the 25 most dangerous in the country *(71)*. Gupta *(6)* reported that the number of emergency room visits linked to inappropriate use or abuse of carisoprodol increased from 15 830 visits in 2004 to 31 763

visits in 2009. The number of patients aged ≥ 50 years tripled (from 2070 to 7115), and the number of patients aged 35–49 doubled (from 6345 to 12 048). Although carisoprodol misuse by adolescents has been documented since 2007 *(6)*, the number of younger patients remained largely unchanged, and 77% of visits involved other medications, primarily narcotic pain relievers (55%) and benzodiazepines (47%). Hospitalization related to carisoprodol was required for 35% of emergency room visits between 2004 and 2009 *(109)*.

According to Masoner et al. *(111)*, who tested a range of pharmaceuticals and contaminants of emerging concern in the final leachates from 22 landfills in 12 US states, the most frequently detected contaminants were lidocaine, the nicotine derivative cotinine and carisoprodol. In 2017, the American Association of Poison Control Centers reported a total of 2236 cases related to carisoprodol, including 901 single exposures and two deaths *(82)*.

The mortality risk associated with carisoprodol may increase when it is taken in combination with other drugs *(112)*. Lee et al. *(113)* investigated fatalities involving drugs reported to the Florida Medical Examiners Commission in the United States between 2001 and 2013. Benzodiazepines, carisoprodol, opioids and zolpidem were more often associated with unintentional fatalities and/or suicide than other drugs. Khan et al. *(114)* conducted a cohort study of use of health care between 2000 and 2019 to quantify the risk of opioid overdose associated with seven prescription skeletal muscle relaxants. The weighted hazard ratio for opioid overdose with carisoprodol was 1.64 (95% CI, 0.81; 3.34), lower than for baclofen. More recently, Chen et al. *(115)* conducted nine retrospective cohort studies, each cohort including person-time exposure to both a skeletal muscle relaxant and hydrocodone, oxycodone or tramadol. In the oxycodone cohort, the adjusted hazard ratio for the occurrence of an injury event was 1.86 (95% CI, 1.23; 2.82). Hutchison et al. *(116)* recently confirmed the frequent occurrence of opioid + benzodiazepine + carisoprodol prescriptions, particularly in rural Texas (United States).

To assess the associations between opioids prescribed for 30 days and the risk for a fatal overdose during the subsequent 15 days, Henry et al. *(117)* designed a statewide cohort study of data for all 5.3 million patients prescribed an opioid analgesic in California (United States) in 2013. Patients prescribed benzodiazepines had a significantly greater risk for overdose, but a prescription of Z-drugs or carisoprodol was not associated with a risk for overdose.

According to the VigiLyze report for 1968–2024 (72; see section 7B above for further details), with assessments of 6015 reports involving carisoprodol,

93% of entries were classified as serious, which was defined as meeting the following criteria: death, life-threatening, caused or prolonged hospitalization, disabling or incapacitating and other medically important condition. The opioids most frequently reported in combination with carisoprodol were hydrocodone (27.1%) and oxycodone (25.1%), while alprazolam (21.4%) was the benzodiazepine most frequently identified in combinations. The most frequently reported terms were: completed suicide (1545 cases; 25.7%), toxicity reactions to various agents (1001 cases; 16.6%) and overdose (740 cases; 12.3%).

Illicit distribution

Carisoprodol can be diverted. In March 2011, the street price for Soma® tablets was US$ 1–5 per tablet.

Paulozzi et al. *(118)* analysed data extracted from the Prescription Behavior Surveillance System, a public health monitoring mechanism for assessment and quantification of appropriate and inappropriate use of prescribed controlled substances in eight states in the United States. Substantial differences were found between states in the rates of prescription, with a twofold difference for opioids and an eightfold difference for carisoprodol. While the factors that contributed to such variation were unknown, the authors recommended that states use their prescription drug monitoring programmes for quantification at population level to measure the efficacy of policies to curtail misuse of prescription drugs.

Driving

Lee et al. *(4)* investigated 80 cases involving drivers who had tested positive for hydrocodone, alprazolam or carisoprodol between 2015 and 2019. Only these three substances were found in 28% of the cases, while 28% had two of the three substances. The cases were found to have impaired driving, such as lane deviation, decreased vigilance, compromised judgement, altered speed and/or impaired braking.

In the United States, Lu et al. *(37)* analysed the results of 1672 tests of driving under the influence of drugs to determine the frequency of the involvement of carisoprodol or meprobamate. These substances were found in 99 samples (5.9%).

Rudisill et al. *(119)* conducted a literature review to identify medications that were associated with an elevated risk of motor vehicle collisions. Of the 53 medications assessed, 15 (28.3%) were associated with an increased risk, including carisoprodol. Bramness et al. (120) in Norway used data from three population-based registries covering the period April 2004–September 2005 to determine the risk of an accident associated with personal injury within the

first week of dispensing of a drug. People who had received a prescription for carisoprodol had a standardized incidence ratio of 3.7 (95% CI: 2.9 ; 4.8), which was comparable to the risk associated with diazepam (2.8; 95% CI: 2.2 ; 3.6).

15. Licit production, consumption and international trade

Carisoprodol is available as a medication in many countries (see section 11) but is no longer used medically in Europe since the European Medicines Agency Committee for Medicinal Products for Human Use suspended all marketing authorizations for carisoprodol throughout the continent *(128)*.

16. Illicit manufacture and traffic and related information

Law enforcement officers reported that young people living in Arizona and California, United States, often obtained carisoprodol at pharmacies in Mexico (108). In February 2020, the National Narcotics Agency in Indonesia seized a reported four million pills of carisoprodol during a raid on four houses running an illicit drug manufacturing operation in West Java *(121)*. According to (unpublished) data from the International Narcotics Control Board, the number of incidents involving carisoprodol has increased worldwide, from 45 incidents before March 2021 from only three countries to 2416 between January 2022 and March 2023 from 23 countries.

A preliminary informal search carried out in July 2023 indicated that carisoprodol can be purchased online without a prescription on various websites, including OutlookIndia *(122)* and Westshore Women's Health *(123)*.

17. Current international controls and their impact

Carisoprodol is not currently under international control.

18. Current and past national controls

Høiseth et al. *(112)* reported that rescheduling and withdrawal of carisoprodol from the Norwegian market reduced the presence of carisoprodol in cases of impaired driving, deaths and intoxications. They also reported that sales decreased from 2 defined daily doses/1000 inhabitants per day in 2007 to 0.5 in May 2008 and then further to 0.09 after withdrawal from the market.

Bramness et al. *(124)* conducted a prospective, longitudinal, register-based study covering a population of 4.9 million inhabitants of Norway between 1 November 2006 and 31 January 2009, before and after withdrawal of carisoprodol from the market in 2008. Participants who had been using opioids and/or benzodiazepines

at the same time as carisoprodol increased their consumption of these substances after withdrawal of carisoprodol. The authors noted that people who were previously prescribed carisoprodol subsequently initiated use of opioids (11%), benzodiazepines (6.5%) and nonsteroidal anti-inflammatory drugs (12.9%).

In response to steps taken by US health-care systems to address the epidemic of opioid overdoses, Losby et al. *(125)* conducted a retrospective pre- and post-evaluation study of outcomes before and after a comprehensive initiative to transform the way in which chronic pain is viewed and treated. The study population comprised 3 203 880 adults, who were observed between 2010 and 2015. All the observed outcomes were reduced, including a 90% decrease in use of the combination of a prescribed opioid with benzodiazepines and carisoprodol.

Also in the United States, Sun et al. *(126)* compared the volume of calls to a state poison control system related to carisoprodol misuse before (2008–2011) and after (2012–2015) the change in scheduling of carisoprodol. The number of calls decreased significantly, leading the authors to conclude that government regulation can reduce potential drug abuse.

Li et al. *(34)* observed a reduction of 20% in carisoprodol dispensing after its scheduling in the United States. The decrease was particularly large among younger people and among patients with injuries. Caulkins et al. *(127)* reported that, while certain states had implemented measures to limit the availability of carisoprodol before its federal scheduling, the impact of those measures did not appear to have influenced the outcomes significantly.

In 2007, the European Medicines Agency Committee for Medicinal Products for Human Use suspended all marketing authorizations for carisoprodol throughout Europe *(128)*. Carisoprodol has been classified under Schedule IV of the US Controlled Substances Act since January 2012. Carisoprodol was taken off the market in Indonesia in September 2013 due to its diversion, dependence and side-effects. Carisoprodol is not on the United Kingdom Home Office list of the most commonly found drugs currently controlled under the legislation on misuse of drugs; however, it was reported in 2014 that marketing authorization for carisoprodol was to be suspended *(70)*. Norwegian medical regulatory authorities conducted a review of carisoprodol in March 2007 and took it off the market in May 2008 *(112)*. Carisoprodol-containing products are not available in Chile *(129)* or Peru *(130)*. Carisoprodol is no longer a licensed product in Australia *(131)*.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

No other matters were identified.

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Annex 1. Report on the WHO Member State questionnaire for review of psychoactive substances

Background

As per the Guidance on the WHO review of psychoactive substances for international control (EB126/2010/REC1, Annex 6), Member States are invited to contribute to ECDD reviews by providing up-to-date, accurate information on the substances under review before each meeting.

The ECDD Member State questionnaire is administered annually to complement the critical review and pre-review reports. Focal points nominated by Member States are invited by email to participate, with the option of completing separate surveys for each substance under review or pre-review. The Member State questionnaire provides insights on the geographical nature of a drug problem (e.g. highly localized or affecting many regions), the extent and nature of public health harm and the extent of therapeutic use (if any). The responses complement the data presented in critical and pre-reviews, which are often limited to published literature, may not contain data from many member states and are older because of publication and reporting delays. The data provided by Member States have not been verified by WHO and are published as received by WHO.

The questionnaire for the 47th ECDD meeting was made available to Member States from 29 July to 23 August 2024. Ninety-eight of the 194 Member States responded to the invitation to participate (17 in the African Region, 17 in the Americas Region, 5 in the South-East Asian Region, 37 in the European Region, 9 in the Eastern Mediterranean Region and 13 in the Western Pacific Region). Ninety-two countries agreed to provide data in accordance with WHO data-sharing policy. For the eight substance-specific surveys, an average of 68 countries responded (range, 64–79), and an average of 21 countries (range, 14–37) provided substance-specific information.

Each substance-specific survey covers: approved medical, scientific or industrial use; epidemiology of non-medical use; perceived negative health impact; emergency department visits; deaths; drug dependence; current national controls; illicit manufacture and trafficking; detection in falsified medicines; seizures; and laboratory capacity in the Member State to analyse the substance.

Respondents can draw on many sources of data, such as on seizures from law enforcement or customs offices, reports from emergency and forensic pathology departments, calls to poison centres and legislation.

The questionnaire can be completed as an online survey or submitted to the questionnaire team. Translated versions of the questionnaire were available in all six official United Nations languages: Arabic, Chinese, English, French, Russian and Spanish.

Hexahydrocannabinol

Of the 79 countries that agreed to provide data, 37 reported that they had information on use of hexahyrdocannabinol in their country for medical, scientific, industrial or other professional purposes, for non-medical consumption or recreational purposes or for any other purpose (Table A1.1).

Table A1.1. Numbers of countries that provided information on hexahydrocannabinol

Region	No. of countries with no information	No. of countries with information
African	10	2
Americas	9	4
South-East Asia	3	1
European	10	25
Eastern Mediterranean	5	1
Western Pacific	5	4
Total	42	37

Approved medical, scientific or industrial use

No country reported approved therapeutic indications for hexahyrdocannabinol. One country reported that hexahyrdocannabinol was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (except as an analytical standard). None reported use for legitimate (legal) industrial purposes.

Epidemiology of non-medical use

Twenty-seven countries (21 in the European, 4 in the Americas, 1 in the Eastern Mediterranean and 1 in the Western Pacific regions) reported evidence of use of hexahydrocannabinol for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived mainly from data on seizures from law enforcement (n = 20), customs (suggesting detection at international border points; n = 9), toxicology reports from emergency departments (n = 7) and poisons information calls (n = 3). Other sources included reports submitted to or published by drug analysis services, prevention organizations, cannabis products shops and reports related to recreational use.

Routes of administration and formulations

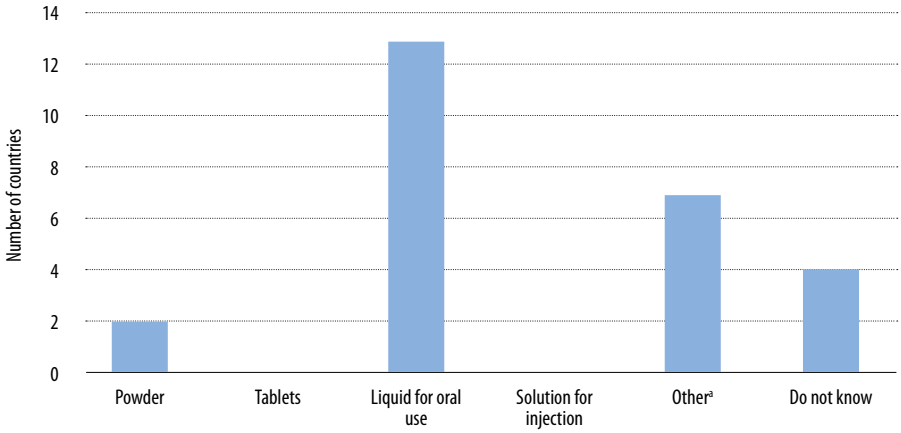
The most common reported route of administration was smoking (Table A1.2).

Table A1.2. Reported routes of hexahydrocannabinol administration

Route of administration	No. of countries
Smoking	21
Oral	16
Inhalation	13
Sniffing	0
Injection	0
Other	6[a]
Do not know	5

[a] "E-liquid for use in electronic vaping devices", "Cannabis products for oral administration containing unlabelled hexahydrocannabinol produced as an unintended by-product of chemical synthesis of other cannabinoids", "topical/transdermal", "edibles" and "vaping" further described in the "Other" section.

The most common formulation of hexahydrocannabinol reported was liquid for oral use (Fig. A1.1).



[a] Other formulations included e-liquid for use in electronic vaping devices, edibles including gummies, candies and cookies, herbal products, plant material, resin, blossom, cannabinoid oil, oils, gel capsules, vitreous substance and contaminated herbal cannabis with HHC and/or its analogues.

Fig. A1.1. Formulations of hexahydrocannabinol

Perceived negative health impact

Seventeen countries (14 in the European, 2 in the Americas and 1 in the Western Pacific regions) reported that the negative health effect of non-medical consumption of hexahydrocannabinol was "especially serious" or "substantial" (Fig. A1.2).

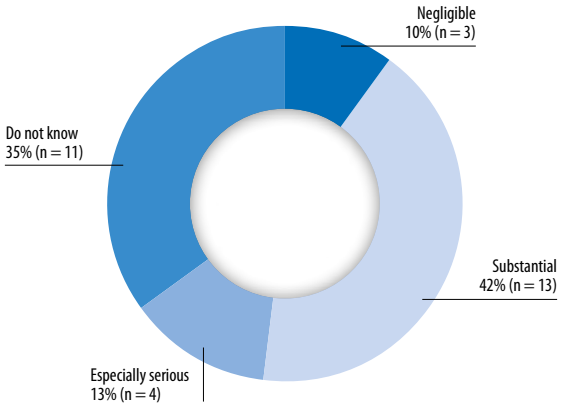


Fig. A1.2. Negative health impacts of non-medical consumption of hexahydrocannabinol

Emergency department visits

Twelve countries (11 in the European and 1 in the Americas regions) were aware of emergency department visits related to hexahydrocannabinol. Four countries described emergency department presentations by people who had consumed hexahydrocannabinol with other substances. Two countries reported the year in which the presentations occurred: 49 presentations in 2024, 171 in 2023 and 23 in 2022 (all in the European Region). Two countries reported the year in which the presentations occurred with other substances: 10 presentations in 2024 (1 in the Americas and 9 in the European regions), 18 presentations in 2023 (in the European region) and 1 presentation in 2022 (in the European region).

The adverse effects (e.g. non-fatal intoxications) seen in patients who presented to emergency departments after use of hexahydrocannabinol included headache, dizziness, confusion, hypertension, agitation, tachycardia, bradycardia, hallucinations, psychosis, anxiety, depression, nausea, vomiting, unconsciousness, respiratory depression, chest pain, sweating, memory loss and seizures/convulsion. Other adverse effects reported included dyspnoea, tremor, eye movement disorder, mental disorder, flashback, poor-quality sleep, psychosis with delusions and paranoia, mydriasis and panic attacks.

Deaths

One country in the European Region reported one death in 2024 in which hexahydrocannabinol and other substances were involved.

Drug dependence

Three countries in the European Region reported presentations for treatment of drug dependence due to the use of hexahydrocannabinol. One country reported that clinicians found that up to 20% of presentations to adolescent addiction services were because of hexahydrocannabinol use.

Current national controls

Eighteen countries (1 in the Americas, 16 in the European and 1 in the Western Pacific regions) reported that the availability of hexahydrocannabinol was controlled under substance-specific legislation, and nine countries (3 in the European, 2 in the Americas, 1 in the South-East Asia, 3 in the Western Pacific regions) reported that the availability of hexahydrocannabinol was controlled under legislation on analogue or generic drugs.

Illicit manufacture and trafficking

Table A1.3 shows the main reported activities involving hexahydrocannabinol.

Table A1.3. Reported activities involving hexahydrocannabinol for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	13
Smuggling (from other countries)	12
Internet sales (other or location of sellers and website unknown)	7
Internet sales (from abroad to buyers in the respondent's country)	11
Internet sales (seller or website located in respondent's country)	12
Manufacture of the substance by chemical synthesis	1
Direct sales	5
Production of consumer products containing the substance	4
Manufacture of the substance by extraction from other products	1
Diversion (from legal supply chain)	0
Do not know	9
Other	0

Detection in falsified medicines

One country in the European Region indicated that hexahydrocannabinol was detected in counterfeit medicines or other products.

Seizures

Fifteen countries (1 in the Americas, 1 in the Eastern Mediterranean, 12 in the European and 1 in the Western Pacific regions) reported seizures in 2024. The number of seizures per country ranged from 1 to 58, and the amounts seized ranged from 1 to 1949 g (Table A1.4).

Seventeen countries (1 in the Americas, 15 in the European and 1 the Western Pacific regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 196, and the amounts seized ranged from < 1 to 7673 g.

Thirteen countries (1 in the Americas, 11 in the European and 1 in the Western Pacific regions) reported seizures in 2022. The number of seizures per country ranged from 1 to 88, and the amounts seized were 1–1719 g.

Table A1.4. Reported seizures of hexahydrocannabinol

Year	No. of countries that reported seizures	No. of seizures
2024	15	179
2023	17	843
2022	3	149

Laboratory capacity

Thirty-two of the 37 countries that provided information (24 in the European, 4 in the Americas, 2 in the Western Pacific, 1 in the Eastern Mediterranean and 1 in the South-East Asia regions) reported that they had the laboratory capacity to analyse hexahydrocannabinol.

N-Pyrrolidino protonitazene (protonitazepyne)

Of the 70 countries that agreed to provide data, 20 reported that they had information on the use of *N*-pyrrolidino protonitazene in their country for medical, scientific, industrial or other professional purposes, for non-medical consumption or recreational purposes or for any other purpose (Table A1.5).

Table A1.5. Numbers of countries that provided information on *N*-pyrrolidino protonitazene

Region	No. of countries with no information	No. of countries with information
African	8	0
Americas	10	2
South-East Asia	3	1
European	19	14
Eastern Mediterranean	6	0
Western Pacific	4	3
Total	50	20

Approved medical, scientific or industrial use

No country reported approved therapeutic indications for *N*-pyrrolidino protonitazene, and none reported that *N*-pyrrolidino protonitazene was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (except as an analytical standard). One country reported use for legitimate (legal) industrial purposes.

Epidemiology of non-medical use

Ten countries (5 in the European, 3 in the Western Pacific and 2 in the Americas regions) reported evidence of use of *N*-pyrrolidino protonitazene for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived mainly from data on seizures during law enforcement (n = 5), toxicology reports after deaths (n = 2) and toxicology reports from emergency departments (n = 1). Other sources included reports submitted to or published by public health, hospitals, cryptomarket listings and reports related to recreational use.

Routes of administration and formulations

The most common reported route of administration was injection (Table A1.6).

Table A1.6. Reported routes of *N*-pyrrolidino protonitazene administration

Route of administration	No. of countries
Smoking	1
Oral	2
Inhalation	0
Sniffing	1
Injection	4
Other	1[a]
Do not know	8

[a] "Has been used by persons who use drugs who bought it as heroin", further described in the "Other" section.

The most common formulation of *N*-pyrrolidino protonitazene reported was powder (Fig. A1.3).

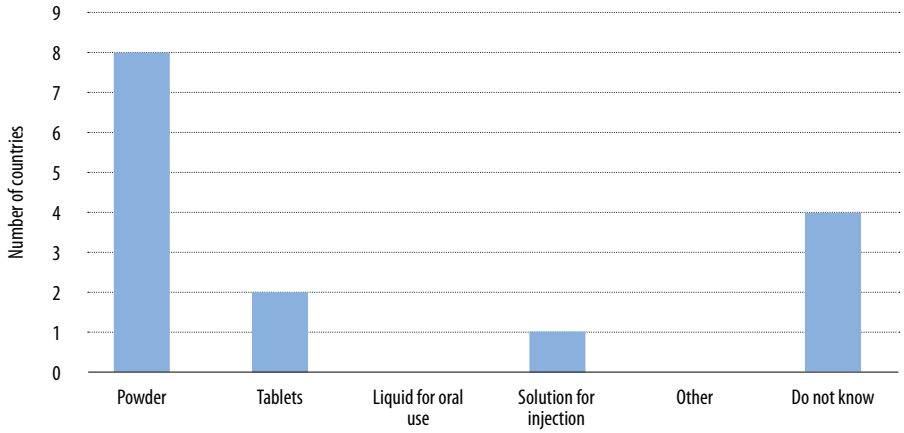


Fig. A1.3. Formulations of *N*-pyrrolidino protonitazene

Perceived negative health impact

Nine countries (7 in the European, 1 in the Americas and 1 in the Western Pacific regions) reported that the negative health effect of non-medical consumption of *N*-pyrrolidino protonitazene was "especially serious" or "substantial" (Fig. A1.4).

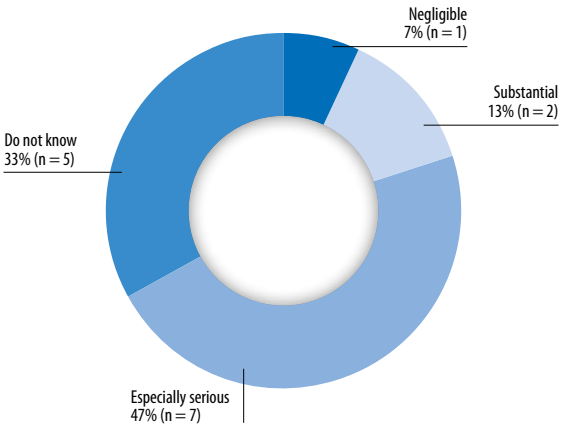


Fig. A1.4. Negative health impacts of non-medical consumption of *N*-pyrrolidino protonitazene

Emergency department visits

Two countries (in the European Region) were aware of emergency department visits related to *N*-pyrrolidino protonitazene. One country described emergency department presentations by people who had consumed *N*-pyrrolidino protonitazene with other substances, and the other country described emergency department presentations by people who had consumed protinitazepyne, in which it was not known whether other substances were involved. One of the two countries reported the years in which the presentations occurred: 5 presentations in 2024 and 77 presentations in 2023.

The adverse effects (e.g. non-fatal intoxications) seen in patients who presented to emergency departments after use of *N*-pyrrolidino protonitazene included dizziness, confusion, hypotension, bradycardia, unconsciousness and respiratory depression. Other adverse effects reported included possible cardiac events when used with other stimulant type drugs such as cocaine.

Deaths

One country (in the European Region) reported one death in 2024 in which *N*-pyrrolidino protonitazene was the only substance involved. One country (in the Americas Region) reported deaths in which *N*-pyrrolidino protonitazene and other substances were involved (n = 3 in 2024; n = 16 in 2023). The country in the European Region reported that there had probably been two deaths in which *N*-pyrrolidino protonitazene and other substances were involved. The country did not report the year in which the deaths occurred.

Drug dependence

No country reported presentations for treatment of drug dependence due to use of *N*-pyrrolidino protonitazene.

Current national controls

Nine countries (8 in the European and 1 in the Western Pacific regions) reported that the availability of *N*-pyrrolidino protonitazene was controlled under substance-specific legislation, and nine countries (4 in the European, 2 in the Americas, 1 in the South-East Asia and 2 in the Western Pacific regions) reported that the availability of *N*-pyrrolidino protonitazene was controlled under legislation on analogue or generic drugs.

Illicit manufacture and trafficking

Table A1.7 shows the main reported activities involving *N*-pyrrolidino protonitazene.

Table A1.7. Reported activities involving *N*-pyrrolidino protonitazene for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	0
Smuggling (from other countries)	2
Internet sales (other or location of sellers and website unknown)	2
Internet sales (from abroad to buyers in the respondent's country)	2
Internet sales (seller or website located in respondent's country)	2
Manufacture of the substance by chemical synthesis	0
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	0
Do not know	8
Other	0

Detection in falsified medicines

Two countries (1 in the Americas and 1 in the Western Pacific regions) indicated that *N*-pyrrolidino protonitazene was detected in counterfeit medicines or other products.

Seizures

Two countries (1 in the Americas and 1 in the European regions) reported seizures in 2024. The number of seizures per country ranged from 2 to 29, and the amounts seized were 1367 g and 52 tablets (Table A1.8).

Two countries (1 in the Americas and 1 in the Western Pacific regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 26, and the amounts seized ranged from 1 to 333 g.

No countries reported seizures in 2022.

Table A1.8. Reported seizures of *N*-pyrrolidino protonitazene

Year	No. of countries that reported seizures	No. of seizures
2024	2	31
2023	2	27
2022	0	0

Laboratory capacity

Eighteen of the 20 countries that provided information (13 in the European, 2 in the Americas, 2 in the Western Pacific and 1 in the South-East Asia regions) reported that they had the laboratory capacity to analyse *N*-pyrrolidino protonitazene.

N-Pyrrolidino metonitazene (metonitazepyne)

Of the 66 countries that agreed to provide data, 14 reported that they had information on the use of *N*-pyrrolidino metonitazene in their country for medical, scientific, industrial or other professional purposes, for non-medical consumption or recreational purposes or for any other purpose (Table A1.9).

Table A1.9. Numbers of countries that provided information on *N*-pyrrolidino metonitazene

Region	No. of countries with no information	No. of countries with information
African	7	0
Americas	7	3
South-East Asia	2	1
European	25	8
Eastern Mediterranean	7	0
Western Pacific	4	2
Total	52	14

Approved medical, scientific or industrial use

No country reported approved therapeutic indications for *N*-pyrrolidino metonitazene, and none reported that *N*-pyrrolidino metonitazene was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (except as an analytical standard). None reported use for legitimate (legal) industrial purposes.

Epidemiology of non-medical use

Five countries (2 in the Americas, 2 in the European and 1 in the Western Pacific regions) reported evidence of use of *N*-pyrrolidino metonitazene for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived mainly from data on seizures from law enforcement (n = 5) and customs (suggesting detection at international border points; n = 1). Other sources included drug checking and reports related to recreational use.

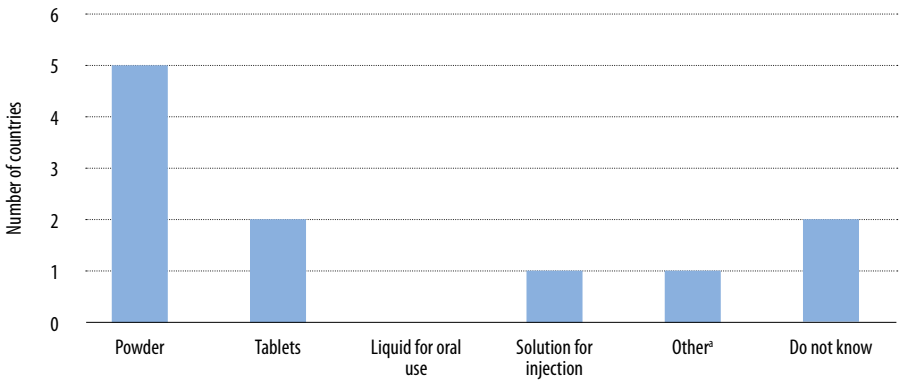
Routes of administration and formulations

The most common reported route of administration was injection (Table A1.10).

Table A1.10. Reported routes of *N*-pyrrolidino metonitazene administration

Route of administration	No. of countries
Smoking	0
Oral	0
Inhalation	0
Sniffing	0
Injection	2
Other	0
Do not know	5

The most common formulation of *N*-pyrrolidino metonitazene reported was powder (Fig. A1.5).



[a] Other formulations included liquid for unknown use.

Fig. A1.5. Formulations of *N*-pyrrolidino metonitazene

Perceived negative health impact

Five countries (3 in the European, 1 in the Americas and 1 in the Western Pacific regions) reported that the negative health effect of non-medical consumption of *N*-pyrrolidino metonitazene was "especially serious" or "substantial" (Fig. A1.6).

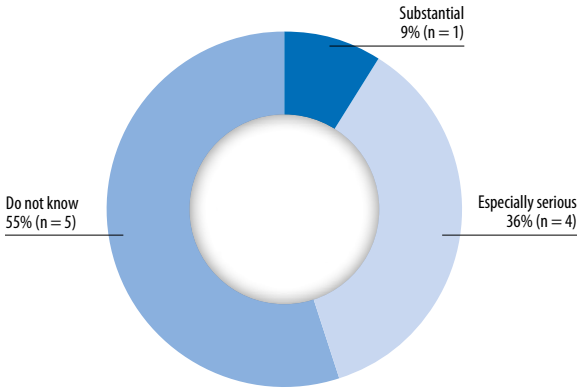


Fig. A1.6. Negative health impacts of non-medical consumption of *N*-pyrrolidino metonitazene

Emergency department visits

No countries were aware of emergency department visits related to *N*-pyrrolidino metonitazene. No countries described emergency department presentations by people who had consumed *N*-pyrrolidino metonitazene with other substances.

Deaths

One country (in the Americas region) reported *N*-pyrrolidino metonitazene-related deaths between 2022 and 2024. The country reported 5 deaths in 2023 in which *N*-pyrrolidino metonitazene and other substances were involved.

Drug dependence

No country reported presentations for treatment of drug dependence due to use of *N*-pyrrolidino metonitazene.

Current national controls

Four countries (in the European Region) reported that the availability of *N*-pyrrolidino metonitazene was controlled under substance-specific legislation, and eight countries (2 in the Americas, 3 in the European, 1 in South-East Asia and 2 in the Western Pacific regions) reported that the availability of *N*-pyrrolidino metonitazene was controlled under legislation on analogue or generic drugs.

Illicit manufacture and trafficking

Table A1.11 shows the main reported activities involving *N*-pyrrolidino metonitazene.

Table A1.11. Reported activities involving *N*-pyrrolidino metonitazene for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	3
Smuggling (from other countries)	1
Internet sales (other or location of sellers and website unknown)	2
Internet sales (from abroad to buyers in the respondent's country)	2
Internet sales (seller or website located in respondent's country)	1
Manufacture of the substance by chemical synthesis	0
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	0
Do not know	5
Other	0

Detection in falsified medicines

No country indicated that *N*-pyrrolidino metonitazene was detected in any counterfeit medicines or other products.

Seizures

Two countries (1 in the Americas and 1 in the European regions) reported seizures in 2024. The number of seizures per country was 1, and the amounts seized were 9.9 g and 10 mL (Table A1.12).

Four countries (2 in the Americas and 2 in the European regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 7, and the amounts seized ranged from 1 to 3031 g.

No country reported seizures in 2022.

Table A1.12. Reported seizures of *N*-pyrrolidino metonitazene

Year	No. of countries that reported seizures	No. of seizures
2024	2	2
2023	4	11
2022	0	0

Laboratory capacity

Twelve of the 14 countries that provided information (8 in the European, 2 in the Americas, 1 in the South-East Asia and 1 in the Western Pacific regions) reported that they had the laboratory capacity to detect *N*-pyrrolidino metonitazene.

Etonitazepipne

Of the 64 countries that agreed to provide data, 17 reported that they had information on the use of etonitazepipne in their country for medical, scientific, industrial or other professional purposes, for non-medical consumption or recreational purposes or for any other purpose (Table A1.13).

Table A1.13. Numbers of countries that provided information on etonitazepipne

Region	No. of countries with no information	No. of countries with information
African	5	1
Americas	9	2
South-East Asia	2	1
European	21	12
Eastern Mediterranean	6	0
Western Pacific	4	1
Total	47	17

Approved medical, scientific or industrial use

No country reported approved therapeutic indications for etonitazepipne, and none reported that etonitazepipne was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (except as an analytical standard). None reported use for legitimate (legal) industrial purposes.

Epidemiology of non-medical use

Four countries (3 in the European and 1 in the Americas regions) reported evidence of use of etonitazepipne for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived mainly from data on seizures for law enforcement (n = 3), customs (suggesting detection at international border points; n = 2), toxicology reports after deaths (n = 2) and toxicology reports from emergency departments (n = 1).

Routes of administration and formulations

The most common reported route of administration was injection (Table A1.14).

Table A1.14. Reported routes of etonitazepipne administration

Route of administration	No. of countries
Smoking	0
Oral	0
Inhalation	0
Sniffing	0
Injection	1
Other	0
Do not know	7

The most common formulation of etonitazepipne reported was powder (Fig. A1.7).

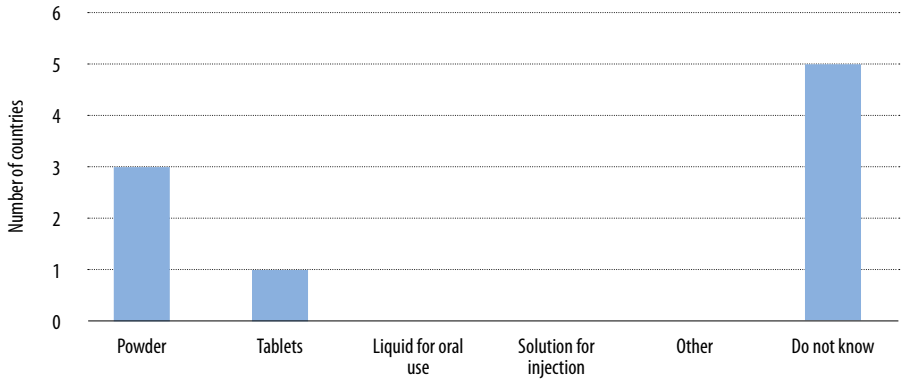


Fig. A1.7. Formulations of etonitazepipne

Perceived negative health impact

Five countries (4 in the European and 1 in the Americas regions) reported that the negative health effect of non-medical consumption of etonitazepipne was "especially serious" or "substantial" (Fig. A1.8).

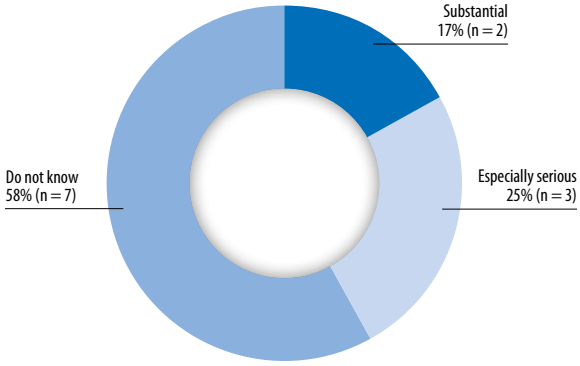


Fig. A1.8. Negative health impacts of non-medical consumption of etonitazepipne

Emergency department visits

One country (in the Americas region) was aware of emergency department visits related to etonitazepipne. This country described emergency department presentations by people who had consumed etonitazepipne with other substances. This country reported the year in which the presentations occurred: 1 presentation in 2024.

No adverse effects (e.g. non-fatal intoxications) were seen in patients who presented to emergency departments after use of etonitazepipne.

Deaths

One country in the Americas Region reported deaths in which etonitazepipne and other substances were involved (n = 1 in 2024, n = 6 in 2023, n = 1 in 2022, n = 1 in another year). One country (in the European Region) reported one death in 2022 in which etonitazepipne and other substances were involved. There were no deaths reported in which etonitazepipne was the only substance involved.

Drug dependence

No country reported presentations for treatment of drug dependence due to use of etonitazepipne.

Current national controls

Nine countries (8 in the European and 1 in the Americas regions) reported that the availability of etonitazepipne was controlled under substance-specific legislation, and six countries (3 in the European, 1 in the Americas, 1 in the South-East Asia and 1 in the Western Pacific regions) reported that the availability of etonitazepipne was controlled under legislation on analogue or generic drugs.

Illicit manufacture and trafficking

Table A1.15 shows the main reported activities involving etonitazepipne.

Table A1.15. Reported activities involving etonitazepipne for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	2
Smuggling (from other countries)	1
Internet sales (other or location of sellers and website unknown)	1
Internet sales (from abroad to buyers in the respondent's country)	1
Internet sales (seller or website located in respondent's country)	1
Manufacture of the substance by chemical synthesis	0
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	0
Do not know	6
Other	0

Detection in falsified medicines

One country (in the Americas Region) indicated that etonitazepipne was falsely sold as oxycodone tablets.

Seizures

No countries reported seizures in 2024 (Table A1.16).

One country (in the Americas Region) reported one seizure in 2023 of 0.12 g.

Two countries (1 in the Americas and 1 in the European regions) reported seizures in 2022. The number of seizures per country ranged from 1 to 9, and the amounts seized were < 1 to 452 g.

Table A1.16. Reported seizures of etonitazepipne

Year	No. of countries that reported seizures	No. of seizures
2024	0	0
2023	1	1
2022	2	10

Laboratory capacity

Fifteen of the 17 countries that provided information (12 in the European, 1 in the Americas, 1 in the South-East Asia and 1 in the Western Pacific regions) reported that they had the laboratory capacity to detect etonitazepipne.

N-Desethyl isotonitazene

Of the 64 countries that agreed to provide data, 18 reported that they had information on use of *N*-desethyl isotonitazene in their country (Table A1.17).

Table A1.17. Numbers of countries that provided information on *N*-desethyl isotonitazene

Region	No. of countries with no information	No. of countries with information
African	5	1
Americas	8	2
South-East Asia	2	1
European	22	11
Eastern Mediterranean	6	0
Western Pacific	3	3
Total	46	18

Approved medical, scientific or industrial use

No country reported approved therapeutic indications for *N*-desethyl isotonitazene, and none reported that it was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (except as an analytical standard). None reported use for legitimate (legal) industrial purposes.

Epidemiology of non-medical use

Nine countries (4 in the European, 3 in the Western Pacific and 2 in the Americas) reported evidence of use of *N*-desethyl isotonitazene for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived from data on seizures for law enforcement (n = 7), toxicology reports from deaths (n = 2) and toxicology reports from emergency departments (n = 1). Other sources included cryptomarket listings (n = 1), counterfeit hydromorphone tablets (n = 1) and reports of use on Internet forums (n = 1).

Routes of administration and formulations

The most common reported route of administration was oral (Table A1.18).

Table A1.18. Reported routes of *N*-desethyl isotonitazene administration

Route of administration	No. of countries
Oral	2
Injection	1
Smoking	0
Inhalation	0
Sniffing	0
Other	0
Do not know	6

The most common formulation of *N*-desethyl isotonitazene reported was powder (Fig. A1.9).

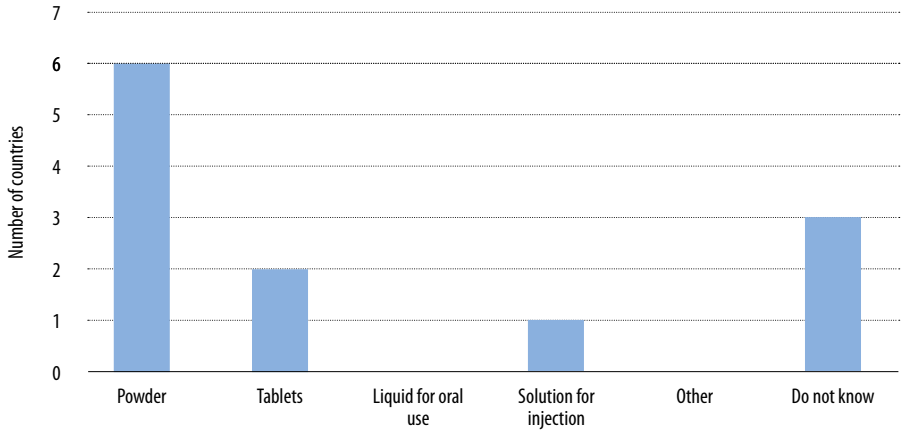


Fig. A1.9. Formulations of *N*-desethyl isotonitazene

Perceived negative health impact

Seven countries (5 in the European, 1 in the Americas, 1 in the Western Pacific regions) reported that the negative health effect of non-medical consumption of *N*-desethyl isotonitazene was "especially serious" or "substantial" (Fig. A1.10).

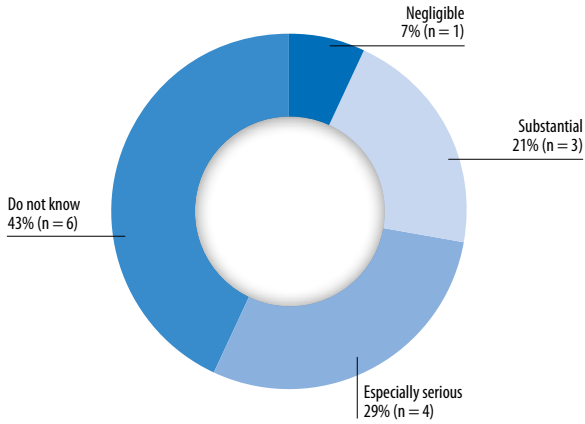


Fig. A1.10. Negative health impacts of non-medical consumption of *N*-desethyl isotonitazene

Emergency department visits

Two countries (1 in the Americas and 1 in the European regions) were aware of emergency department visits related to *N*-desethyl isotonitazene. The European country reported one emergency department presentation in 2024 and five in 2023 by people who had consumed *N*-desethyl isotonitazene with other substances. The country in the Americas reported one emergency department presentation in 2023 in which it was not known whether *N*-desethyl isotonitazene was combined with other substances. No information was provided on the adverse effects seen in patients who presented to emergency departments after use of *N*-desethyl isotonitazene.

Deaths

One European country reported *N*-desethyl isotonitazene-related deaths in which other substances were involved (n = 1 in 2024, n = 2 in 2023). One country in the Americas Region reported *N*-desethyl isotonitazene-related deaths in which it was not known whether other substances were also involved (n = 9 in 2023). No deaths were reported in which *N*-desethyl isotonitazene was known to be the only substance involved.

Drug dependence

No country reported presentations for treatment of drug dependence due to use of *N*-desethyl isotonitazene.

Current national controls

Seven countries (5 in the European, 1 in the Americas and 1 in the Western Pacific regions) reported that the availability of *N*-desethyl isotonitazene was controlled under substance-specific legislation, and eight countries (4 in the European, 2 in the Western Pacific, 1 in the Americas and 1 in the South-East Asia regions) reported that the availability of *N*-desethyl isotonitazene was controlled under analogue or generic legislation.

Illicit manufacture and trafficking

Table A1.19 shows the main reported activities involving *N*-desethyl isotonitazene.

Table A1.19. Reported activities involving *N*-desethyl isotonitazene for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	2
Internet sales (other or location of sellers and website unknown)	2
Internet sales (from abroad to buyers in the respondent's country)	2
Internet sales (seller or website located in respondent's country)	1
Manufacture of the substance by chemical synthesis	1
Smuggling (from other countries)	0
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	0
Do not know	6
Other	0

Detection in falsified medicines

Two countries (1 in the Americas and 1 in the Western Pacific regions) indicated that *N*-desethyl isotonitazene was detected in counterfeit medicines or other products. The country in the Americas Region reported that *N*-desethyl isotonitazene was detected in falsified hydromorphone tablets.

Seizures

Three countries (1 in the Americas, 1 in the European and 1 in the Western Pacific regions) reported seizures in 2024. The number of seizures reported per country ranged from 1 to 21, and the amounts seized ranged from 1 to 370 g (Table A1.20).

Four countries (1 in the Americas, 1 in the European and 2 in the Western Pacific regions) reported seizures in 2023. The number of seizures reported per country ranged from 1 to 8, and the amounts seized from 1 to 7 g.

One country in the Americas Region reported that it had made four seizures, of a total of 2 g, in 2022.

Table A1.20. Reported seizures of *N*-desethyl isotonitazene

Year	No. of countries that reported seizures	No. of seizures
2024	3	23
2023	3	14
2022	1	4

Laboratory capacity

Sixteen of the 18 countries that provided information (11 in the European, 2 in the Americas, 2 in the Western Pacific and 1 in the South-East Asia regions) reported that they had the laboratory capacity to detect *N*-desethyl isotonitazene.

3-Hydroxyphencyclidine (3-OH-PCP)

Of the 66 countries that agreed to provide data, 19 reported that they had information on use of 3-hydroxyphencyclidine in their country for medical, scientific, industrial or other professional purposes, for non-medical consumption or recreational purposes or for any other purpose (Table A1.21).

Table A1.21. Numbers of countries that provided information on 3-hydroxyphencyclidine

Region	No. of countries with no information	No. of countries with information
African	7	0
Americas	9	2
South-East Asia	3	1
European	19	14
Eastern Mediterranean	6	0
Western Pacific	3	2
Total	47	19

Approved medical, scientific or industrial use

No country reported approved therapeutic indications for 3-hydroxyphencyclidine, and none reported that 3-hydroxyphencyclidine was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (except as an analytical standard). None reported use for legitimate (legal) industrial purposes.

Epidemiology of non-medical use

Fourteen countries (10 in the European, 2 in the Americas and 2 in the Western Pacific regions) reported evidence of use of 3-hydroxyphencyclidine for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived mainly from data on seizures for law enforcement (n = 9), customs (suggesting detection at international border points; n = 4), toxicology reports after deaths (n = 1), toxicology reports from emergency departments (n = 2) and poisons information calls (n = 1). Other sources included reports submitted to or published by public health organizations, open web sales listings, discussion forum postings on sourcing and drug checking services.

Routes of administration and formulations

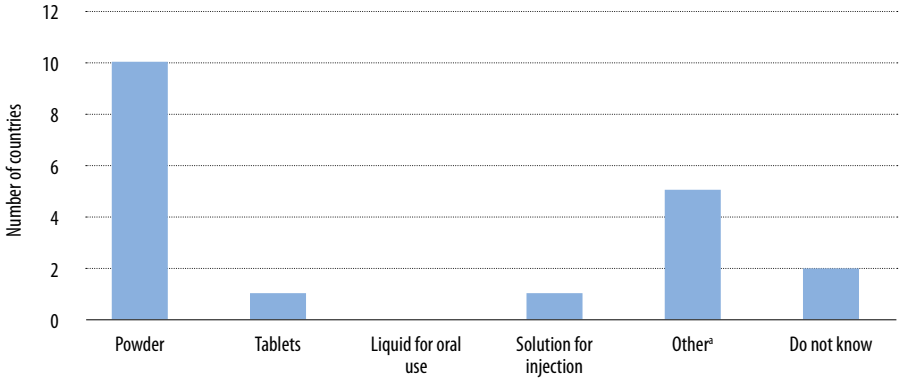
The most common reported route of administration was oral (Table A1.22).

Table A1.22. Reported routes of 3-hydroxyphencyclidine administration

Route of administration	No. of countries
Smoking	1
Oral	3
Inhalation	1
Sniffing	2
Injection	0
Other[a]	1
Do not know	8

[a] "Rectal administration", further described in the "Other" section.

The most common formulation of 3-hydroxyphencyclidine reported was powder (Fig. A1.11).



[a] Other formulations included crystalline substance, crystals, liquid for inhalation, capsules and chocolates.

Fig. A1.11. Formulations of 3-hydroxyphencyclidine

Perceived negative health impact

Four countries (3 in the European and 1 in the Americas regions) reported that the negative health effect of non-medical consumption of 3-hydroxyphencyclidine was "especially serious" or "substantial" (Fig. A1.12).

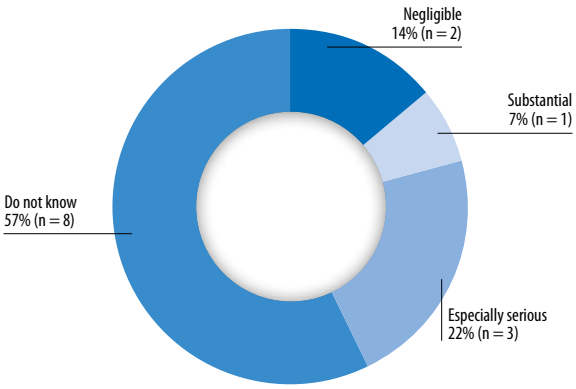


Fig. A1.12. Negative health impacts of non-medical consumption of 3-hydroxyphencyclidine

Emergency department visits

Three countries (in the European Region) were aware of emergency department visits related to 3-hydroxyphencyclidine. Two countries described emergency department presentations by people who had consumed 3-hydroxyphencyclidine with other substances. One country described emergency department presentations by people who had consumed 3-hydroxyphencyclidine in which it was not known whether other substances were involved. Two of the three countries reported the year in which the presentations occurred: 3 presentations in 2023 and 8 presentations in another year.

The adverse effects (e.g. non-fatal intoxications) seen in patients who presented to emergency departments after use of 3-hydroxyphencyclidine included confusion, hypertension, agitation, tachycardia, hallucinations, anxiety and seizures/convulsions. Other adverse effects reported included reduced consciousness, urine retention and hyperthermia.

Deaths

One country (in the Americas Region) reported deaths in which 3-hydroxyphencyclidine and other substances were involved (n = 1 in 2023, n = 5 in 2022, n = 17 in another year). One country (in the European Region) reported 1 death in 2022 in which 3-hydroxyphencyclidine and other substances were involved. No deaths were reported in which 3-hydroxyphencyclidine was the only substance involved.

Drug dependence

No country reported presentations for treatment of drug dependence due to use of 3-hydroxyphencyclidine.

Current national controls

Nine countries (8 in the European and 1 in the Western Pacific regions) reported that the availability of 3-hydroxyphencyclidine was controlled under substance-specific legislation, and six countries (3 in the European, 1 in the Americas, 1 in the South-East Asia and 1 in the Western Pacific regions) reported that the availability of 3-hydroxyphencyclidine was controlled under legislation on analogue or generic drugs.

Illicit manufacture and trafficking

Table A1.23 shows the main reported activities involving 3-hydroxyphencyclidine.

Table A1.23. Reported activities involving 3-hydroxyphencyclidine for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	4
Smuggling (from other countries)	5
Internet sales (other or location of sellers and website unknown)	3
Internet sales (from abroad to buyers in the respondent's country)	4
Internet sales (seller or website located in respondent's country)	3
Manufacture of the substance by chemical synthesis	1
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	0
Do not know	7
Other	0

Detection in falsified medicines

No country indicated that 3-hydroxyphencyclidine was detected in any counterfeit medicines or other products.

Seizures

One country (in the European Region) reported one seizure in 2024. The amount seized was 0.5 g (Table A1.24).

Six countries (4 in the European, 1 in the Americas and 1 in the Western Pacific regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 43, and the amounts seized ranged from < 1 to 197 g.

Seven countries (5 in the European, 1 in the Americas and 1 in the Western Pacific regions) reported seizures in 2022. The number of seizures per country ranged from 1 to 335, and the amounts seized ranged from < 1 to 1846 g.

Table A1.24. Reported seizures of 3-hydroxyphencyclidine

Year	No. of countries that reported seizures	No. of seizures
2024	1	1
2023	6	56
2022	7	350

Laboratory capacity

Nineteen countries that provided information (14 in the European, 2 in the Americas, 2 in the Western Pacific and 1 in the South-East Asia regions) reported that they had the laboratory capacity to detect 3-hydroxyphencyclidine.

N-Ethylheptedrone

Of the 67 countries that agreed to provide data, 19 reported that they had information on use of N-ethylheptedrone in their country (Table A1.25).

Table A1.25. Numbers of countries that provided information on *N*-ethylheptedrone

Region	No. of countries with no information	No. of countries with information
African	6	0
Americas	8	3
South-East Asia	21	12
European	6	0
Eastern Mediterranean	3	1
Western Pacific	4	3
Total	48	19

Approved medical, scientific or industrial use

No country reported approved therapeutic indications for *N*-ethylheptedrone, and none reported that *N*-ethylheptedrone was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (except as an analytical standard). None reported use for legitimate industrial purposes.

Epidemiology of non-medical use

Nine countries (5 in the European, 3 in the Americas and 1 in the Western Pacific regions) reported evidence of use of *N*-ethylheptedrone for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived from data on seizures for law enforcement (n = 8), seizures at customs (n = 2), poisons information calls (n = 1), drug checking (n = 1) and toxicology reports (n = 1).

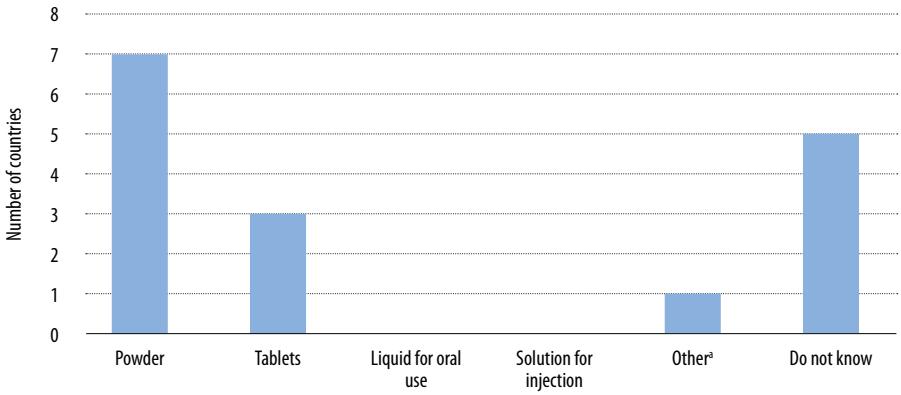
Routes of administration and formulations

The only reported routes of administration were oral and smoking (Table A1.26).

Table A1.26. Reported routes of *N*-ethylheptedrone administration

Route of administration	No. of countries
Smoking	1
Oral	1
Inhalation	0
Sniffing	0
Injection	0
Other	0
Do not know	11

The most common formulation of *N*-ethylheptedrone reported was powder (Fig. A1.13).



[a] Other formulations included capsule or crystalline substance.

Fig. A1.13. Formulations of *N*-ethylheptedrone

Perceived negative health impact

Three European region countries reported that the negative health effect of non-medical consumption of *N*-ethylheptedrone was "especially serious" or "substantial" (Fig. A1.14).

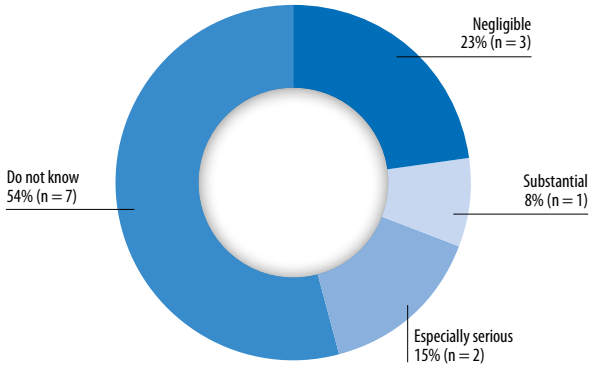


Fig. A1.14. Negative health impacts of non-medical consumption of *N*-ethylheptedrone

Emergency department visits

One European country was aware of two emergency department visits related to *N*-ethylheptedrone in which other substances were involved. The visits occurred in 2021 or earlier, and the adverse effects seen in patients after use of *N*-ethylheptedrone included tachycardia, vomiting and psychomotor agitation.

Deaths

No countries reported *N*-ethylheptedrone-related deaths.

Drug dependence

No country reported presentations for treatment of drug dependence due to use of *N*-ethylheptedrone.

Current national controls

Seven countries (6 in the European and 1 in the Western Pacific regions) reported that the availability of *N*-ethylheptedrone was controlled under substance-specific legislation, nine countries (4 in the European, 2 in the Americas, 2 in the Western Pacific and 1 in the South-East Asia regions) reported that the availability of *N*-ethylheptedrone was controlled under analogue or generic legislation, and three countries reported that it was not currently controlled under national legislation (2 in the European and 1 in the Americas regions).

Illicit manufacture and trafficking

Table A1.27 shows the main reported activities involving *N*-ethylheptedrone.

Table A1.27. Reported activities involving *N*-ethylheptedrone for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	4
Internet sales (seller or website located in respondent's country)	2
Smuggling (from other countries)	2
Internet sales (other or location of sellers and website unknown)	1
Internet sales (from abroad to buyers in the respondent's country)	1
Manufacture of the substance by chemical synthesis	1
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	0
Do not know	6
Other	0

Detection in falsified medicines

One country in the Americas Region indicated that *N*-ethylheptedrone was detected in falsified medicines or other products.

Seizures

Two countries (1 in the Americas and 1 in the European regions) reported seizures of *N*-ethylheptedrone in 2024. The number of seizures reported per country ranged from 1–2, and the amounts seized ranged from 55–662 g (Table A1.28).

Two countries (1 in the Americas and 1 in the European regions) reported seizures in 2023. The number of seizures reported per country ranged from 1–9, and the amounts seized ranged from 157–701 g.

Four countries (3 in the European and 1 in the Americas regions) reported seizures in 2022. The number of seizures reported per country ranged from 1–7, and the amounts seized ranged from 3–322 g.

One country in the Americas Region further reported that *N*-ethylheptedrone was detected in 99 law enforcement seizures between 2019 and 2021.

Table A1.28. Reported seizures of *N*-ethylheptedrone

Year	No. of countries that reported seizures	No. of seizures
2024	2	3
2023	2	10
2022	4	12

Laboratory capacity

All 19 countries that provided information reported that they had the laboratory capacity to detect *N*-ethylheptedrone.

Carisoprodol

Of the 70 countries that agreed to provide data, 25 reported that they had information on use of carisoprodol in their country for medical, scientific, industrial or other professional purposes, for non-medical consumption or recreational purposes or for any other purpose (Table A1.29).

Table A1.29. Numbers of countries that provided information on carisoprodol

Region	No. of countries with no information	No. of countries with information
African	8	0
Americas	5	6
South-East Asia	2	2
European	23	10
Eastern Mediterranean	4	3
Western Pacific	3	4
Total	45	25

Approved medical, scientific or industrial use

Ten countries reported approved therapeutic indications for carisoprodol. Two countries (in the European Region) reported that carisoprodol was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (except as an analytical standard). Three countries reported use for legitimate (legal) industrial purposes, all describing manufacture of pharmaceutical products for exportation.

Epidemiology of non-medical use

Eight countries (3 in the Americas, 2 in the Eastern Mediterranean, 1 in the South-East Asia, 1 in the European and 1 in the Western Pacific regions) reported evidence of use of carisoprodol for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived mainly from data on seizures for law enforcement (n = 7), customs (suggesting detection at international border points; n = 3), toxicology reports after deaths (n = 2), toxicology reports from emergency departments (n = 2) and poisons information calls (n = 2). Other sources included drug checking, domestic open-web sales listings, reports submitted to or published by ministries of health and reports related to recreational use.

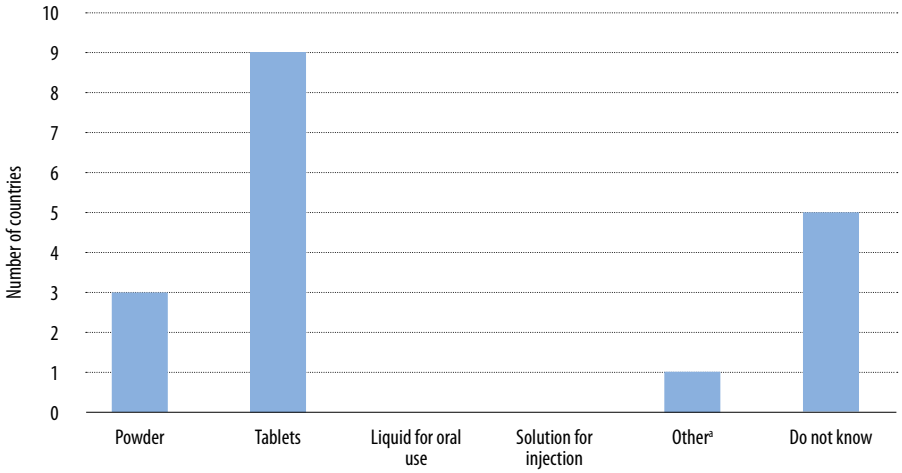
Routes of administration and formulations

The most common reported route of administration was oral (Table A1.30).

Table A1.30. Reported routes of carisoprodol administration

Route of administration	No. of countries
Smoking	0
Oral	9
Inhalation	0
Sniffing	0
Injection	0
Other	0
Do not know	4

The most common formulation of carisoprodol reported was tablets (Fig. A1.15).



[a] Other formulations included capsule.

Fig. A1.15. Formulations of carisoprodol

Perceived negative health impact

Six countries (3 in the Americas, 2 in the European and 1 in the South-East Asia regions) reported that the negative health effect of non-medical consumption of carisoprodol was "especially serious" or "substantial" (Fig. A1.16).

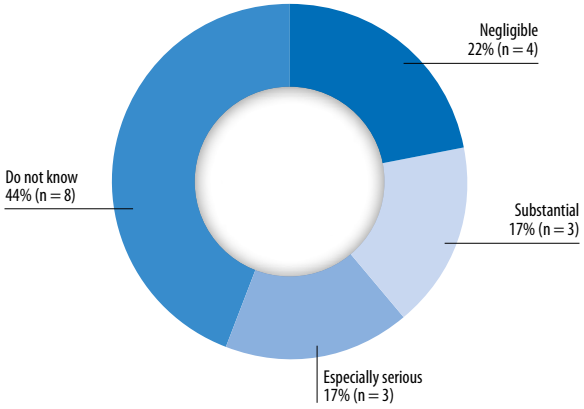


Fig. A1.16. Negative health impacts of non-medical consumption of carisoprodol

Emergency department visits

Three countries (1 in the Americas, 1 in the European and 1 in the South-East Asia regions) were aware of emergency department visits related to carisoprodol. These countries described emergency department presentations by people who had consumed carisoprodol with other substances. Two countries reported the year in which the presentations occurred: 2 presentations in 2024 and 11 presentations in 2022 (all in the European region). Two countries reported presentations in another year: 1 presentation in the Americas Region and 76 presentations in the South-East Asia Region.

The adverse effects (e.g. non-fatal intoxications) seen in patients who presented to emergency departments after use of carisoprodol included headache, dizziness, confusion, hypotension, tachycardia, hallucinations, depression, nausea, vomiting and seizures/convulsions. Other adverse effects reported included abdominal pain, increased C-reactive protein, eosinophilia, hiccups, intentional overdose, pancytopenia, pruritus, rash, somnolence, suicide attempt, urticaria, increased liver enzymes, facial angioedema, tiredness, muscle pain, inflammation, heavy limbs, stupor, coma, respiratory depression, death, reduced consciousness and difficulty in maintaining clear airways.

Deaths

One country (in the Americas Region) reported deaths in which carisoprodol was the only substance involved (n = 1 in 2022; n = 5 in another year). This country also reported deaths in which carisoprodol and other substances were involved (n = 56 in 2023; n = 104 in 2022; n = 117 in another year). One country (in the European Region) reported deaths in which carisoprodol and other substances were involved

(n = 3 in 2024; n = 3 in 2023; n = 4 in another year). One country (in the South-East Asia Region) reported 1 death in another year, in which carisoprodol and other substances were involved.

Drug dependence

No country reported presentations for treatment of drug dependence due to use of carisoprodol.

Current national controls

Thirteen countries (4 in the Western Pacific, 3 in the Americas, 3 in the European, 2 in the Eastern Mediterranean and 1 in the South-East Asia regions) reported that the availability of carisoprodol was controlled under substance-specific legislation, and two countries (1 in the European and 1 in the South-East Asia regions) reported that the availability of carisoprodol was controlled under legislation on analogue or generic drugs.

Illicit manufacture and trafficking

Table A1.31 shows the main reported activities involving carisoprodol.

Table A1.31. Reported activities involving carisoprodol for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	4
Smuggling (from other countries)	4
Internet sales (other or location of sellers and website unknown)	2
Internet sales (from abroad to buyers in the respondent's country)	3
Internet sales (seller or website located in respondent's country)	1
Manufacture of the substance by chemical synthesis	1
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	2
Do not know	9
Other	0

Detection in falsified medicines

Six countries (3 in the Americas, 2 in the Western Pacific and 1 in the European regions) indicated that carisoprodol was detected in counterfeit medicines or other products. The countries reported that carisoprodol was detected in falsified

Flexicamin B12, Piromed Relax, Alvedon (paracetamol), Tamol-X-225, muscle relief products, "Carisoprodol Tablets", "Soma-Dol", "Caridol", unlabelled tablets and cough syrups.

Seizures

Five countries (2 in the Western Pacific, 1 in the Americas, 1 in the European and 1 in the South-East Asia regions) reported seizures in 2024. The number of seizures per country ranged from 1 to 156, and the amounts seized ranged from 30 to 2431 tablets, 17 070 g and 42 819 units (Table A1.32).

Seven countries (2 in the European, 2 in the Western Pacific, 1 in the Americas, 1 in the Eastern Mediterranean and 1 in the South-East Asia regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 323, and the amounts seized ranged from 100 to 13 000 tablets, six parcels, 5272 units and 5469 g.

Four countries (1 in the European, 1 in the Americas and 2 in the Western Pacific regions) reported seizures in 2022. The number of seizures per country ranged from 1 to 423, and the amounts seized ranged from 20–28 323 tablets, 21 131 units and 59 094 g.

Table A1.32. Reported seizures of carisoprodol

Year	No. of countries that reported seizures	No. of seizures
2024	5	243
2023	7	386
2022	4	466

Laboratory capacity

Nineteen of the 25 countries that provided information (7 in the European, 5 in the Americas, 4 in the Western Pacific, 2 in the South-East Asia and 1 in the Eastern Mediterranean regions) reported that they had the laboratory capacity to detect carisoprodol.

Annex 2. List of participants

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Claudia Nannini, International, Constitutional, and Global Health Law

Dilkushi Poovendran (Secretary), Health Products Policy and Standards

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Pradeep Dua, Traditional Complementary, and Integrative Medicine

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The Forty-seventh Meeting of the World Health Organization (WHO)'s Expert Committee on Drug Dependence (ECDD) was convened from 14 to 18 October 2024 and was coordinated from the WHO headquarters in Geneva.

The Forty-seventh WHO ECDD critically reviewed seven new psychoactive substances, comprising one synthetic cannabinoid (hexahydrocannabinol), four novel synthetic opioids (protonitazepyne, metonitazepyne, etonitazepipne, *N*-desethyl isotonitazene), one dissociative-type substance (3-hydroxyphencyclidine) and one cathinone/stimulant (*N*-ethylheptedrone). It also reviewed the medicine carisoprodol. A critical review to consider international scheduling measures was undertaken for each substance so that the Expert Committee could consider whether information about these substances may justify the scheduling or a change in scheduling of a substance in the 1961 or 1971 Conventions.

This report summarizes the findings of the Forty-seventh ECDD meeting.