WHO Technical Report Series

1057

WHO Expert Committee on Drug Dependence

Forty-sixth report

World Health Organization

The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective, reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences. To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

The WHO Technical Report Series makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO. To purchase WHO publications, please contact: WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel. +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int; http://www.who.int/bookorders).

WHO Technical Report Series

1057

WHO Expert Committee on Drug Dependence

Forty-sixth report

WHO Expert Committee on Drug Dependence: forty-sixth report

(WHO Technical Report Series, No. 1057)

ISBN 978-92-4-009246-4 (electronic version)
ISBN 978-92-4-009247-1 (print version)
ISSN 0512-3054

Suggested citation. WHO Expert Committee on Drug Dependence: forty-sixth report. Geneva: World Health Organization; 2024 (WHO Technical Report Series, No. 1057). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

Sales, rights and licensing. To purchase WHO publications, see https://www.who.int/publications/book-orders. To submit requests for commercial use and queries on rights and licensing, see https://www.who.int/copyright.

Contents

Acknowledgements ..... **iv**

Executive summary ..... **vi**

1. Information session **1**

2. Meeting report of the 46th Expert Committee on Drug Dependence **2**
2.1 Welcoming remarks **2**
2.2 Procedural matters **2**
2.3 Updates on ECDD meeting recommendations and outcomes **3**
2.3.1 Recommendations from the 45th ECDD 3
2.3.2 Recommendations of the ECDD Working Group 4
2.3.3 Updates on priorities from international agencies 5
2.4 Recommendations for international control of psychoactive substances **8**
2.4.1 Bromazolam 9
2.4.2 Flubromazepam 10
2.4.3 Butonitazene 12
2.4.4 3-Chloromethcathinone (3-CMC) 14
2.4.5 Dipentylone 15
2.4.6 2-Fluorodeschloroketamine 17
2.5 Recommendations on preliminary reviews (pre-reviews) **19**
2.5.1 Nitrous oxide 19
2.5.2 Carisoprodol 21

3. Critical review and pre-review reports **23**
3.1 Critical review reports **23**
3.1.1 Bromazolam 23
3.1.2 Flubromazepam 35
3.1.3 Butonitazene 47
3.1.4 3-CMC 57
3.1.5 Dipentylone 72
3.1.6 2-Fluorodeschloroketamine 86
3.2 Pre-review reports **101**
3.2.1 Nitrous oxide 101
3.2.2 Carisoprodol 145

Annex 1. Report on the WHO Member State questionnaire for review of psychoactive substances **171**

Annex 2. List of participants **212**

Acknowledgements

The 46th meeting of the Expert Committee on Drug Dependence (ECDD) was organized under the overall direction of Yukiko Nakatani (Division of Access to Medicines and Health Products, WHO, Geneva, Switzerland) and Gilles Forte (WHO). Dilkushi Poovendran (WHO) coordinated the work of the meeting with the support of Thomas Le Ruez and Patricia Gevrey.

The secretariat gratefully acknowledges the technical guidance and input of all contributors (in alphabetical order):

Authors of critical and pre-review reports:
Bromazolam: Giuseppe Cannazza[1], Cinzia Citti[2], Jenny Wiley[3].
Flubromazepam: Giuseppe Cannazza[1], Cinzia Citti[2], Jenny Wiley[3].
Butonitazene: Giuseppe Cannazza[1], Cinzia Citti[2], João Silva[4].
3-CMC: Giuseppe Cannazza[1], Cinzia Citti[2], Alex Krotulski[5].
Dipentylone: Giuseppe Cannazza[1], Cinzia Citti[2], João Silva.
2-Fluorodeschloroketamine: Giuseppe Cannazza[1], Cinzia Citti[2], Jenny Wiley[3].
Nitrous oxide: Giuseppe Cannazza[1], Cinzia Citti[2], David Gorelick[6].
Carisoprodol: Giuseppe Cannazza[1], Cinzia Citti[2], Fabrizio Schifano[7].
Amira Guirguis (Swansea University, United Kingdom), John M Corkery (University of Hertfordshire, United Kingdom), Giuseppe Fioresta (University of Catania, Italy), Davide Arillotta (University of Florence, Italy), Stefania Chiappini (Unicamillus University, Italy), Valeria Catalani (University of Hertfordshire, United Kingdom), Giovanni Martinott (University of Chieti-Pescara, Italy) contributed to the writing of the carisoprodol report.

Analysis and writeup of the Member State Questionnaire was overseen by Suzanne Nielsen with the support of Tina Lam, Myfanwy Graham, and Thomas Le Ruez.

Peer review
Patrick Beardsley, Wim Best, Sandra Comer, Ifeoma Ekwere, Simon Elliott, Raka Jain, Pamela Kaduri, Junichi Kitanaka, Antonio Pascale Prieto, Afarin Rahimi-Movaghar (Co-Chair), Sutisa Thanoi and Jason White.

[1] University of Modena and Reggio Emilia, Italy
[2] Institute of Nanotechnology, National Research Council, Italy
[3] Richmond (VA), USA
[4] University of Porto, Portugal
[5] Center for Forensic Science Research and Education (PA), USA
[6] University of Maryland (MD), USA
[7] University of Hertfordshire, United Kingdom

Provision of data
The 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 Monitoring Centre for Drugs and Drug Addiction (EMCCDA) and from Member States, which contributed to prioritization of substances and provided information to the secretariat on the Member State questionnaire.

Executive summary

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

At its 46th meeting, the ECDD critically reviewed six new psychoactive substances, comprising two benzodiazepines (bromazolam, flubromazepam), one novel synthetic opioid (butonitazene), two cathinone stimulants (3-CMC and dipentylone) and one dissociative-type substance (2-fluorodeschloroketamine). 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. In addition, the meeting pre-reviewed nitrous oxide and carisoprodol, to determine whether the current information justified a critical review.

After the 46th 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)	**Butonitazene**	2-(2-(4-Butoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)-*N*,*N*-diethylethan-1-amine
To be added to Schedule II of the Convention on Psychotropic Substances (1971)	**3-CMC**	1-(3-chlorophenyl)-2-(methylamino)-1-propanone
	Dipentylone	1-(1,3-Benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one
	2-Fluorodeschloroketamine	2-(2-Fluorophenyl)-2-(methylamino)cyclohexan-1-one
To be added to Schedule IV of the Convention on Psychotropic Substances (1971)	**Bromazolam**	8-Bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4] benzodiazepine
Subject to a future critical review	**Carisoprodol**	(2*RS*)-2-[(Carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl) carbamate
To be kept under surveillance	**Flubromazepam**	7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one
	Nitrous oxide	Nitrous oxide, N_2O

1. Information session

On 16 October 2023, before the Expert Committee convened, an information session was held for presentations and questions from representatives of interested parties about data that had been provided on the substances under review.

The session was opened and chaired by Gilles Forte, Secretary of the ECDD.

Dilkushi Poovendran, Technical Officer, described the role and mandate of the ECDD with respect to the international drug control conventions. WHO has the mandate to assess the risks of abuse, dependence and harm to health of psychoactive substances and make recommendations to the Commission on Narcotic Drugs about the appropriate level of international control. When relevant, the ECDD also considers whether a substance has a medical or scientific application. This mandate is reinforced by several resolutions of the United Nations General Assembly and the Commission on Narcotic Drugs. WHO fulfils its mandate through the ECDD in accordance with WHO guidance on the review of psychoactive substances for international control. The processes and procedures were developed by the World Health Assembly, and revisions were approved by the WHO Executive Board in 2010.

The 46th ECDD information session did not receive any written statements for consideration.

2. Meeting report of the 46th Expert Committee on Drug Dependence

The 46th meeting of the WHO ECDD was convened on 16–19 October 2023 and coordinated from WHO headquarters in Geneva, Switzerland.

2.1 Welcoming remarks

Yukiko Nakatani 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. She reiterated 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. She recalled that evidence-based assessment of psychoactive substances as mandated by the international drug control conventions is central to the work of the ECDD. She 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 recalled that the Expert Committee is convened in accordance with WHO's Regulations for Expert Advisory Panels and Committees and the Guidance on WHO review of psychoactive substances for international control. The functions of the ECDD are therefore to review the information available 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.

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.

Before the opening of the meeting, 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 Jason White as Chair, Afarin Rahimi-Movaghar as Co-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 ECDD meeting recommendations and outcomes

2.3.1 Recommendations from the 45th ECDD

The 45th Expert Committee on Drug Dependence, which convened on 10–13 October 2022, made the following recommendations.

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

- 2-Methyl-AP-237
- Etazene
- Etonitazepyne
- Protonitazene

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

- ADB-BUTINACA
- Alpha-PiHP
- 3-MMC

In addition, the Committee recommended that the following substances be kept under surveillance:

- Adinazolam
- Bromazolam
- Zopiclone

The WHO Director-General communicated these recommendations to the United Nations Secretary-General, and the recommendations were presented to the Commission on Narcotic Drugs at its 65th session in December 2022. Subsequently, at its 66th session, on 15 March 2023, the Commission decided by 47 votes to none, with no abstentions, to include 2-methyl-AP-237 in Schedule I of the 1961 Convention (Decision 66/1), to include etazene in Schedule I of the 1961 Convention (Decision 66/2), to include etonitazepyne in Schedule I of the 1961 Convention (Decision 66/3) and to include protonitazene in Schedule I of the 1961 Convention (Decision 66/4).

The Commission decided by 47 votes to none, with no abstentions, to include ADB-BUTINACA in Schedule II of the 1971 Convention (Decision 66/5), to include alpha-PiHP in Schedule II of the 1971 Convention (Decision 66/6) and to include 3-methylmethcathinone in Schedule II of the 1971 Convention (Decision 66/7).

Therefore, all the recommendations made by the 45th ECDD were accepted by the Commission on Narcotic Drugs, effectively placing seven new psychoactive substances under international control.

2.3.2 Recommendations of the ECDD Working Group

The ECDD working group met in May 2023 in preparation for the 46th meeting. The secretariat initiated a process for prioritizing substances by requesting information on harmful psychoactive substances from international agencies and geographically representative Member States and received the nominations for review. The Working Group also considered priorities for collecting data on substances recommended for surveillance by the ECDD.

After review of the information by the secretariat and the ECDD working group, eight substances were recommended by the working group for prioritized ECDD review. The working group also recommended that a discussion paper be drafted on xylazine for consideration at a future working group meeting.

The ECDD secretariat has received a formal request from the Plurinational State of Bolivia for a critical review by the ECDD of coca leaf, in order to consider its scheduling under the 1961 Single Convention on Narcotic Drugs. The ECDD secretariat is taking action on this request.

2.3.3 Updates on priorities from international agencies

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

The priorities of the unit include the provision of normative guidance and technical support on prevention, identification and management of disorders due to use of psychoactive substances, documenting the health and social consequences of substance use, and global monitoring of the health burden due to substance use and of service capacity for treatment of substance use disorders.

In June 2023, the 4th WHO Forum on Alcohol, Drugs and Addictive Behaviours took place in Geneva. The Department finished updating the recommendations on identification and management of substance use disorders as well as major mental health conditions for primary health care and non-specialized health-care settings. The unit secured funding to update guidelines on pharmacotherapy of opioid dependence and community management of opioid overdose. The list of medicines for treatment of substance use disorders has been extended by the Expert Committee on Essential Medicines by the inclusion of acamprosate and naltrexone for treatment of alcohol use disorders, including the extended-release formulation of naltrexone. Another project began on postgraduate education of medical doctors on prevention and management of substance use and substance use disorders.

Opioid-related deaths continue to be a major public health issue. The latest WHO estimate was that there are approximately 450 000 deaths annually due to opioid overdose. An important trend in countries is use of a combination of opioids with stimulants and other substances. Amphetamine-type stimulants are more frequently reported in toxicological analyses of drug overdose. There is also concern about the presence of nitazenes and xylazine as adulterants in common street drugs.

A special initiative on mental health has been initiated in nine countries to support development of treatment systems for substance use disorders. A new project has begun with UNITAID on the feasibility and effectiveness of use of extended-release formulations of buprenorphine in the treatment of opioid dependence.

Cannabis continues to be an important issue in many countries, and many are considering revising their legislation. A second edition of a WHO technical document on the health and social effects of non-medical cannabis use will be published. There is growing evidence that commercialization of cannabis has had significant consequences for health and the prevalence of cannabis use disorders in various segments of populations.

WHO Division of Access to Medicines and Health Products

A recent important development was the launch of the ECDD Repository on 1 June 2023.

The Division is revising 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 their justification. Four domains were identified as priorities for the guidelines: quantification, procurement and supply of medicines; medicine regulation and control; prescribing, dispensing and administration; and education, knowledge and attitude. Systematic reviews of evidence have been conducted in all four domains. The draft guideline is in development.

The second important stream of work is related to the availability of morphine for medical use. A published report on access to medical morphine became available in June 2023, which describes the extent and causes of global differences in access to morphine for medical use, including enablers and barriers to safe access to morphine for medical use and balanced policy to address issues. Three open webinars were organized during Pain Awareness Month, and three short films presented stories from front-line clinical workers for policy-makers.

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 carried out by WHO with support from scientific advisory groups or expert panels. The Commission on Narcotic Drugs has taken decisions to place 78 substances under various schedules of the 1961 and 1971 Conventions since 2014. In addition, five precursors of fentanyl and its analogues and five 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 310 forensic drug testing and toxicology laboratories in 90 countries in the past year. The UNODC Early Warning Advisory is monitoring over 1200 new psychoactive substances reported in 141 countries and territories and is providing evidence for identification of the most harmful, persistent, prevalent novel psychoactive substances (NPS) through its toxicology portal. The sixth in the series of Current NPS Threats reports was recently published, 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 reduction 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 involved in 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 300 cross-coding tools and practical resources from the United Nations system, including WHO and the INCB. The toolkit now has over 56 000 users worldwide. Its resources are organized into 12 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 and scientific 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;
- possiby 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 main priorities 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.

2.4 Recommendations for 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 carries out either a pre-review or critical review. A pre-review is initiated when a proposal and supporting information have been submitted to the Expert Committee by the WHO secretariat, Member States, any member of the Expert Committee or a representative of any other organization invited to participate in the Expert Committee meeting. In the second step, if a meeting of the Committee found that a critical review of a substance was warranted, the secretariat prepares the required material for a thorough review at a future meeting of the Committee.

According to the Guidance *(4)*, 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.

2.4.1 Bromazolam

Substance identification

Bromazolam (IUPAC name: 8-bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3 *a*][1,4]benzodiazepine) is a triazolobenzodiazepine. Bromazolam has been described as a white or crystalline solid and has been identified in tablets, capsules, powders, solutions and chewable candy products ("gummies"). Bromazolam has been identified in falsified pharmaceutical benzodiazepine products.

WHO review history

Bromazolam was critically reviewed at the 45th ECDD meeting. Because of lack of information on its pharmacological effects, it was not recommended for international control but was placed under surveillance. New information on such effects was brought to WHO's attention, in addition to ongoing evidence 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

Bromazolam is a benzodiazepine with relatively high potency and a short–intermediate duration of action. It is structurally related to alprazolam. Like other benzodiazepines, bromazolam binds to γ-aminobutyric acid ($GABA_A$) receptors, and its effects can be reversed by administration of the benzodiazepine receptor antagonist flumazenil.

Unconfirmed online reports by people who use bromazolam describe benzodiazepine-like effects, including hypnotic, sedative, muscle relaxant and euphoric effects.

Dependence potential

No controlled studies in experimental animals or in humans have examined the dependence potential of bromazolam. In view of its pharmacological effects and similarity to other benzodiazepines, however, it would be expected to produce dependence. Online self-reports describe withdrawal symptoms after cessation of chronic use.

Actual abuse and/or evidence of likelihood of abuse

No studies in humans were found of the abuse liability of bromazolam. In an animal model predictive of abuse liability, bromazolam had effects similar to those of midazolam and diazepam, which are controlled under Schedule IV of the Convention on Psychotropic Substances of 1971. The effects were attenuated by pre-administration of the benzodiazepine receptor antagonist flumazenil, confirming bromazolam's action as a benzodiazepine.

Seizures of bromazolam have been reported increasingly in multiple countries in regions. Bromazolam has been analytically confirmed as a causal or contributory agent in several deaths and non-fatal intoxications, and its presence has been confirmed in instances of driving under the influence of drugs. These harms have been reported in multiple countries and regions.

Therapeutic use

Bromazolam is not known to have any therapeutic use, is not listed on the WHO Model Lists of Essential Medicines and has never been marketed as a medicinal product.

Rationale and recommendation

The mechanism of action and ill effects of bromazolam are similar to those of other benzodiazepines, such as alprazolam and diazepam, that are listed under Schedule IV of the Convention on Psychotropic Substances of 1971. Reports of seizures and detection in fatal and non-fatal intoxications have increased over time. There is sufficient evidence of its abuse to conclude that it constitutes a significant risk to public health and has no known therapeutic use.

The Committee recommended that bromazolam (IUPAC name: 8-bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine) be added to Schedule IV of the Convention on Psychotropic Substances of 1971.

2.4.2 Flubromazepam

Substance identification

Flubromazepam (IUPAC name: 7-bromo-5-(2- fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) is a 1,4-benzodiazepine. Flubromazepam is described as a white powder or a crystalline solid and has been found in infused paper forms.

WHO review history

Flubromazepam has not been formally 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 the central nervous system

The chemical structure of flubromazepam is similar to that of other benzodiazepines, including phenazepam. Currently, there is insufficient information on the pharmacological profile of flubromazepam from controlled studies in experimental animals or humans to conclude that it has effects that are similar to those of benzodiazepines that are controlled under the Convention on Psychotropic Substances of 1971.

Online self-reports by people who claim to have used flubromazepam describe sedative, muscle relaxant and euphoric effects and its use to self-manage benzodiazepine withdrawal. There are, however, no clinical reports to confirm such effects.

Dependence potential

No controlled study in experimental animals or humans have addressed the dependence potential of flubromazepam.

Actual abuse and/or evidence of likelihood of abuse

No studies in humans were found of the abuse liability of flubromazepam. People who self-report flubromazepam use describe euphoric effects and other benzodiazepine-like effects that would suggest it has a similar likelihood of abuse, but their use of flubromazepam cannot be confirmed. Results from limited studies in experimental animals suggest abuse liability.

Seizures have been reported in multiple countries in several regions. Although flubromazepam has been detected in several deaths and cases of driving under the influence of drugs, other drugs were also detected, and the contribution of flubromazepam was unclear.

Therapeutic use

Flubromazepam is not known to have any therapeutic use, is not listed on the WHO Model Lists of Essential Medicines and has never been marketed as a medicinal product.

Rationale and recommendation

Flubromazepam is a 1,4-benzodiazepine. Although it is chemically similar to other benzodiazepines listed under Schedule IV of the Convention on Psychotropic Substances of 1971, little information is available on its effects. Few studies in experimental animals and no studies in humans were found on its effects or abuse potential. The limited information on its effects provides insufficient evidence to justify the placement of flubromazepam under international control.

The Committee recommended that flubromazepam (IUPAC name: 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) be kept under surveillance by the WHO ECDD secretariat.

2.4.3 Butonitazene

Substance identification

Butonitazene (IUPAC name: *N,N*-diethyl-2-[(4-butoxyphenyl)methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine), also known as butoxynitazene, is a benzimidazole-derived synthetic opioid. Butonitazene is found as a crystalline solid and a white or yellow-brown powder.

WHO review history

Butonitazene has not been reviewed formally 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 the central nervous system

The chemical structure and pharmacological effects of butonitazene are similar to those of opioid drugs such as etonitazene and isotonitazene that are controlled under Schedule I of the United Nations Conventions on Narcotic Drugs of 1961. Butonitazene is an agonist at μ-opioid receptors and has similar analgesic effects as morphine and fentanyl.

Dependence potential

No studies in experimental animal or humans were found on the dependence potential of butonitazene; however, as it is a μ-opioid receptor agonist, it would be expected to produce dependence.

Actual abuse and/or evidence of likelihood of abuse

No studies on the abuse potential of butonitazene in humans were found. In an animal model predictive of abuse potential, butonitazene had morphine-like effects, which were blocked by the opioid antagonist naltrexone. As it is a μ-opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability.

Butonitazene is reported to be administered by various routes, including smoking, intranasally and by injection. Non-fatal intoxications that involved butonitazene and required hospitalization have been reported.

Seizures of butonitazene have been reported in multiple countries in two regions.

Therapeutic use

Butonitazene is not known to have any therapeutic use, is not listed on the WHO Model Lists of Essential Medicines and has never been marketed as a medicinal product.

Rationale and recommendation

Butonitazene, also known as butoxynitazene, is a synthetic opioid that is liable to abuse and to production of ill effects similar to those of other opioids that are controlled under Schedule I of the Single Convention on Narcotic Drugs, 1961. Its use has been reported in a number of countries. It has no known therapeutic use and is likely to cause substantial harm.

The Committee recommended that butonitazene (IUPAC name: *N,N*-diethyl-2-[(4-butoxyphenyl)methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine), also known as butoxynitazene, be added to Schedule I of the Single Convention on Narcotic Drugs, 1961.

2.4.4 3-Chloromethcathinone (3-CMC)

Substance identification

3-Chloromethcathinone or 3-CMC (IUPAC name: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one), is a synthetic cathinone. 3-CMC has been described as a grey or white solid and as a white powder. It has been identified in capsule, tablet and liquid forms.

WHO review history

3-CMC has not been reviewed formally 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 the central nervous system

3-CMC is a chemical analogue of methcathinone, which is controlled under Schedule I of the United Nations Convention on Psychotropic Substances of 1971. Its structural isomer, 4-CMC, is controlled under Schedule II of the United Nations Convention on Psychotropic Substances of 1971.

In common with other cathinone psychostimulants, 3-CMC has been shown to act via dopamine, serotonin and norepinephrine transporters in the central nervous system to increase the concentrations of these neurotransmitters.

Dependence potential

No controlled experimental studies of the dependence potential of 3-CMC in experimental animals or humans were available; however, clinical admissions associated with dependence to 3-CMC have been reported. Given its action in the central nervous system, 3-CMC would be expected to produce a state of dependence similar to that produced by amphetamine and other psychostimulants.

Actual abuse and/or evidence of likelihood of abuse

No controlled studies of the abuse potential of 3-CMC in experimental animals or humans were available. In experimental animals, 3-CMC produced locomotor effects consistent with a psychostimulant.

Cases of intoxication with 3-CMC alone and with other drugs requiring hospitalization have been reported. The adverse effects included agitation, restlessness, seizures, high blood pressure, sweating, and chest pain. These adverse effects are similar to those of other psychostimulants, such as amphetamine and various cathinones. Fatal intoxications involving 3-CMC have been documented, including cases in which 3-CMC was the only substance identified. It is reported to be administered by various routes, including smoking, intranasally and by injection.

3-CMC has been detected in an increasing number of countries in most regions of the world. Seizures of 3-CMC have been reported in multiple countries and regions, with recent increases coinciding with international control of 4-CMC.

Therapeutic use

3-CMC is not known to have any therapeutic uses and has never been marketed as a medicinal product.

Rationale and recommendation

3-Chloromethcathinone or 3-CMC is a synthetic cathinone with effects similar to those of other synthetic cathinones, such as mephedrone and 4-CMC, which are listed as Schedule II substances under the Convention on Psychotropic Substances of 1971. Its mode of action and effects are similar to those of other cathinones. There is evidence of use of 3-CMC in a number of countries and regions, where it has resulted in fatal and non-fatal intoxications. The substance causes substantial harm, constitutes a substantial risk to public health and has no therapeutic use.

The Committee recommended that 3-chloromethcathinone or 3-CMC (IUPAC name: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.4.5 Dipentylone

Substance identification

Dipentylone or *N*-methylpentylone (IUPAC name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one, also known as *N,N*-dimethylpentylone, dimethylpentylone or bk-DMBDP) is a synthetic cathinone. It is distributed mainly as crystals or tablets.

WHO review history

Dipentylone has not been reviewed formally 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 the central nervous system

In common with other cathinone psychostimulants, dipentylone has been shown to act via dopamine, serotonin and norepinephrine transporters in the central nervous system to increase the concentrations of these neurotransmitters. Online self-reports describe insomnia, hallucinations, paranoia and confusion after its use. Adverse effects documented in clinical presentations include agitation and tachycardia. These effects are consistent with a psychostimulant mechanism of action.

Dependence potential

No controlled experimental studies of the dependence potential of dipentylone in experimental animals or humans were available. In view of its action in the central nervous system, however, dipentylone would be expected to produce a state of dependence similar to that produced by amphetamine and other psychostimulants.

Actual abuse and/or evidence of likelihood of abuse

Studies in experimental animals demonstrate that dipentylone has an abuse potential similar to that of methamphetamine, which is listed under Schedule II of the Convention on Psychotropic Substances of 1971, and cocaine, which is listed under Schedule I of the Convention on Narcotic Drugs of 1961. Dipentylone has been shown to produce locomotor stimulant effects in animal models.

No controlled studies on the abuse potential of dipentylone in humans were identified.

Non-fatal intoxications involving dipentylone that required hospitalization have been reported, and fatal intoxications have been reported by a number of countries, with at least one case in which no other substance was involved. Cases of driving under the influence of dipentylone have been reported by some countries.

Seizures of dipentylone have been reported in a number of countries and regions. Dipentylone appears to be commonly sold as cocaine or MDMA.

Therapeutic use

Dipentylone is not known to have any therapeutic uses and has never been marketed as a medicinal product.

Rationale and recommendation

Dipentylone or *N*-methylpentylone is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants, such as methamphetamine that are listed under Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the likelihood of abuse, and it poses a substantial risk to public health. It has no known therapeutic use.

The Committee recommended that dipentylone or *N*-methylpentylone (IUPAC name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.4.6 2-Fluorodeschloroketamine

Substance identification

2-Fluorodeschloroketamine (IUPAC name: 2-(2-fluorophenyl)-2-(methylamino) cyclohexan-1-one) is an arylcyclohexylamine that is chemically related to the dissociative anaesthetic ketamine. It has been described as a brown oil in its free base form or as a crystalline solid or white powder as a salt. It has been identified in some food products (chocolates).

WHO review history

2-Fluorodeschloroketamine has not been reviewed formally 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 the central nervous system

The mechanism of action of 2-fluorodeschloroketamine is uncertain, but it has effects similar to those of *N*-methyl-D-aspartate receptor antagonists such as phencyclidine, which are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Effects documented during clinical admissions due to 2-fluorodeschloroketamine intoxication include dissociation, confusion,

agitation, tachycardia and hypertension. Unverified reports from people who use 2-fluorodeschloroketamine describe hallucinogenic and dissociative effects. The clinical and self-reported effects of 2-fluorodeschloroketamine are consistent with the effects of phencyclidine.

Dependence potential

No controlled studies in experimental animals or humans were found on the dependence potential of 2-fluorodeschloroketamine; however, clinical admissions for dependence on 2-fluorodeschloroketamine have been reported in various countries and regions.

Actual abuse and/or evidence of likelihood of abuse

Studies in experimental animals indicate that 2-fluorodeschloroketamine has behavioural (locomotor) effects consistent with central nervous system stimulation. Such studies confirm that it has rewarding properties and effects predictive of abuse liability.

Cases of intoxication that involved 2-fluorodeschloroketamine and required hospitalization have been reported. The adverse effects included central nervous system effects such as dissociation, confusion, agitation, combativeness, nystagmus, hallucinations and impaired consciousness, loss of consciousness and cardiovascular effects such as tachycardia and hypertension. Fatal intoxications involving 2-fluorodeschloroketamine have been documented, including at least one case in which no other substance was involved. 2-Fluorodeschloroketamine has been analytically confirmed in people driving under the influence of drugs and in clinical admissions due to drug intoxication. It is reported to be administered by various routes including orally, intranasally and by injection.

Seizures have been reported in a number of countries in several regions.

Therapeutic use

2-Fluorodeschloroketamine is not known to have any therapeutic use, is not listed on the WHO Model Lists of Essential Medicines and has never been marketed as a medicinal product.

Rationale and recommendation

2-Fluorodeschloroketamine has effects similar to those of dissociative substances such as phencyclidine, which are controlled under Schedule II of the Convention

on Psychotropic Substances of 1971. The results of studies in experimental animals indicate a high likelihood of abuse. There is evidence that this substance is used in a number of countries in several regions. 2-Fluorodeschloroketamine causes substantial harm, including impaired driving, emergency department presentations and deaths. It has no known therapeutic use.

The Committee recommended that 2-fluorodeschloroketamine (IUPAC name: 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.5 Recommendations on preliminary reviews (pre-reviews)

2.5.1 Nitrous oxide

Substance identification

Nitrous oxide (IUPAC name: Nitrous oxide, N_2O) is an inhalational anaesthetic marketed under a range of trade names as both a single ingredient gas and in multi-ingredient preparations. It is also manufactured for industrial use, including in food production, as small metal canisters, bulbs and larger cylinders. It is described as a colourless gas.

WHO review history

Nitrous oxide is not currently under international control and has never been reviewed by the ECDD. Information was brought to WHO's attention by a Member State of increased nonmedical use, such that it presented a risk to public health.

Similarity to known substances and effects on the central nervous system

Nitrous oxide appears to have multiple mechanisms of action that are not entirely understood. There is some evidence for effects on opioid, GABAergic, glutamatergic and other neurotransmitter systems. Nitrous oxide produces anaesthesia, analgesia and, in laboratory studies with humans, subjective effects such as perceptual distortion, paranoia, delusions, anhedonia and cognitive disorganization.

Dependence potential

Acute and chronic tolerance to the effects of nitrous oxide have been documented in experimental animals, with signs of withdrawal when exposure was ended abruptly. Animals that were tolerant to nitrous oxide were partially cross-tolerant to ethanol but not to barbiturates or morphine.

Laboratory studies in humans provide evidence of tolerance to some effects of nitrous oxide, but the degree of tolerance varied according to the effect and between individuals. Epidemiological and clinical studies provide evidence of dependence.

Actual abuse and/or evidence of likelihood of abuse

The evidence from studies in experimental animals on the likelihood of abuse of nitrous oxide is inconsistent.

The abuse potential of nitrous oxide has been reported since the 19th century, including its euphoric effects and ability to cause auditory and visual distortions. Nitrous oxide was originally promoted for recreational use as "laughing gas"; however, laboratory studies with humans have produced inconsistent results on abuse liability.

The global prevalence of non-medical use of nitrous oxide is unknown. Reports from several countries indicate that nonmedical use is highest among adolescents and young adults, and evidence from some countries indicates an increase in use in recent years. Nitrous oxide used nonmedically is typically obtained from legal manufacturers, with no evidence of illicit manufacture and minimal evidence of cross-border trading.

Nitrous oxide use has been implicated in cases of impaired driving. Deaths directly related to nonmedical use of nitrous oxide appear to be rare and to be due to intended or unintended asphyxia. Long-term exposure can result in neurological and haematological toxicity.

Therapeutic use

Nitrous oxide is widely used globally for analgesia and sedation during childbirth and in painful short procedures in dentistry and emergency medicine. It is used commonly as a supplementary agent in anaesthesia. Nitrous oxide is listed on the 2023 WHO Model List of Essential Medicines and the Essential Medicines List for Children as an inhalational anaesthetic. Clinical trials of nitrous oxide are being conducted to explore its value as a medication for other indications such as treatment-resistant depression and management of alcohol withdrawal symptoms.

Rationale and recommendation

Nitrous oxide is a widely used inhalation anaesthetic and is listed on the 2023 WHO Model List of Essential Medicines and Essential Medicines List for Children.

While the Committee acknowledged the concerns raised by some countries, it recommended that nitrous oxide not proceed to critical review because of the absence of evidence of illicit manufacture and of common trading across borders, and in recognition of its global therapeutic value.

The Committee recommended that nitrous oxide not proceed to critical review but be kept under surveillance by the WHO secretariat.

2.5.2 Carisoprodol

Substance identification

Carisoprodol (IUPAC name: 2-[(carbamoyloxy)methyl]-2-methylpentyl(1-methylethyl)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. The Committee did not recommend critical review of carisoprodol at that time, 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 information was received from an international agency that suggested a significant increase in the reported number of trafficking cases and seizures involving carisoprodol.

Similarity to known substances and effects on the central nervous system

Carisoprodol is an analogue of meprobamate and has effects similar to those of other central nervous system depressants such as meprobamate, pentobarbital, diazepam and chlordiazepoxide that are listed under schedules III and 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, the therapeutic effects of carisoprodol appear to be due to modulation of $GABA_A$ receptors 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 the potential for dependence on carisoprodol is considered to be similar to that of barbiturates and benzodiazepines. Tolerance, withdrawal and craving have been documented in humans, and increasing numbers of cases of carisoprodol dependence have been documented in pharmacovigilance reporting systems.

Actual abuse and/or evidence of likelihood of abuse

In animal models indicative of abuse liability, the effects of carisoprodol were similar to those of pentobarbital, chlordiazepoxide and meprobamate in a dose-dependent manner. In humans, carisoprodol produces central nervous system depressant effects, including drowsiness, sedation, confusion and coma.

Public health harm associated with use of carisoprodol has included cases of driving under the influence of the drug.

Nonmedical use of carisoprodol is widely documented in multiple countries and regions, including in combination with opioids and/or benzodiazepines. The incidence of poisoning and other public health harm has been reported to have decreased in some countries after increased restrictions on carisoprodol prescription or removal of the drug from the market.

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 use in some countries because of concern about increased rates of diversion, nonmedical use, dependence, intoxication and psychomotor impairment.

Rationale and recommendation

The increasing evidence of misuse and abuse of carisoprodol in a number of countries is a growing cause for concern. Carisoprodol has been shown to produce a state of dependence and central nervous system depression. It has only limited medical use.

The Committee recommended that carisoprodol be subject to a future critical review.

3. Critical review and pre-review reports

3.1 Critical review reports

3.1.1 Bromazolam

1. Substance identification

A. International Nonproprietary Name (INN)

Not assigned

B. Chemical Abstracts Service (CAS) registry number

71368-80-4

C. Other chemical names

8-Bromo-1-methyl-6-phenyl-4H-s-triazolo[4,3-*a*][1,4]benzodiazepine

8-Bromo-1-methyl-6-phenyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine

DE(chloro)-bromo-alprazolam

8-Bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine (ACI)

8-Bromo-1-methyl-6-phenyl-4H-s-triazolo[4,3-*a*][1,4]benzodiazepine

Canonical SMILES
BrC=1C=CC2=C(C1)C(=NCC3=NN=C(N32)C)C=4C=CC=CC4

InChI
InChI=1S/C17H13BrN4/c1-11-20-21-16-10-19-17(12-5-3-2-4-6-12)14-9-13(18)7-8-15(14)22(11)16/h2-9H,10H2,1H3

InChI key
KCEIOBKDDQAYCM-UHFFFAOYSA-N

D. Trade names

Bromazolam is sold under its own name.

E. Street names

Bromazolam is sold as tablets or powders under its own name or as XLI-268 *(1)*.

NPS in the benzodiazepines class can be purchased mainly in the drug online market under various street names such as "legal benzodiazepines", "designer benzodiazepines" and "research chemicals" *(2)*.

F. Physical appearance

Bromazolam has been described as a white solid *(3)* or a crystalline solid *(4)*.

Bromazolam has been found in orange or green tablets and as a yellow powder *(5)*.

G. WHO review history

Bromazolam was reviewed critically at the 45th ECDD meeting, when it was recommended that it be kept under surveillance by the WHO secretariat.

2. Chemistry

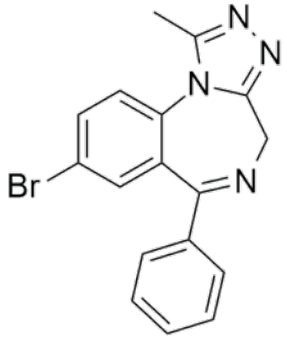
A. Chemical name

IUPAC name:
8-bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

CA Index name:
4H-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine, 8-bromo-1-methyl-6-phenyl-(9CI, ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{17}H_{13}BrN_4$

Molecular weight: 353.22 g/mol

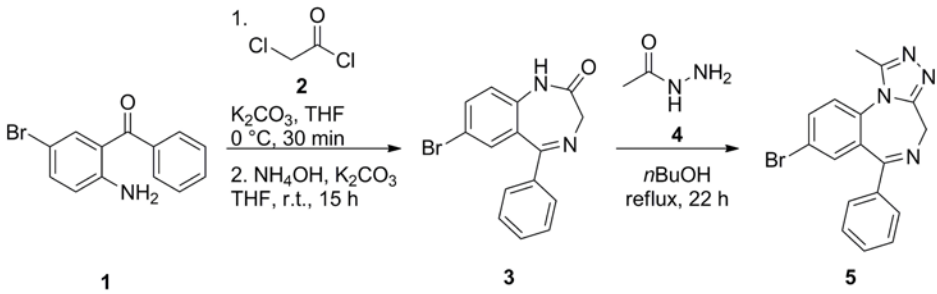
C. Stereoisomers

No stereoisomers of bromazolam have been described.

D. Methods and ease of illicit manufacture

Bromazolam is a triazolo-benzodiazepine and is structurally related to the internationally controlled substance alprazolam, in which the chlorine atom has been replaced with a bromine atom. Bromazolam is also structurally related to flubromazolam, from which it differs in lack of a fluorine atom on the C2 of the phenyl ring. Bromazolam is also structurally similar to pyrazolam, in which the pyridinyl group has been replaced by a phenyl group *(2)*.

Bromazolam was first synthesized in the 1970s by Hester and von Voigtlander *(6)*. A convenient method of synthesis has been reported in the patent literature *(3,7–9)*. Introduction of a triazole ring into the 1,4 benzodiazepine precursor (**3**) with hydroxyacetic acid hydrazide (**4**) gives bromazolam (**5**) (Hester & von Voigtlander, 1979). The 1,4 benzodiazepine precursor (**3**) can be prepared by cyclization of 2-amino-5-bromobenzophenone (**1**) with chloroacetylchloride (**2**), followed by treatment with ammonia to promote ring closure through imine formation, all in a one-pot procedure (scheme 1) *(10)*.



Scheme 1. Synthesis of bromazolam

No information was available on the routes of synthesis used for the bromazolam products circulating on the market. The synthesis reported in the literature, although simple, requires a chemical synthetic laboratory and qualified personnel.

E. Chemical properties

Melting-point
272.0–275 °C (3,6)

Boiling-point
No information was found.

Solubility
Bromazolam is soluble in dimethylformamide (DMF) at a concentration of 30 mg/mL, in dimethyl sulfoxide at a concentration of 20 mg/mL, in ethanol at a concentration of 10 mg/mL, in methanol at a concentration of 1 mg/mL and in a 1:1 mixture of DMF:phosphate-buffered saline (pH 7.2) at a concentration of 0.5 mg/mL *(4)*.

F. Identification and analysis

Synthetic bromazolam was characterized by proton and carbon nuclear magnetic resonance (1H NMR and ^{13}C NMR), mass spectrometry (MS) and infra-red spectroscopy (IR) *(3)*. Bromazolam is available as a reference material that can be purchased from various commercial suppliers and used in routine analysis for forensic and clinical investigations *(4)*.

Analytical methods for identification of bromazolam in seized sample matrices include IR, ^{1}H NMR, gas chromatography–MS and liquid chromatography (LC)-MS *(11, 12)*.

Bromazolam was analysed in urine with an immunochemical assay *(13)*, in human blood and urine by LC coupled with either high-resolution MS or triple-quadrupole MS *(11, 12, 14)*.

3. Ease of conversion into controlled substances

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

4. General pharmacology

A. Routes of administration and dosage

Seizures by law enforcement personnel indicate that bromazolam is typically formulated in tablets or as a powder *(5)*. Oral use (e.g. tablets, capsules or powder formulations in solutions or mixed into food) has been reported in online forums *(15–17)*. Bromazolam-containing chewable candy products ("gummies") have also been observed *(17)*. While injection is assumed to have been used from the presence of a syringe filled with bromazolam-containing

solution next to an overdose victim *(5)*, this route of administration does not appear to be common.

No studies were found of human dosage; however, one informational website has categorized doses according to their intoxicating effects as "light" (0.5–1 mg), "common" (1–2 mg) and "strong" (2–≥ 4 mg). Forr comparison, the website lists the following doses for diazepam: "light" (2.5–5 mg), "common" (5–15 mg) and "heavy" (15–30 mg) *(18)*. A review of novel psychoactive benzodiazepines gave 1 mg as a "typical recreational dose" *(19)*. The onset of effects is estimated to occur 15–45 min after administration, the duration of action is 5–8 h, and the after-effects last for 1–12 h *(20)*. The basis for this information is not clear, and, given its anecdotal nature, caution is suggested in interpreting it.

B. Pharmacokinetics

In the only study available, the pharmacokinetics of bromazolam was studied in pooled human liver S9 fractions, with further analysis of authentic blood and urine samples from two patients *(21)*. The primary metabolic reactions were hydroxylation, glucuronidation and combinations of the two, resulting in eight metabolites. Two prominent monohydroxylated metabolites were formed, tentatively identified as 4-hydroxylated bromazolam and a-hydroxy bromazolam, as well as one dehydroxylated metabolite, α-4-dihydroxy-bromazolam. Glucuronidation resulted in a-hydroxy glucuronide and *N*-glucuronide as the most abundant phase-II metabolites. The parent compound was detected in the urine of both patients, whereas the monohydroxylated metabolites were detected in only one. Recommended screening targets in urine were the parent compound and the α-hydroxy metabolite if conjugate cleavage was performed or a-hydroxy glucuronide and N-glucuronide if it was not. Isoenzymes involved in phase I metabolism included CYP2B6, CYP2C19, CYP3A4, CYP3A5 and CYP2C9, whereas phase II metabolism involved the isoenzymes UGT1A4 and UGT2B10.

C. Pharmacodynamics

In one study of the in-vitro binding and functional activity of bromazolam at $GABA_A$ (α1β3γ2) receptors expressed in human embryonic kidney (HEK) cells *(22)*, bromazolam displaced the tritiated benzodiazepine ligand, [^{3}H] flunitrazepam, with an affinity (K_i) of 54 (± 17) nM when GABA was present in the assay and 1,750 (± 440) nM when GABA was absent. Bromazolam also enhanced $GABA_A$ receptor signaling with an EC_{50} of 7.62 ± 0.82 nM and an E_{max} of 88.0 ± 9.7%. Diazepam produced similar results in the binding and functional assays.

These results are consistent with those of a single published study on the pharmacodynamics of bromazolam *(23)*. In this study, bromazolam was tested for its binding to a subunits of the g-aminobutyric acid type A ($GABA_A$) / benzodiazepine receptor complex. Affinity for compounds in HEK cell membranes expressing recombinant $GABA_A$/benzodiazepine receptor subtypes (α1β3γ2, α2β3γ2, α3β3γ2, α4β3γ2, α5β3γ2 and α6β3γ2) was measured. Bromazolam was non-selective for the α subunits, with measurable binding affinity at receptors containing a1 (K_i = 2.8 nM), α2 (K_i = 0.69 nM) and α5 (K_i = 0.62 nM) subunits.

In summary, the profile of bromazolam in these assays is consistent with the typical benzodiazepine mechanism of action: positive allosteric modulation of $GABA_A$ receptor functioning via binding to a site within the $GABA_A$ receptor complex (presumably, the benzodiazepine receptor). These in-vitro results are also consistent with the finding that bromazolam acted similarly to known benzodiazepines in vivo in a drug discrimination assay in rats (see section 8A).

5. Toxicology

No studies on the preclinical toxicology of bromazolam were available.

6. Adverse reactions in humans

The presence of measurable concentrations of bromazolam in post-mortem blood samples has been reported in Canada, Finland, and the USA *(5, 24, 25)*; however, other drugs were also detected in many of the cases, and the extent to which bromazolam contributed to the deaths was not specified. In Germany, two patients with confirmed bromazolam use were found unconscious or minimally responsive *(21)*. Bromazolam has also been reported in blood samples from impaired drivers in the USA *(24, 26)*. The reports do not provide details of the physical or behavioural effects of bromazolam use.

People who used bromazolam described its effects as "hypnotic" and "sedative" *(15)* and referred to its "muscle relaxing" and "pain relieving" properties *(17)*. Other reported effects include euphoria, increased confidence and empathy *(27)*. Some people who used bromazolam reported amnesia, while others stated that amnesia was less common with bromazolam than with other benzodiazepines *(28)*. Posts on online forums describing self-reported experience of use of bromazolam 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

The abuse potential of bromazolam at 0.1–3 mg/kg was evaluated in male rats trained to discriminate the benzodiazepine midazolam in a standard two-lever drug discrimination study *(29)*. Like midazolam and diazepam, bromazolam resulted in full dose-dependent substitution for the 0.3 mg/kg training dose of midazolam, with an ED_{50} (± 95% confidence interval [CI]) of 0.54 (0.26 ; 1.12) mg/kg. In comparison, the ED50 (± 95% CI) was 0.09 (0.06; 0.14) mg/kg for midazolam and 0.66 (0.40 ; 1.12) mg/kg for diazepam. At the dose range tested, bromazolam did not affect response rates. The midazolam-like effects of bromazolam at 3 mg/kg were significantly attenuated by pre-administration of the benzodiazepine receptor antagonist flumazenil at 1 mg/kg. Morphine, tested as a negative control, did not produce a response on the midazolam-associated lever at doses that suppressed the overall response rate.

B. Studies in humans

No information was found.

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

There is no known therapeutic use for bromazolam.

10. Listing on the WHO Model List of Essential Medicines

Bromazolam 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)

Bromazolam has no known marketing authorizations.

12. Industrial use

Bromazolam has no known industrial use.

13. Non-medical use, abuse and dependence

Bromazolam appeared on the European recreational drug market in 2016 in Sweden and in 2019 in the USA *(24, 30)*. In addition to intentional use of bromazolam for its benzodiazepine-like psychoactive effects (see section 6), some people have reported self-medication with bromazolam for indications such as anxiety, to aid sleep and to reduce stimulation caused by another drug such as methamphetamine *(17, 31)*. Bromazolam has been detected in formulations that contain combinations of benzodiazepines in a single preparation (e.g. tablet, capsule, powder), including preparations falsely labelled as legal prescription drugs (e.g. alprazolam, diazepam, zolpidem) *(27, 32)*. The compound has been used in combination with other drugs, including fentanyl, other opioids and methamphetamine *(17, 24, 25, 33)*.

The prevalence of chronic use of and dependence on bromazolam has not been reported. On online forums, several people have reported difficulty in withdrawing from bromazolam after chronic use, and at least one case of withdrawal-associated psychosis and hallucinations was reported after bromazolam was taken repeatedly in combination with phenibut *(31, 34, 35)*. These reports should be considered anecdotal, as no analytical confirmation of chronic use of bromazolam (or its sole use) was reported.

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

Since 2020, bromazolam has been confirmed analytically in post-mortem samples as well as in samples collected from impaired drivers in Canada, Europe and the USA. It has also been detected in product samples submitted to Welsh laboratories. In Finland, bromazolam was found in a post-mortem blood sample with other benzodiazepines *(5)*. In Germany, bromazolam was present in biological samples from two patients, one of whom was found unconscious and one of whom was "confused and slow to respond" *(21)*. In the USA as of June 2022, bromazolam was confirmed analytically in more than 250 cases, comprising 236 detections in post-mortem blood and 14 in biological samples from impaired drivers *(24)*. While no additional information was available on the clinical course of the cases or on any other drugs present, the average concentration of bromazolam in post-mortem blood samples was 65 ng/mL (± 79 standard deviation). In the samples from impaired drivers, the average blood concentration was 61 ng/mL (± 47 standard deviation) *(24)*. Between October 2020 and March 2023, 11 cases

(seven post-mortem) of analytically confirmed bromazolam were reported by the USA to the Early Warning System Tox-Portal *(36)*. Bromazolam was designated as contributory (medium) on the causality scale used in the system in all but one case (for which no determination was made). Bromazolam was the only substance detected in half of the cases. In 2022, bromazolam was the sole (or one of only a few) substance(s) detected in over 200 samples analysed by Welsh authorities *(27)*. A substantial number of products were falsely labelled as an approved prescription benzodiazepine (e.g., diazepam, alprazolam, zolpidem).

Bromazolam has also been detected in has been detected in Scottish prisons *(37)*. Of the 475 samples containing novel benzodiazepines seized between February 2019 and January 2023, bromazolam alone was identified in 38 samples and bromazolam in combination with another novel benzodiazepine was found in an additional 5 samples. Samples included tablets and powder in the early part of the sampling period; however, visitation restriction during the COVID-19 pandemic was associated with increased formulation as infused paper/cards that were sent via the mail.

15. Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

The first documented seizure of bromazolam in Europe was in Sweden in 2016 *(38)*, while reports first appeared in the USA in 2019 *(24)*. In the USA, its detection increased from 1% of samples in the first quarter of 2021 to 13% in the second quarter of 2022 and to 37.4% in the second quarter of 2023 *(38, 39)*. Samples containing bromazolam submitted to an anonymous testing site (from 2020 to the present) were received from Austria (n=1), China and other Asian countries (n=19), Germany (n=1), India (n=1), Switzerland (n=6), the United Kingdom (n=1) and the USA (n=77) *(40)*. As submission of samples was voluntary, the distribution of sites of origin may not represent the global distribution or trafficking of bromazolam.

Detection of bromazolam with fentanyl has increased dramatically: 75% of bromazolam-positive samples in the USA also contained fentanyl in the months before a trend report was issued in June 2022 *(24)*. Similarly, fentanyl was detected in 88% of 41 post-mortem bromazolam-positive samples collected between July 2020 and December 2021 in Canada *(25)*. In these cases, bromazolam was the only benzodiazepine detected in 41% (n=17) of the cases.

17. Current international controls and their impact

Bromazolam is not currently under international control.

18. Current and past national controls

Bromazolam is classified as a schedule IV substance under Canadian law and is regulated under psychoactive drug control regulations in Germany and the United Kingdom. Recently, the Finnish Medicines Agency listed bromazolam as a new substance to be subjected to formal surveillance *(41)*. To prepare a response to WHO queries after last year's critical review of bromazolam, the US Food and Drug Administration published a "Request for comments" concerning the abuse potential of this drug *(42)*. Bromazolam does not appear to be controlled under national regulations in other countries.

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

Novel psychoactive substances were found in 65 chocolate samples submitted to the National Anti-Drug Laboratory of China for analysis *(43)*. Of these, two contained bromazolam. Information on the source of the chocolate samples or on prevalence was not provided. The presence of bromazolam and other novel psychoactive substances in food may increase the risk of unintentional exposure (including paediatric).

References

1. Narcotics Act (373/2008), section 3a: Bromazolam. Helsinki: Finnish Medicines Agency; 2021 (https://finlex.fi/en/laki/kaannokset/2008/en20080373?search[type]=pika&search[pika]=373%2F2008).
2. Orsolini L, Corkery JM, Chiappini S, Guirguis A, Vento A, de Berardis D et al. "New/designer benzodiazepines": an analysis of the literature and psychonauts' trip reports. Curr Neuropharmacol. 2020 ;18:809–37. doi:10.2174/1570159X18666200110121333.
3. Cook JM, Huang S, Edwankar R, Namjoshi OA, Wang ZJ. Selective agents for pain suppression. US Patent US20100317619A1 (https://patents.google.com/patent/US20100317619A1/en).
4. Bromazolam (item no. 22665). Ann. Arbor (MI): Cayman Chemical Company; 2022 (https://www.caymanchem.com/product/22665/bromazolam, accessed 16 June 2022).
5. Bromazolam assessment form. Finnish Medicines Agency, 2021. Brussels: European Union; 2021
6. Hester JB Jr, von Voigtlander P. 6-Aryl-4H-s-triazolo[4,3-a][1,4]benzodiazepines. Influence of 1-substitution on pharmacological activity. J Med Chem. 1979;22:1390–8. doi: 10.1021/jm00197a021.
7. Cook JM, Edwankar RV, Edwankar CR, Huang S, Jain H, Yang J et al. Selective anticonvulsant agents and their uses. US Patent T08025. US Utility, Serial # 12/725,763, filed 17 March 2010.
8. Cook JM, Huang Q, He X, Li X, Yu J, Han D et al. Anxiolytic agents with reduced sedative and ataxic effects. US Patent US20040082573A1 (https://patents.google.com/patent/US20040082573A1/en).

9. Cook JM, Zhou H, Huang S, Sarma PVVS, Zhang C (2006) Stereospecific anxiolytic and anticonvulsant agents with reduced muscle-relaxant, sedative-hypnotic and ataxic effects. US Patent US20060003995A1 (https://patents.google.com/patent/US20060003995A1/en).

10. Safei-Ghomi J, Hatami A. Facile and efficient one-pot protocol for synthesis of 5-phenyl-1,4-benzodiazepine-2-one derivatives. Synth Commun. 2008;38:297–302. doi:10.1080/00397910701750078.

11. Bromazolam. Willow Grove (PA) NMS-Labs; 2020.

12. Bromazolam. Springfield (VA): Drug Enforcement Administration, Special Testing and Research Laboratory; 2019 (https://www.swgdrug.org/Monographs/Bromazolam.pdf).

13. Erdmann J, Mossmann B. Cross reactivity of the CEDIA and HEIA benzodiazepine kits for 29 designer benzodiazepines and tofisopam. Drug Test Anal. 2021;13;1686–8. doi:10.1002/dta.3111.

14. Sofalvi S, Lavins E, Kaspar C, Michel H, Michell-Mata C, Huestis M et al. Development and validation of an LC-MS-MS method for the detection of 40 benzodiazepines and three Z-drugs in blood and urine by solid-phase extraction. J Anal Toxicol. 2020;44(7):208–17. Doi:10.1093/jat/bkaa072.

15. Bromazolam. Bluelight; 2020 (https://bluelight.org/xf/threads/bromazolam.887294/, accessed 2 August 2022).

16. First time bromazolam. Bluelight; 2022 (https://bluelight.org/xf/threads/first-time-bromazolam.922459/, accessed 2 August 2022).

17. Suboxone andbromazolam? Bluelight; 2022 (https://bluelight.org/xf/threads/suboxone-and-bromazolam.922688/, accessed 2 August 2022).

18. Diazepam. Springfield (PA): Tripsit; 2022 (https://drugs.tripsit.me/diazepam, accessed 22 August 2022).

19. Manchester KR, Lomas EC, Waters L, Dempsey FC, Maskell PD. The emergence of new psychoactive substance (NPS) benzodiazepines: a review. Drug Test Anal. 2018;10:37–53. doi:10.1002/dta.2211.

20. Bromazolam. Tripsit; 2022 (https://drugs.tripsit.me/bromazolam#dose, accessed 25 July 2022).

21. Wagmann L, Manier SK, Felkse C, Gampfer TM, Richter MJ, Eckstein N et al. Flubromazolam-derived designer benzodiazepines: toxicokinetics and analytical toxicology of clobromazolam and bromazolam. J Anal Toxicol. 2021;45(9):1014–27. doi:10.1093/jat/bkaa161.

22. Janowsky A. Bromazolam. Portland (OR): Oregon Health and Science University; 2022

23. Clayton T, Poe MM, Rallapalli S, Biawat P, SaviĆ MM, Latyon T et al. A review of the updated pharmacophore for the alpha 5 GABA(A) benzodiazepine receptor model. Int J Med Chem. 2015:430248. doi:10.1155/2015/430248.

24. Papsun DM, Krotulski AJ, Mastrovito R, Walton SE, Logan BK. Bromazolam prevalence surging across the United States driven in part by increasing detections alongside fentanyl. Florida International University, Center for Forensic Science Research and Education; 2022 (https://www.cfsre.org/images/content/reports/public_alerts/Public-Alert_Bromazolam_NPS-Discovery_061522.pdf, accessed 2 August 2022).

25. Merette SAM, Thériault S, Piramide LEC, Davis MD, Shapiro AM. Bromazolam blood concentrations in postmortem cases – A British Columbia perspective. J Anal Toxicol. 2023;47:38–92. doi:10.1093/jat/bkad005.

26. Papsun DM, Chan-Hosokawa A, Lamb ME, Logan B. Increasing prevalence of designer benzodiazepines in impaired driving; a 5 year analysis from 2017–2021. J Anal Toxicol. 2023. doi:10.1093/jat/bkad036.

27. Bromazolam. Cardiff: Welsh Emerging Drugs and Identification of Novel Substances Project; 2023 (https://www.wedinos.org/sample-results#mylocation, accessed 17 July 2023).

28. Bromazolam review – it's legit. San Francisco (CA): Reddit; 2022 (https://www.reddit.com/r/researchchemicals/comments/uqiy78/bromazolam_review_its_legit/, accessed 2 August 2022).

29. Paronis CA. Bromazolam: Test of midazolam-like discriminative stimulus effects. Belmont (MA): McLean Hospital; 2022.

31. Bromazolam feeling a lot like alprazolam with a longer life. San Francisco (CA): Reddit; 2022 (https://www.reddit.com/r/researchchemicals/comments/w6gi4p/bromazolam_feeling_a_lot_like_alprazolam_with_a/, accessed 2 August 2022).

32. Novel benzodiazepines (benzos) produce some similar effects to prescription benzos but are often more potent and unpredictable. Melbourne: Victoria Department of Health; 2022 (https://www.health.vic.gov.au/drug-alerts/high-potency-benzodiazepine-tablets, accessed 3 August 2022).

33. Ellefsen K, Shoff E, Papsun D. New drugs on the block: Spring 2022 line-up. ToxTalk. 2022;46:10–1.

34. McDermott S, Johnson BE, Balasanova AA. Phenibut and bromazolam use disorders requiring hospitalization for medically supervised withdrawal. Prim Care Companion CNS Disord. 2022;24:21cr03119. doi:10.4088/PCC.21cr03119.

35 Bromazolam has the worst delusions of sobriety of and RC benzo I've tried. San Francisco (CA): Reddit; 2022 (https://www.reddit.com/r/researchchemicals/comments/vpbt9h/bromazolam_has_the_worst_delusions_of_sobriety_of/, accessed 2 August 2022).

36. Bromazolam. Vienna: United Nations Office on Drugs and Crime; 2023 (https://www.unodc.org/tox/#/admin/search/detailed/%7B%22textQuery%22:%22bromazolam%22,%22selected%22:%7B%7D,%22page%22:1,%22itemsPerPage%22:10,%22showMyOnly%22:false%7D), accessed 17 July 2023].

37. Marland V, Reid R, Brandon AM, Hill K, Cruickshanks F, McKenzie C et al. Changing trends in novel benzodiazepine use within Scottish prisons: detection, quantitation, prevalence, and modes of use. Drug Test Anal. 2023;in press. doi: 10.1002/dta.3560.

38. New benzodiazepines in Europe – a review. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2021 (https://www.emcdda.europa.eu/publications/rapid-communications/new-benzodiazepines-europe-review_en).

39. NPS benzodiazepines in the United States. Willow Grove (PA): Center for Forensic Science Research and Education; 2023 (https://www.cfsre.org/nps-discovery/trend-reports/nps-benzodiazepines/report/49?trend_type_id=1, accessed 17 July 2023].

40. Bromazolam. Drugsdata.org. 2023 (https://drugsdata.org/results.php?search_field=all&s=bromazolam, accessed 17 July 2023].

41. Finnish Medicines Agency (2022) New designer drugs are subject to supervision on February 14, 2022 (online) https://www.fimea.fi/web/sv/-/nya-designdroger-ar-foremal-for-tillsyn-den-14-februari-2022, accessed 17 July 2023].

42. Food and Drug Administration. International drug sheduling; convention on psychotropic substances; Single Convention on Narcotic Drugs; ADB-BUTINACA; adinazolam; bromazolam; protonitazene (propoxynitazene);etazene (etodesnitazene); etonitazepyne (N-pyrrolidinoetonitazene); 2-methyl-AP-237; alpha-PiHP; 3methylmethcathinone (3-MMC); zopiclone; request for comments. Fed Regist. 2022;87:47428 (https://www.federalregister.gov/documents/2022/08/03/2022-16572/international-drug-scheduling-convention-on-psychotropic-substances-single-convention-on-narcotic).

43. Song CH, Jia W, Liu CM, Hua ZD, Meng X, Zhao YB et al. New trends of new psychoactive substances (NPS)-infused chocolate: identification and quantification of trace level of NPS in complex matrix by GC-MS and NMR. Talanta. 2023;255:124257. doi:10.1016/j.talanta.2023.124257.

3.1.2 Flubromazepam

1. Substance identification

A. International Nonproprietary Name (INN)

Not assigned

B. Chemical Abstract Service (CAS) registry number

2647-50-9

C. Other chemical names

2*H*-1,4-Benzodiazepin-2-one, 7-bromo-5-(*o*-fluorophenyl)-1,3-dihydro- (7CI, 8CI)

7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (ACI)

7-Bromo-5-(2-fluorophenyl)-1,3-dihydrobenzo[*e*]-1,4-diazepin-2-one

Canonical SMILES
O=C1NC=2C=CC(Br)=CC2C(=NC1)C=3C=CC=CC3F

InChI
InChI=1S/C15H10BrFN2O/c16-9-5-6-13-11(7-9)15(18-8-14(20)19-13)10-3-1-2-4-12(10)17/h1-7H,8H2,(H,19,20)

InChI Key
ZRKDDZBVSZLOFS-UHFFFAOYSA-N

D. Trade names

Flubromazepam is sold principally under its own name *(1)*.

E. Street names

Flubromazepam is sold principally as tablets, capsules or powders under its own name *(1)*. "Liquid Xanax" is a street name for flubromazepam *(2)*.

F. Physical appearance

Synthetic flubromazepam has been described as a white powder *(3,4)* or a crystalline solid *(5)*.

G. WHO review history

Flubromazepam has not previously been reviewed by the WHO Expert Committee on Drug Dependence.

2. Chemistry

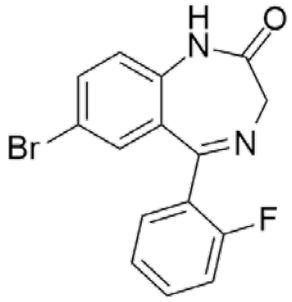
A. Chemical name

IUPAC name:
7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one

CA Index Name:
2*H*-1,4-Benzodiazepin-2-one, 7-bromo-5-(2-fluorophenyl)-1,3-dihydro- (9CI, ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{15}H_{10}BrFN_2O$

Molecular weight: 333.16 g/mol

C. Stereoisomers

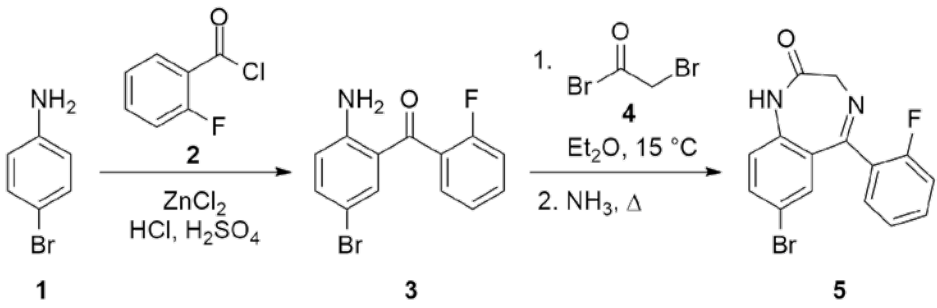
No stereoisomers of flubromazepam have been described.

D. Methods and ease of illicit manufacture

Flubromazepam is a 1,4-benzodiazepine that is structurally related to the internationally controlled substance phenazepam, in which the chlorine atom has been replaced by a fluorine atom. Flubromazepam was first prepared and studied by Sternbach and co-workers in the early 1960s *(6–9)*.

Flubromazepam is conveniently prepared by the method depicted in scheme 1 *(10)*, in which *p*-bromoaniline (**1**) undergoes Friedel-Crafts acylation with *o*-fluorobenzoyl chloride (**2**) to form the 2-aminobenzophenone (**3**). Then, a two-step annulation sequence involving 2-bromoacetyl bromide (**4**) (step 1) to prepare the 2-bromoacetamidobenzophenone intermediate (not shown) and treatment with ammonia and heat to promote ring closure through imine formation (step 2) afford the final product flubromazepam (**5**) *(10)*.

No information was available on the routes of synthesis used for the flubromazolam products circulating on the market. The synthesis reported in the literature, although simple, requires a chemical synthetic laboratory and qualified personnel.



Scheme 1. Synthesis of flubromazepam

E. Chemical properties

Melting-point
189–190 °C *(3,11)*

Boiling-point
No information was found.

Solubility
Flubromazepam is soluble in dimethylformamide and in dimethyl sulfoxide (DMSO) at a concentration of 25 mg/mL, in ethanol at a concentration of 10 mg/mL, in methanol at a concentration of 1 mg/mL and in a 1:1 mixture of DMSO:phosphate-buffered saline (pH 7.2) at a concentration of 0.5 mg/mL *(5)*.

F. Identification and analysis

Flubromazepam and its deuterated derivative are available as reference materials that can be purchased from various commercial suppliers and used in routine analysis associated with forensic and clinical investigations *(5)*.

Analytical methods for the identification of flubromazepam in seized sample matrices include infrared spectroscopy, proton nuclear magnetic resonance and gas chromatography–mass spectrometry (MS) *(4)*.

Flubromazepam was analysed in urine by an immunochemical assay *(12)*. Several analytical methods have been developed for qualitative and quantitative determination of flubromazepam in human blood, urine,

vitreous humour, bile, hair, brain and muscle by liquid chromatography (LC) coupled either to high-resolution (MS) or triple-quadrupole MS *(13)*.

3. Ease of conversion into controlled substances

Flubromazepam can be convert to flubromazolam in a single one-pot synthesis that requires the equipment of a chemical synthetic laboratory and qualified personnel *(14)*.

4. General pharmacology

A. Routes of administration and dosage

The available data and user reports indicate that oral consumption of flubromazepam is the most common route of administration. Most submitted samples positive for flubromazepam have been in the form of tablets or powder *(15,16)*, and online sales sites advertise flubromazepam in the form of pellets, powder, liquid, capsules and infused blotters *(17,18)*. Further, people who use flubromazepam have reported oral use in the form of tablets or powder solubilized with a solvent such as propylene glycol *(19,20)*.

No studies were found on human dosage; however, one informational website categorized doses according to their intoxicating effects as "light" (3–5 mg), "common" (5–8 mg) and "strong" (8–12 mg) *(21)*. For comparison, the website lists the following doses for diazepam: "light" (2.5–5 mg), "common" (5–15 mg) and "heavy" (15–30 mg) *(22)*. These data agree with the dose range of 4–12 mg reported in published summaries of online surveillance research *(17,23)*. Higher doses may be used; for example, the estimated flubromazepam dose in one fatal case of co-ingestion of flubrobromazepam and an opioid (U-47700) was 40 mg (based on measured blood concentrations of flubromazepam and its metabolites and knowledge of its pharmacokinetics, see section 4B) *(24)*. The basis for the information on typical recreational doses is not clear, and, given its anecdotal nature, caution is suggested in interpreting the data.

B. Pharmacokinetics

Analysis of the pharmacokinetics of flubromazepam showed that, like other benzodiazepines, it is lipophilic (log $D_{7.4}$ = 2.87 ± 0.05), highly protein bound (96.4% ± 0.9), and has acid-base dissociation constants of 3.25 ± 0.10 (pK_a1) and 10.74 ± 0.05 (pK_a2) *(25)*. Its metabolism is extensive, with only small amounts of unmetabolized drug detectable in urine *(26)*. The major phase-I metabolites are monohydroxylated (3-hydroxyflubromazepam, hydroxyflubromazepam), debrominated (debromoflubromazepam) and monohydroxylated debrominated (debrominated 3-hydroxy-flubromazepam)

compounds *(24,26–28)*, whereas the phase-II metabolites consisted of the glucuronides of the hydroxylated metabolites *(26)*.

Although reports that flubromazepam has a long half-life are consistent, estimates of the duration of the half-life vary. According to one online source, the onset of effects occurs 15–90 min after administration, the duration of action is 12–18 h, and the after-effects last for more than 36 h *(21)*. Other sources suggest that the effects of flubromazepam may last for up to 3 days *(18)*. The basis for the information is not clear. Laboratory studies of pharmacokinetics have reported an elimination half-life of 100–106 h *(18, 26)*. A pattern of decreasing serum levels followed by increasing serum levels, with a plateau between 24–57 or 76 h and then a return to decreasing levels suggests enterohepatic circulation of flubromazepam, which may contribute to its long half-life *(23, 26)*. It is not known whether its metabolites are psychoactive.

C. Pharmacodynamics

Little information is available about the pharmacodynamics of flubromazepam. The results of a quantitative structure–activity relationship model indicate that the predicted binding value of flubromazepam for the $GABA_A$ receptor, expressed as log 1/c, is 8.37 *(29)*. In comparison, the predicted log 1/c values for flubromazepam and midazolam are identical. Log 1/c is defined as the logarithm of the reciprocal of the IC_{50} for displacement of [^{3}H]-diazepam from rat cerebral cortex synaptosomes.

5. Toxicology

Little information was available on the toxicology of flubromazepam. A single published study of the cardiotoxicity of the compound found that flubromazepam impaired the viability of cardiomyocytes and inhibited hERG potassium channels in cell models *(30)*. In vivo, the compound increased the RR interval in rats (e.g., bradycardia) but did not affect QTc intervals. It also did not affect levels of PAK1 protein, a biomarker of cardiotoxicity.

6. Adverse reactions in humans

Measurable concentrations of flubromazepam have been found in post-mortem blood samples in several countries, including Australia *(31)*, Germany *(24)*, Norway *(32)*, the United Kingdom *(17)* and the USA *(33)*; however, other drugs were also detected in many cases, and the extent to which flubromazepam contributed to the deaths was not often specified. In cases in which clinical observation of the patient was possible, the symptoms included agitation, delirium, central nervous system depression, dilated pupils and tachycardia *(34,35)*. Flubromazepam has also been reported in

blood samples from impaired drivers in Europe and the USA *(36–38)*. In these studies, the blood concentrations of flubromazepam were from 4.7 to 1200 ng/mL, and other chemicals were often present. While driver impairment was reported in one case (maximum flubromazepam concentration = 161 ng/mL), the driver also tested positive for several stimulants *(39)*. No or mild impairment has been reported in other cases *(34, 36, 37)*. In two cases, flubromazepam was the sole compound, with blood concentrations ranging from 7 to 600 ng/ml *(36)*.

Several sources have consolidated subjective reports from people who used flubromazepam *(16, 17, 23)*. At typical recreational doses, the common effects of flubromazepam included anxiolysis, euphoria, relaxation, increased confidence, muscle relaxation, empathy, confusion and amnesia. These self-reported experiences of use of flubromazepam 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

Conditioned place preference procedures are sometimes used to assess the rewarding effects of a drug according to the principles of classical conditioning. Flubromazepam (0.1 mg/kg intraperitoneally) induced conditioned place preference (as compared with the vehicle) in male C57BL/6J mice in a three-compartment procedure *(30)*. At this dose, flubromazepam did not affect motor behaviour. A lower dose (0.01 mg/kg) did not significantly affect place preference. In the same study, flubromazepam (0.01 and 0.1 mg/kg/infusion) was assessed in a separate group of mice trained in an intravenous self-administration assay. Mice did not self-administer flubromazepam; however, the dosage may have been too low for adequate evaluation. For example, the training dose for diazepam self-administration in rodents is typically 0.5–2 mg/kg/infusion *(40)*.

Data on human use suggest that flubromazepam is only slightly less potent than diazepam (see section 4A).

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 flubromazepam.

10. Listing on the WHO Model List of Essential Medicines

Flubromazepam 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 authorization (as a medicinal product)

Flubromazepam has no known marketing authorization.

12. Industrial use

Flubromazepam has no known use in industry.

13. Non-medical use, abuse and dependence

Although flubromazepam was first synthesized in the 1960s as part of medication development, it was never submitted for regulatory approval or brought to the legal drug market. In 2013, it appeared on the European recreational drug market, and its use quickly spread throughout Europe and to other areas of the world, including North America *(41, 42)*. In addition to intentional use of flubromazepam for its benzodiazepine-like psychoactive effects (see section 6), some people have reported self-medication with flubromazepam for indications such as anxiety, to aid sleep and to offset the effects of stimulant use *(17, 35)*. Flubromazepam has been detected only rarely as the sole analyte in biological samples collected postmortem or pursuant to suspected intoxication while driving or upon clinical contact (e.g., emergency department admission). In some cases, flubromazepam is co-ingested because it is a constituent of a product that contains combinations of benzodiazepines (e.g. tablet, capsule, powder), including preparations falsely labelled as legal prescription drugs (e.g. alprazolam, diazepam) *(16)*. In other cases, the compound has been used in combination with drugs in other classes, including opioids and stimulants *(24, 35, 39)*.

The prevalence of chronic use and dependence of flubromazepam have not been reported. On online forums, one of the motivations mentioned for

using flubromazepam is avoidance of withdrawal from other benzodiazepines *(17)*, perhaps because of its long half-life. These reports should be considered anecdotal, as no analytical confirmation of chronic use of flubromazepam (or its sole use) was reported.

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

Since its emergence as a novel psychotropic substance in 2013, flubromazepam has been analytically confirmed in post-mortem samples as well as in samples collected from impaired drivers and emergency department admissions in several countries, including Australia *(31)*, Belgium *(39)*, Canada *(43)*, Germany *(24)*, Italy *(35)*, Norway *(36, 37)*, Sweden *(44)*, the United Kingdom *(17, 33)* and the USA *(38, 42)*. It has also been detected in over 100 product samples submitted to laboratories in Wales and the USA *(15, 16)*.

Between July 2016 and October 2021, 23 cases (four post-mortem) of analytically confirmed flubromazepam were reported to the Early Warning System Tox-Portal *(33)*. Flubromazepam was the only listed substance detected in 20 cases. In five nonfatal cases, flubromazepam was designated as contributory (medium) on the causality scale used in the system. Between March 2014 and June 2023, flubromazepam was the sole (or one of only a few) substance(s) detected in 88 samples analysed by Welsh authorities *(16)* and in 23 samples analysed by a laboratory based in the USA *(15)*. A substantial number of products were falsely labelled as approved prescription benzodiazepine (e.g., diazepam, alprazolam). Flubromazepam has also been detected in has been detected in infused paper/cards in post sent to prison inmates in Scotland *(45)*. Of the 475 samples containing novel benzodiazepines seized between February 2019 and January 2023, flubromazepam alone was identified in 34 samples and flubromazepam in combination with another novel benzodiazepine was found in an additional 63 samples. Samples included tablets and powder in the early part of the sampling period; however, visitation restriction during the Covid-19 pandemic was associated with increased formulation as infused paper/cards that were sent via the mail.

While flubromazepam has been associated with fatalities, intoxication while driving and clinical admissions, the extent to which it contributed to the negative health outcomes in these instances is uncertain. In most of the reported deaths, flubromazepam was only one of several substances identified in analysis of the biological sample(s) *(17, 24, 31, 32)*. While impaired driving after use of flubromazepam has been reported, co-use with

another psychoactive substance is common, and only mild impairment was reported in a couple of cases in which flubromazepam was the sole or major substance detected *(36, 37)*.

15 Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

In Europe, the first appearance of flubromazepam was in Sweden in 2013 *(41)*, while the first reports in the USA appeared in 2014 *(42, 46)*. Between 2014 and 2018, flubromazepam use increased, with 99 cumulative detections and a peak of 57 detections in 2017 *(42)*. Between 2017 and 2021, the number of detections of flubromazepam in biological samples decreased, representing less than 1% of the total benzodiazepine detections *(38)*. In the last quarter of 2022, nine samples contained flubromazepam *(47)*.

Samples containing flubromazepam submitted to an anonymous testing site from 2016 to the present were received from Austria (n=1), China and other Asian countries (n=4) and the USA (n=11) *(15)*. As submission of samples was voluntary, the distribution of sites of origin may not represent the distribution or trafficking of flubromazepam in the world. Other countries in which flubromazepam has been detected include Australia *(31, 33)*, Belgium *(39)*, Canada *(43)*, Germany *(24)*, Italy *(35)*, Norway *(36, 37)*, Sweden *(18, 44)* and the United Kingdom *(16, 17, 33)*.

17. Current international controls and their impact

Flubromazepam is not under current international control.

18. Current and past national controls

Flubromazepam is classified as a schedule IV substance under Canadian law and is regulated under psychoactive drug control regulations in Germany, the Russian Federation, Switzerland, Türkiye, the United Arab Emirates and the United Kingdom. Flubromazepam does not appear to be controlled under national regulations in other countries.

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

No other matters were identified.

References

1. New benzodiazepines in Europe – a review. Luxembourg: European Monitoring Centre for Drugs and Drug Addiction; 2021 (https://www.emcdda.europa.eu/publications/rapid-communications/new-benzodiazepines-europe-review_en).
2. Flubromazepam detected in fentanyl in the Northwest Territories. Yellowknife (NT): Government of Northwest Territories, Health and Social Services; 2023 (https://www.hss.gov.nt.ca/en/newsroom/flubromazepam-detected-fentanyl-northwest-territories, accessed 20 June 2023).
3. Cook JM, Huang S, Edwankar R, Namjoshi OS, Wang ZJ. Selective agents for pain suppression. US Patent No. US8835424B2 (https://www.rti.org/publication/selective-agents-pain-suppression).
4. Flubromazepam. Springfield (VA): Drug Enforcement Administration, Special Testing and Research Laboratory; 2017 (https://www.swgdrug.org/Monographs/Flubromazepam.pdf).
5. Flubromazepam (Item No. 15157). Ann Arbor (MI): Cayman Chemicals Company; 2020 (https://www.caymanchem.com/product/15157/flubromazepam).
6. Reeder E, Sternbach LH. Amino substituted benzophenone oximes and derivatives thereof. US Patent US3136815A; 1964 (https://patents.google.com/patent/US3136815A/en).
7. Sternbach LH, Fryer RI, Metlesics W, Reeder E, Sach G, Saucy G et al. Quinazolines and 1,4-benzodiazepines. VI. 1a Halo-, methyl-, and methoxy-substituted 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones1b,c. J Organic Chem. 1962;27:3788–96. doi:10.1021/jm00339a010.
8. Sternbach LH, Fryer RI, Metlesics W, Sach G, Stempel A. Quinazolines and 1,4-benzodiazepines. V. o-Aminobenzophenones 1a,b. J Organic Chem. 1962;27:3781–8. doi:10.1021/JO01058A009.
9. Sternbach LH, Reeder E. Quinazolines and 1,4-benzodiazepines. IV. 1,2 Transformations of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide3. J Organic Chem. 1961;26:4936–41. doi:10.1021/JO01070A038.
10. Ligon ES, Nawyn J, Jones LV, Allred BM, Reinhardt DV Jr, France S. Synthesis of flubromazepam positional isomers for forensic analysis. J Organic Chem. 2019;84:10280–91. doi:10.1021/acs.joc.9b01433.
11. Hester JB Jr, von Voigtlander P. 6-Aryl-4H-s-triazolo[4,3-a][1,4]benzodiazepines. Influence of 1-substitution on pharmacological activity. J Med Chem. 1979;22:1390–8. doi:10.1021/jm00197a021.
12. Erdmann J, Moosmann B. Cross reactivity of the CEDIA and HEIA benzodiazepine kits for 29 designer benzodiazepines and tofisopam. Drug Test Anal. 2021;13:1686–8. doi:10.1002/dta.3111.
13. Sofalvi S, Lavins ES, Kaspar CK, Michel HM, Mitchell-Mata CL, Huestis MA et al. Development and validation of an LC–MS-MS method for the detection of 40 benzodiazepines and three Z-drugs in blood and urine by solid-phase extraction. J Anal Toxicol. 2020;44:708–17. doi:10.1093/jat/bkaa072.
14. Cook JM, Zhou H, Huang S, Sarma PVVS, Zhang C. Stereospecific anxiolytic and anticonvulsant agents with reduced muscle-relaxant, sedative-hypnotic and ataxic effects. US Patent US 20060003995A1; 2006 (https://patents.google.com/patent/US20060003995A1/en).
15. Flubromazepam. Grass Vallet (CA): Erowid Center, DrugsData.org; 2023 (https://drugsdata.org/results.php?search_field=all&s=flubromazepam, accessed 25 July 2023).
16. Flubromazepam. Cardiff: Welsh Emerging Drugs and identification of Novel Substances Project; 2023 (https://www.wedinos.org/sample-results#mylocation, accessed 25 July 2023).
17. Abouchedid R, Gilks T, Dargan PI, Archer JRH, Wood DM. Assessment of the availability, cost, and motivations for use over time of the new psychoactive substances – benzodiazepines diclazepam, flubromazepam, and pyrazolam – in the United Kingdom. J Med Toxicol. 2018;4:134–43. doi:10.1007/s13181-018-0659-3.
18. Orsolini L, Corkery JM, Chiappini S, Guiruis A, Vento A, de Bereardis D et al. "New/designer benzodiazepines": an analysis of the literature and psychonauts' trip reports. Curr Neuropharmacol. 2020;18{809–37. doi:10.2174/1570159X18666200110121333.

19. Flubromazepam. Bluelight; 2023 (https://bluelightorg/xf/search/2459820/?q=flubromazepam&t=post&o=relevance, accessed 25 July 2023).

20. Flubromazepam. San Francisco (CA): Reddit; 2023 (https://www.reddit.com/r/researchchemicals/search/?q=flubromazepam&restrict_sr=1, accessed 25 July 2023).

21. Flubromazepam. Springfield (PA): Tripsit; 2023 (https://drugs.tripsit.me/flubromazepam, accessed 25 July, 2023).

22. Diazepam. Springfield (PA): Tripsit; 2022 (https://drugs.tripsit.me/diazepam, accessed 22 August 2022).

23. El Balkhi S, Monchaud C, Herault F, Géniaux H, Saint-Marcoux F. Designer benzodiazepines' pharmacological effects and potencies: How to find the information. J Psychopharmacol. 2020;34:1021–9. doi:10.1177/0269881119901096.

24. Koch K, Auwärter V, Hermanns-Clausen M, Wilde M, Neukamm MA. 2018. Mixed intoxication by the synthetic opioid U-47700 and the benzodiazepine flubromazepam with lethal outcome: pharmacokinetic data. Drug Test Anal. 2018. doi:10.1002/dta.2391.

25. Manchester KR, Maskell PD, Waters L. Experimental versus theoretical log D(7.4), pK(a) and plasma protein binding values for benzodiazepines appearing as new psychoactive substances. Drug Test Anal. 2018. doi:10.1002/dta.2387.

26. Moosmann B, Huppertz LM, Hutter M, Buchwald A, Ferlaino S, Auwärter V. Detection and identification of the designer benzodiazepine flubromazepam and preliminary data on its metabolism and pharmacokinetics. J Mass Spectrom. 2013;48:1150–9. doi:10.1002/jms.3279.

27. El Balkhi S, Chaslot M, Picard N, Dulaurent S, Delage M, Mathieu O et al. Characterization and identification of eight designer benzodiazepine metabolites by incubation with human liver microsomes and analysis by a triple quadrupole mass spectrometer. Int J Legal Med. 2017;131:979–88. doi:10.1007/s00414-017-1541-6.

28. Partridge E, Trobbiani S, Stockham P, Charlwood C, Kostakis C. A case study involving U-47700, diclazepam and flubromazepam – application of retrospective analysis of HRMS data. J Anal Toxicol. 2018;42:655–60. doi:10.1093/jat/bky039.

29. Waters L, Manchester KR, Maskell PD, Haegeman C, Haider S. The use of a quantitative structure–activity relationship (QSAR) model to predict GABA-A receptor binding of newly emerging benzodiazepines. Sci Justice. 2018;58:219–25. doi:10.1016/j.scijus.2017.12.004.

30. Hong E, Gu SM, Kim JM, Yoon KS, Lee JM, Kim YH et al. The designer benzodiazepine, flubromazepam, induces reward-enhancing and cardiotoxic effects in rodents. Toxicol Res (Camb). 2022;11:644–53. doi:10.1093/toxres/tfac039.

31. Darke S, Peacock A, Duflou J, Farrell M, Lappin J. Characteristics of fatal "novel" benzodiazepine toxicity in Australia. Forensic Sci Int. 2022;331:111140. doi:10.1016/j.forsciint.2021.111140.

32. Gundersen POM, Broecker S, Slørdal L, Spigset O, Josefsson M. Retrospective screening of synthetic cannabinoids, synthetic opioids and designer benzodiazepines in data files from forensic post mortem samples analysed by UHPLC-QTOF-MS from 2014 to 2018. Forensic Sci Int. 2020;311:110274. doi:10.1016/j.forsciint.2020.110274.

33. Flubromazepam. Vienna: United Nations Office on Drugs and Crime; 2023 (https://www.unodc.org/tox/#/admin/search/detailed/%7B%22textQuery%22:%22flubromazepam%22%7D, accessed 25 July 2023).

34. Brunetti P, Giorgetti R, Tagliabracci A, Huestis MA, Busardò FP. Designer benzodiazepines: a review of toxicology and public health risks. Pharmaceuticals (Basel). 2021;14:560. doi:10.3390/ph14060560.

35. Valli A, Lonati D, Locatelli CA, Buscaglia E, Tuccio MD, Papa P. Analytically diagnosed intoxication by 2-methoxphenidine and flubromazepam mimicking an ischemic cerebral disease. Clin Toxicol (Phila). 2017;55:611–2. doi:10.1080/15563650.2017.1286016.

36. Høiseth G, Tuv SS, Karinen R. Blood concentrations of new designer benzodiazepines in forensic cases. Forensic Sci Int. 2016;268:35–8. doi:10.1016/j.forsciint.2016.09.006.

37. Heide G, Høiseth G, Middlekoop G, Øiestad ÅML. Blood concentrations of designer benzodiazepines: relation to impairment and findings in forensic cases. J Anal Toxicol. 2020;44:905–14. doi:10.1093/jat/bkaa043.

38. Papsun DM, Chan-Hosokawa A, Lamb ME, Logan B. Increasing prevalence of designer benzodiazepines in impaired driving; a 5 year analysis from 2017–2021. J Anal Toxicol. 2023;bkad036. doi:10.1093/jat/bkad036.

39. Wille SMR, Bouazzati M, Rubbens J, di Fazio V, Samyn N. Combined use of flubromazepam and stimulants: blood and oral fluid concentrations and impact on driving ability. J Anal Toxicol. 2023;46:e280–4. doi:10.1093/jat/bkac071.

40. Naruse T, Asami T. Intravenous self-administration of diazepam in rats. Eur J Pharmacol. 1987;135:365–73. doi:10.1016/0014-2999(87)90686-8.

41. New benzodiazepines in Europe – a review. Lisbon: European Monitroing Centre for Drugs and Drug Addiction; 2021 (https://www.emcdda.europa.eu/publications/rapid-communications/new-benzodiazepines-europe-review_en).

42. Bollinger K, Weimer B, Heller D, Bynum N, Grabenauer M, Pressley D et al. Benzodiazepines reported in NFLIS-Drug, 2015 to 2018. Forensic Sci Int Synerg. 2021;3:100138. doi:10.1016/j.fsisyn.2021.100138.

43. Laing MK, Ti L, Marmel A, Tobias S, Shapiro AM, Laing R et al. 2021. An outbreak of novel psychoactive substance benzodiazepines in the unregulated drug supply: preliminary results from a community drug checking program using point-of-care and confirmatory methods. Int J Drug Policy. 2021;93:103169. doi:10.1016/j.drugpo.2021.103169.

44. Bäckberg M, Pettersson Bergstrand M, Beck O, Helander A. Occurrence and time course of NPS benzodiazepines in Sweden – results from intoxication cases in the STRIDA project. Clin Toxicol (Phila). 2019;57:203–12. doi:10.1080/15563650.2018.1506130.

45. Marland V, Reid R, Brandon AM, Hill K, Cruickshanks F, McKenzie C et al. Changing trends in novel benzodiazepine use within Scottish prisons: detection, quantitation, prevalence, and modes of use. Drug Test Anal. 2023;in press. doi: 10.1002/dta.3560.

46. Papsun DM, Krotulski AJ, Mastrovito R, Ealton SE, Logan BK. Bromazolam prevalence surging across the United States driven in part by increasing detections alongside fentanyl. Willow Grove (PA): Center for Forensic Science Research and Education; 2022 (https://forensiclibrary.org/archives/18811, accessed 2 August 2022).

47. NPS benzodiazepines in the United States: Trend report Q4. Willow Grove (PA): Center for Forensic Science Research and Education; 2022 (https://www.cfsre.org/images/trendreports/2022-Q4-NPS-Benzodiazepines-Trend-Report.pdf, accessed 27 July 2023).

3.1.3 Butonitazene

1. Substance identification

A. International Nonproprietary Name (INN)

Not assigned.

B. Chemical Abstract Service (CAS) registry number

95810-54-1 (free base)

118951-34-1 (hydrochloride salt)

Free base
Canonical SMILES
O=N(=O)C=1C=CC2=C(N=C(N2CCN(CC)CC)CC3=CC=C(OCCCC)C=C3)C1

InChI
InChI=1S/C24H32N4O3/c1-4-7-16-31-21-11-8-19(9-12-21)17-24-25-22-18-20(28(29)30)10-13-23(22)27(24)15-14-26(5-2)6-3/h8-13,18H,4-7,14-17H2,1-3H3

InChI Key
UZZPOLCDCVWLAZ-UHFFFAOYSA-N

Hydrochloride salt
Canonical SMILES
Cl.O=N(=O)C=1C=CC2=C(N=C(N2CCN(CC)CC)CC3=CC=C(OCCCC)C=C3)C1

InChI
InChI=1S/C24H32N4O3.ClH/c1-4-7-16-31-21-11-8-19(9-12-21)17-24-25-22-18-20(28(29)30)10-13-23(22)27(24)15-14-26(5-2)6-3;/h8-13,18H,4-7,14-17H2,1-3H3;1H

InChI Key
WIJPAKBZQWABKM-UHFFFAOYSA-N

C. Other chemical names

2-[(4-Butoxyphenyl)methyl]-*N,N*-diethyl-5-nitro-1*H*-benzimidazole-1-ethanamine (ACI)

Benzimidazole, 2-(*p*-butoxybenzyl)-1-[2-(diethylamino)ethyl]-5-nitro- (7CI)

1H-Benzimidazole-1-ethanamine, 2-((4-butoxyphenyl)methyl)-N,N-diethyl-5-nitro-

2-[2-[(4-butoxyphenyl)methyl]-5-nitrobenzimidazol-1-yl]-*N,N*-diethylethanamine

2-(2-(4-butoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)-*N,N*-diethylethan-1-amine

Butoxynitazene

D. Trade names

Butonitazene is sold as hydrochloride salt under its own name, butonitazene (hydrochloride) as analytical reference standard *(1)*.

E. Street names

Butonitazene is known under its own name or as butoxynitazene *(2)*.

F. Physical appearance

Pure analytical standard of butonitazene hydrochloride is described as a crystalline solid *(1)*. Several companies that sell butonitazene on the internet show the compound as a white powder or yellow-brown powder *(3, 4)*.

G. WHO review history

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

2. Chemistry

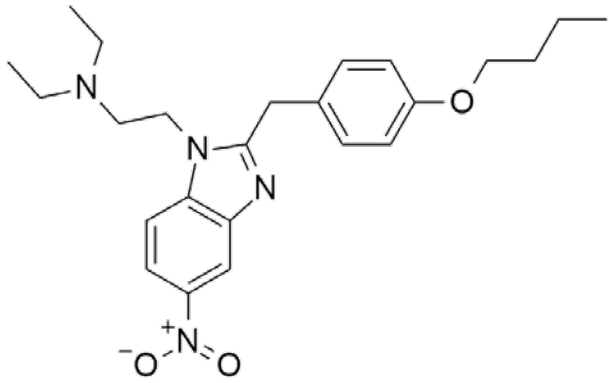
A. Chemical name

IUPAC name: N,N-diethyl -2-[(4-Butoxyphenyl)methyl]- 5-nitro-1H-benzimidazole-1-ethanamine

CA Index name: 1*H*-Benzimidazole-1-ethanamine, 2-[(4-butoxyphenyl) methyl]-*N,N*-diethyl-5-nitro- (ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{24}H_{32}N_4O_3$

Molecular weight: 424.54 g/mol

C. Stereoisomers

There are no stereoisomers described for butonitazene.

D. Methods and ease of illicit manufacturing

Butonitazene is a 5-nitro-2-benzylbenzimidazole belonging to the series of 2-benzylbenzimidazole compounds developed in the late 1950s as opioid analgesics *(5)*. It is a metonitazene, etonitazene and protonitazene homologue in which the C4 position of the benzyl moiety is substituted by a methoxy, ethoxy and *n*-propoxy group, respectively. The molecule of butonitazene presents an *n*-butoxy substituent on the benzyl moiety.

Synthesis of butonitazene was reported by Hunger et al. *(6)* and more recently by Vandeputte et al. *(7)*. The activated chlorine atom of 1-chloro-2,4-dinitrobenzene can be easily substituted with 2-diethylaminoethylamine. Subsequently, the nitro group in the *ortho* position can be selectively reduced to yield the corresponding amino function of the *ortho*-phenylenediamine species. The latter can be condensed with the *n*-butoxyphenyl imidate, which is obtained from the n-butoxyphenylacetonitrile derivative. The reaction affords the 5-nitro-substituted product butonitazene.

Butonitazene can be also obtained through other synthetic routes reported for the synthesis of its 5-nitro-2-benzylbenzimidazole homologues (metonitazene, etonitazene and protonitazene) *(8-11)*.

Although no information was found on the actual method and scale of manufacture of butonitazene, the synthetic methods are simple and cost-efficient and do not require regulated precursors *(5)*.

E. Chemical properties

Melting point
Butonitazene hydrochloride: 154-156 °C *(6)*

Boiling point
No information could be identified.

Solubility
Butonitazene hydrochloride salt is soluble in dimethylformamide (DMF) at 25 mg/mL and in dimethyl sulfoxide (DMSO) at 20 mg/mL. It was soluble at 0.5 mg/mL in a 1:1 mixture of DMF and phosphate-buffered saline (PBS, pH 7.2) and at 10 mg/mL in ethanol *(1)*. No definitive data on the solubility of butonitazene free base or its hydrochloride salt was found.

F. Identification and analysis

Synthetic butonitazene was characterized by Fourier-Transform InfraRed (FTIR), nuclear magnetic resonance (NMR) spectroscopy, high-performance liquid chromatography coupled to diode-array detection (HPLC-DAD), gas chromatography coupled to mass spectrometry (GC-MS) and LC coupled to high-resolution mass spectrometry (HPLC-HRMS) *(7, 12, 13)*.

Butonitazene hydrochloride is available as a reference material from commercial suppliers for routine analysis in forensic and clinical investigations *(1)*.

Two LC-MS/MS methods have been published for the identification of butonitazene in human blood in two cases of intoxication *(14)* and in post-mortem blood, serum, and urine samples *(15)*.

3. Ease of convertibility into controlled substances

It is not known from the literature whether butonitazene can be converted into a controlled substance.

4. General pharmacology

A. Routes of administration and dosage

One report from Wedinos (ref. W024931) *(16)* acknowledged the test results from a sample that was smoked. No other reports from participants in online discussion forums could be identified reporting the use of butonitazene to determine its preferred route of administration or dosage.

B. Pharmacokinetics

No data on the absorption, distribution, metabolism, and excretion of butonitazene could be found. Of note, although the metabolism of butonitazene has not been assessed, it has been described that benzimidazole opioids (a class of opioids that includes butonitazene) usually undergo N-dealkylation at the N-ethylamine chain and O-dealkylation at the phenylalkyl chain. As such, it is reasonable to expect that 4'-OH-nitazene might be a major butonitazene metabolite formed through O-dealkylation. 4'-OH-nitazene was detected in serum and quantified in urine at 9.8 ng/mL (although the validation methods were not described) *(17)*.

C. Pharmacodynamics

Studies on the binding and functional activity of butonitazene at human δ and κ opioid receptors, and rat μ opioid receptors transfected into Chinese hamster ovary (CHO) cells *(18)* showed that butonitazene has a similar binding affinity to μ-opioid receptors as morphine, but lower than fentanyl. The binding affinities of butonitazene to δ and κ-opioid receptors were lower than those of fentanyl and morphine.

Butonitazene was more potent at μ-opioid receptors than at δ and κ-opioid receptors. Butonitazene showed higher agonism to μ-opioid receptors, and lower agonism to κ-opioid receptors, than fentanyl and morphine. Also, butonitazene showed similar agonism to δ-opioid receptors as fentanyl and morphine (unpublished data provided in confidence).

Butonitazene was tested for its ability to produce analgesic effects in the warm-water tail-flick assay in ten Swiss-Webster mice, using a cumulative-dosing procedure (from 0.1 to 10 mg/kg) followed by a time-course of the peak effect of butonitazene. Butonitazene increased tail-flick latencies to a maximum effect of 100% after administration of 10 mg/kg in a dose-dependent manner. Potency ratios (ED_{50} test compound/ED_{50} reference compound) indicated that butonitazene was less potent than morphine and fentanyl. Butonitazene was considered to be as efficacious as morphine and fentanyl. The peak analgesic effects of butonitazene lasted 90 min, and returned to baseline after 180 min.

Subcutaneous injection of naltrexone before administration of 3.2 mg/kg butonitazene (peak dose that did not produce adverse effects) blocked the analgesic effect of butonitazene, supporting the involvement of opioid receptors in the action of butonitazene *(19)*. Of note, lethality was observed in 3 mice, one at 45 min, one at 60, and another at 75 min following administration of 10 mg/Kg butonitazene.

5. Toxicology

According to the UNODC Early Warning Advisory, butonitazene was reported in a total of 8 countries between 2019 and 2022 *(20)*. However, no reports were found on the toxic doses of butonitazene for humans.

Butonitazene was reported in one death case (42-year-old male, in Ohio, USA), in combination with metonitazene. The cause of death was attributed to metonitazene overdose. Butonitazene concentrations were determined to be 3.2, 2.4, and 10 ng/mL in the peripheral blood (median concentration), serum, and urine, respectively *(17, 15)*.

6. Adverse reactions in humans

No reports were found on the adverse reactions of butonitazene in humans.

Unverified information found online *(21)* referred to butonitazene inducing analgesia, euphoria, sleepiness, as well as vomiting and respiratory depression at high doses (not specified).

Butonitazene was analytically confirmed in one death case, but the cause of death was attributed to an overdose of another opioid (metonitazene).

Activation of the μ-opioid receptor by butonitazene involves the interaction with β- arrestin-2 *(22)*. Of note, the interaction of β-arrestin-2 with μ-opioid receptors has been shown to mediate some of the adverse health effects of some opioid analgesics. For example, morphine has been shown to produce less physical dependence, constipation, and respiratory suppression in β-arrestin-2 knockout (KO) mice compared to wild-type mice *(23)*.

7. Dependence potential

A. Animal studies

No studies were identified.

B. Human studies

No studies were identified.

8. Abuse potential

A. Animal studies

In drug discrimination studies (two-lever choice method), butonitazene fully substituted for the discriminative stimulus effects of 3.2 mg/kg morphine after subcutaneous administration to 8 Sprague-Dawley rats at doses of

0.1–3.2 mg/kg. Assessment of the potency ratio (ED50 test compound:ED50 reference compound) showed that butonitazene was more potent than morphine but less potent than fentanyl. Butonitazene was considered to be as efficacious as morphine and fentanyl.

Subcutaneous injection of naltrexone to the rats before administration of 3.2 mg/kg butonitazene blocked the morphine-like discriminative stimulus effects of butonitazene, indicating the involvement of opioid receptors in the discriminative stimulus effects of butonitazene *(24)*.

B. Human studies

No studies that examined the human abuse potential of butonitazene were identified.

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

In 1957, the synthesis of a group of benzimidazole derivatives with analgesic properties was described *(25)*. However, none of those derivatives was medically approved.

Butonitazene is not known to have any medical use.

10. Listing on the WHO Model List of Essential Medicines

Butonitazene 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)

Butonitazene is not known to be authorized for marketing.

12. Industrial use

Butonitazene is not known to have any industrial use.

13. Non-medical use, abuse and dependence

No information was found on nonmedical use or dependence on butonitazene.

Butonitazene was identified on an online forum (Wedinos), in a sample where the purchaser intended to buy 5-CLA-DBA, suggesting non-intentional use. Nevertheless, the detection of butonitazene indicated in 51 reports from the US National Forensic Laboratory Information System (NFLIS-Drug) between 2021 and 2022 *(26)*, as further detailed in section 15, suggests its use.

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

No information was found to determine on the nature and magnitude of health problems with butonitazene.

15. Licit production, consumption and international trade

Butonitazene is used as reference material in scientific research and forensic applications.

16. Illicit manufacture and traffic and related information

Butonitazene was first detected in Ohio in January 2021.

Reports from the US National Forensic Laboratory Information System (NFLIS-Drug) indicate that butonitazene was first detected in the USA in January 2021 in Ohio. Between 2021 and 2022, there were 51 reports to NFLIS-Drug mentioning butonitazene in the following US states: Alabama (1), Florida (4), Iowa (1), Kentucky (3), Ohio (34), and West Virginia (8). Of the 39 reports to NFLIS-Drug in 2021, 26 reported weights, totaling 824.48 grams *(26)*.

According to the UNODC Early Warning Advisory on New Psychoactive Substances (2022), butonitazene was reported in a total of 8 countries between 2019 and 2022 *(20)*.

17. Current international controls and their impact

Butonitazene is not currently controlled under the 1961, 1971, or 1988 United Nations Convention.

18. Current and past national controls

Butonitazene is a Schedule I controlled substance in the United States.

Butonitazene is controlled as Class B by the United Kingdom Misuse of Drugs Act.

In Germany, butonitazene is classified as "Neue-psychoaktive-Stoffe-Gesetz (NpSG)", which authorizes its use only for industrial and scientific purposes.

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

Nil.

References

1. Cayman. (2022). Butonitazene (Item No. 30278). Available at: https://www.caymanchem.com/product/30278/butonitazene. Accessed on 04/07/2023.
2. 908devices.com. (2021). New Update: Threat-Focused Targets. Available at: https://908devices.com/blog/feature-release-more-of-the-right-targets/. Accessed on 04/07/2023.
3. ecasb.com. (2023). cas 95810-54-1 Butonitazene. Available at: https://www.ecasb.com/en/product/67657/cas-95810-54-1-Butonitazene. Accessed on 04/07/2023.
4. globalsources.com. (2023). Research Chemical 99.5% Butonitaze CAS 95810-54-1 With Factory Bulk Price. Available at: https://www.globalsources.com/Organic-chemical/Butonitaze-1192474136p.htm. Accessed on 04/07/2023.
5. Ujváry I, Christie R, Evans-Brown M, Gallegos A, Jorge R, de Morais J, Sedefov R (2021). DARK Classics in Chemical Neuroscience: Etonitazene and Related Benzimidazoles. ACS Chemical Neuroscience. 12 (7):1072-1092. doi: 10.1021/acschemneuro.1c00037
6. Hunger A, Kebrle J, Rossi A, Hoffmann K (1960). Benzimidazol-Derivate und verwandte Heterocyclen III. Synthese von 1-Aminoalkyl-2-nenzyl-nitro-benzimidazolen. Helvetica Chimica Acta. 43 (4):1032-1046. doi: 10.1002/hlca.19600430412
7. Vandeputte MM, Van Uytfanghe K, Layle NK, St. Germaine DM, Iula DM, Stove CP (2021). Synthesis, Chemical Characterization, and μ-Opioid Receptor Activity Assessment of the Emerging Group of "Nitazene" 2-Benzylbenzimidazole Synthetic Opioids. ACS Chemical Neuroscience. 12 (7):1241-1251. doi: 10.1021/acschemneuro.1c00064
8. Kim Y, Kumar MR, Park N, Heo Y, Lee S (2011). Copper-Catalyzed, One-Pot, Three-Component Synthesis of Benzimidazoles by Condensation and C–N Bond Formation. The Journal of Organic Chemistry. 76 (23):9577-9583. doi: 10.1021/jo2019416
9. Renton P, Green B, Maddaford S, Rakhit S, Andrews JS (2012). NOpiates: Novel dual action neuronal nitric oxide synthase inhibitors with μ-opioid agonist activity. ACS Medicinal Chemistry Letters. 3 (3):227-231.
10. Thomas JB, Fall MJ, Cooper JB, Burgess JP, Carroll FI (1997). Rapid in-plate generation of benzimidazole libraries and amide formation using EEDQ. Tetrahedron Letters. 38 (29):5099-5102. doi: 10.1016/S0040-4039(97)01136-2
11. Bucha M, Eppakayala L, Chary MT (2018). A Facile Synthesis and Molecular Docking for Anti-inflammatory Activity of 2-(4-Chlorobenzyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-5-amine and 2-(4-Chlorobenzyl)-1-((1-ethylpyrrolidin-2-yl)methyl)-1H-benzo[d]imidazol-5-amine. Indian Journal of Heterocyclic Chemistry. 28 321. doi:
12. Slovenian National Forensic Laboratory (SFNL). (2021). Analytical report: Butonitazene (C24H32N4O3) ((2-{2-[(4-butoxyphenyl)methyl]-5-nitro-1H-1,3-benzodiazol-1-yl}ethyl)diethylamine). Slovenian National Forensic Laboratory, Vodovodna, Ljubljana (Slovenia).
13. Slovenian National Forensic Laboratory (SFNL). (2021). Analytical report: Butonitazene (C24H32N4O3) ((2-{2-[(4-butoxyphenyl)methyl]-5-nitro-1H-1,3-benzodiazol-1-yl}ethyl)diethylamine) in its salt form. Slovenian National Forensic Laboratory, Vodovodna, Ljubljana (Slovenia).
14. Schumann JL, Syrjanen R, Alford K, Mashetty S, Castle JW, Rotella J, Maplesden J, Greene SL (2023). Intoxications in an Australian Emergency Department Involving 'Nitazene' Benzylbenzimidazole Synthetic Opioids (Etodesnitazene, Butonitazene and Protonitazene). Journal of Analytical Toxicology. 47 (1):e6-e9. doi: 10.1093/jat/bkac062
15. Walton SE, Krotulski AJ, Logan BK (2022). A Forward-Thinking Approach to Addressing the New Synthetic Opioid 2-Benzylbenzimidazole Nitazene Analogs by Liquid Chromatography-Tandem Quadrupole Mass Spectrometry (LC-QQQ-MS). Journal of Analytical Toxicology. 46 (3):221-231. doi: 10.1093/jat/bkab117

16. Wedinos. (2023). Sample results for Butonitazene. Available at: https://www.wedinos.org/sample-results#mylocation. Accessed on 24/07/2023.

17. Montanari E, Madeo G, Pichini S, Busardò FP, Carlier J. Acute Intoxications and Fatalities Associated With Benzimidazole Opioid (Nitazene Analog) Use: A Systematic Review. Therapeutic Drug Monitoring. 2022 44(4).

18. Janowsky A. 2021. Butonitazene - Binding and Functional Activity at Delta, Kappa and Mu Opioid Receptors. in: DEA-VA Interagency Agreement Title: "In Vitro Receptor and Transporter Assays for Abuse Liability Testing for the DEA by the VA".

19. Gatch MB. Test of analgesic effects alone and in combination with naltrexone. in Call Order: 15DDHQ21F00000340 - "Evaluation of Abuse Potential of Synthetic Opioids Using in Vivo Pharmacological Studies". 2021.

20. United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) on New Psychoactive Substances, 2022.

21. Overdose Prevention Strategies. Butonitazene. Available at: https://www.overdosepreventionstrategies.org/glossary/butonitazene/. Accessed on 28/07/2023.

22. Drug Enforcement Administration, Diversion Control Division. (2022). Benzimidazole-Opioids.

23. Raehal KM, Bohn LM. β-arrestins: regulatory role and therapeutic potential in opioid and cannabinoid receptor-mediated analgesia. Handbook of Experimental Pharmacology. 2014 219:427-43. doi: 10.1007/978-3-642-41199-1_22

24. Gatch MB. Test of substitution for the discriminative stimulus effects of morphine. In Call Order: 15DDHQ21F00000340 - "Evaluation of Abuse Potential of Synthetic Opioids Using in Vivo Pharmacological Studies". 2021.

25. Hunger A, Kebrle J, Rossi A, Hoffmann K. Synthese basisch substituierter, analgetisch wirksamer Benzimidazol-Derivate. Experientia. 1957 13(10):400-401. doi: 10.1007/BF02161116

26. National Forensic Laboratory Information System (NFLIS-Drug). Butonitazene summary. 2023.

3.1.4 3-CMC

1. Substance identification

A. International Nonproprietary Name (INN)

Not assigned

B. Chemical Abstracts Service (CAS) registry number

1049677-59-9 (free base)

1607439-32-6 (hydrochloride salt)

2291021-63-9 ((2R)-enantiomer)

2107425-89-6 ((2S)-enantiomer)

C. Other chemical names

1-(3-Chlorophenyl)-2-(methylamino)-1-propanone (ACI)

1-(3-Chloro-phenyl)-2-methylamino-propan-1-one

3′-Chloro-2-methylaminopropiophenone

2-(Methylamino)-1-(3′-chlorophenyl)-1-oxopropane

(2S)-1-(3-Chlorophenyl)-2-(methylamino)-1-propanone (ACI)

(S)-3-Chloromethcathinone

(2*R*)-1-(3-Chlorophenyl)-2-(methylamino)-1-propanone (ACI)

(*R*)-3-Chloromethcathinone

3-Chloromethcathinone

3-Cl-methcathinone

3-Cl-MCAT

Clophedrone

Metaclephedrone

Meta-chloro-*N*-methyl-cathinone

Meta-chloromethcathinone

PAL-434

D. Trade names

The hydrochloride salt form of 3-CMC is sold as a reference analytical standard under the names "3-chloromethcathinone (hydrochloride)" and "1-(3-chlorophenyl)-2-(methylamino)propan-1-one hydrochloride" *(1)*.

E. Street names

Street names for 3-CMC include its own chemical names, principally 3-CMC, 3CMC, clophedrone and metaclephedrone. In Sweden, the drug is referred to as "Kristall" on the street.

F. Physical appearance

In pure form, the hydrochloride salt of 3-CMC has been described as a grey solid *(2)*, a white solid *(3)* and a white powder *(4)*.

Seized samples containing 3-CMC have been mostly in powder form and, to a lesser extent, capsule, tablet and liquid form *(5)*.

G. WHO review history

3-CMC has not been reviewed previously by WHO.

2. Chemistry

A. Chemical Name

IUPAC name: 1-(3-chlorophenyl)-2-(methylamino)propan-1-one

Chemical Abstracts index name: 1-Propanone, 1-(3-chlorophenyl)-2-(methylamino)-(ACI)

Free base
Canonical SMILES
O=C(C=1C=CC=C(Cl)C1)C(NC)C

InChI
InChI=1S/C10H12ClNO/c1-7(12-2)10(13)8-4-3-5-9(11)6-8/h3-7,12H,1-2H3

InChI Key
VOEFELLSAAJCHJ-UHFFFAOYSA-N

Hydrochloride salt
Canonical SMILES
Cl.O=C(C=1C=CC=C(Cl)C1)C(NC)C

InChI
InChI=1S/C10H12ClNO.ClH/c1-7(12-2)10(13)8-4-3-5-9(11)6-8;/h3-7,12H,1-2H3;1H

InChI Key
QXEPSICDXPPHTO-UHFFFAOYSA-N

(2R)-enantiomer
Canonical SMILES
O=C(C=1C=CC=C(Cl)C1)C(NC)C

Isomeric SMILES
C([C@H](NC)C)(=O)C1=CC(Cl)=CC=C1

InChI
InChI=1S/C10H12ClNO/c1-7(12-2)10(13)8-4-3-5-9(11)6-8/h3-7,12H,1-2H3/t7-/m1/s1

InChI Key
VOEFELLSAAJCHJ-SSDOTTSWSA-N

(2S)-enantiomer
Canonical SMILES
O=C(C=1C=CC=C(Cl)C1)C(NC)C

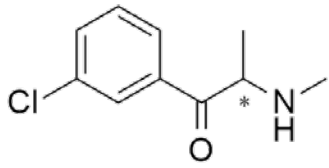
Isomeric SMILES
C([C@@H](NC)C)(=O)C1=CC(Cl)=CC=C1

InChI
InChI=1S/C10H12ClNO/c1-7(12-2)10(13)8-4-3-5-9(11)6-8/h3-7,12H,1-2H3/t7-/m0/s1

InChI Key
VOEFELLSAAJCHJ-ZETCQYMHSA-N

B. Chemical structure

Free base:

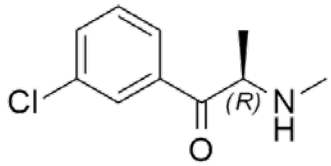


Molecular formula: $C_{10}H_{12}ClNO$

Molecular weight: 197.66 g/mol

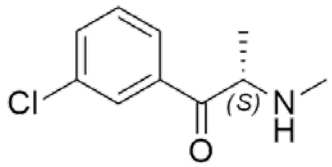
C. Stereoisomers

As 3-CMC contains a chiral centre, two enantiomers may exist: (*R*)-3-CMC and (*S*)-3-CMC. No information was available on the enantiomeric composition of 3-CMC 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 *(5)*.



(2R)-1-(3-Chlorophenyl)-2-(methylamino)-1-propanone

CAS RN 2291021-63-9



(2S)-1-(3-Chlorophenyl)-2-(methylamino)-1-propanone

CAS RN 2107425-89-6

D. Methods and ease of illicit manufacture

Two methods have been reported for the synthesis of 3-CMC *(2, 3)*.

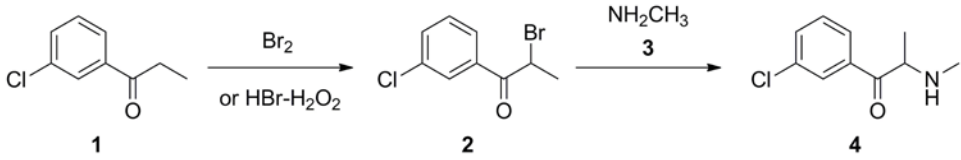
Two methods have been reported for the synthesis of 3-CMC *(2, 3)*.

Shalabi et al. (**3**) used a general procedure according to Scheme 1, in which 3-CMC is obtained from 2-bromo-1-(3-chlorophenyl)propan-1-one (**2**) by nucleophilic substitution with methylamine (**3**) to give 3-CMC free base (**4**) *(3)*.

Blough et al. (**2**) used a slightly different method, involving an *N*-protected amine, also starting from 2-bromo-1-(3-chlorophenyl)propan-1-one *(2)*.

2-Bromo-1-(3-chlorophenyl)propan-1-one (**2**) is a commercially available chemical, which can be used to prepare different cathinones according to the amine in the nucleophilic substitution, facilitating synthesis.

The α-bromoketone 2 can be obtained by α-bromination of 1-(3-chlorophenyl)-1-propanone (**1**), a commercially available compound.

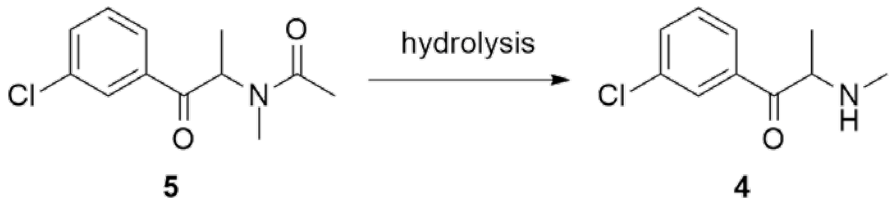


Scheme 1. Synthesis of 3-CMC

As cathinones are generally unstable as a free base, 3-CMC has been isolated as chlorohydrate in both synthetic methods.

Alternative synthetic methods have been reported, but no information was available about that used for illicit manufacture of 3-CMC, although the method shown in scheme 1 is the most probable *(5)*.

For other cathinones, such as 3-methylmethcathinone (3-MMC), so-called "masked derivatives", "masked precursors" or "designer precursors" have been seized *(6)*. In these cathinones, the amino group has been reacted with "masking" or "protecting" groups, such as acetyl groups (see Scheme 2), generating different chemical entities, which are easily hydrolysed to produce the controlled cathinones *(6)*. Various protecting groups can be used to this purpose.



Scheme 2. Hydrolysis of N-acetyl-3-CMC

While the total synthesis of 3-CMC requires qualified personnel and equipped laboratories, both preparation by amination of 2-bromo-1-(3-chlorophenyl)propan-1-one (**2**) and hydrolysis of the acetyl derivative can be achieved with only simple equipment and unskilled personnel.

E. Chemical properties

Stability

Romańczuk et al. *(7)* reported that 3-CMC is unstable in biological samples (e.g. blood, urine), and its major degradation product is the dehydro-3-CMC metabolite. As this metabolite was highly stable under all storage conditions tested, it can be monitored to assess consumption of 3-CMC and avoid false negative results. Acidification of the biological matrix and/or storage at low temperature were recommended to preserve 3-CMC concentrations.

Melting-point

Hydrochloride salt
182–183 °C *(2)*
193 °C *(3)*

Boiling-point

No information was found.

Solubility

Little information was available. Analytical standards are reported to have been prepared by dissolving 3-CMC in dimethyl sulfoxide or chloroform *(1, 4)*.

The hydrochloride salt of 3-CMC should be more soluble in water-soluble than the free base.

F. Identification and analysis

The analytical standard 3-CMC in its hydrochloride form is commercially available for identification and quantification purposes *(1)*.

In its pure form, 3-CMC has been fully characterized by proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance, Fourier transform infrared spectroscopy, gas chromatography–mass spectrometry (GC-MS) and liquid chromatography high-resolution mass spectrometry (LC-HRMS) *(2–4)*.

3-CMC can be identified and quantified in seized samples by the general procedure described by the United Nations Office on Drugs and Crime (UNODC) for cathinones, involving presumptive colour tests followed by confirmation with, for example, GC-MS or GC-IR *(8)*.

Published methods for chiral separation of the two enantiomers of 3-CMC are based on LV–ultraviolet detection and capillary electrophoresis *(9–12)*. In view of the high cost of enantiomerically pure material, however, the products on the market are probably in the racemic form *(5)*.

Generic GC-MS methods may not allow distinction between 3-CMC and its positional isomers, 2-CMC and 4-CMC, as they have close retention

times and identical MS/MS spectra *(13)*; however, the isomers can be resolved with special GC-MS methods. The isomeric forms can also be separated after derivatization and their retention time compared with that of the corresponding analytical standards *(5,7,13,14)*. Kadkhodaei et al. *(12)* showed that chiral analysis with a specific stationary phase can be used to discriminate between different cathinones, including 2-, 3- and 4-CMC *(12)*. Positional isomers of 3-CMC, including 2-CMC *(15)* and 4-CMC *(16)*, are commercially available as standards.

3-CMC can be analysed in biological matrices such as blood, urine, vitreous fluid and oral fluid by LC coupled with either low-resolution (e.g. triple quadrupole) *(17)* or high-resolution (e.g. quadrupole time-of-flight) MS *(18, 19)*. 3-CMC has been characterized in whole blood and urine by direct analysis in real time coupled to tandem MS, a screening method with the advantage of fast sample preparation and low environmental impact *(20)*.

3. Ease of conversion into controlled substances

No information was available on whether 3-CMC can be converted into a controlled substance.

4. General pharmacology

A. Routes of administration and dosage

No clinical studies on 3-CMC were found, and information on dosage and routes of administration from Internet discussion forums was limited. The routes of administration most commonly reported were oral ingestion and intranasal application. It was reported that an oral dose of 350 mg resulted in high euphoric effects *(21)*. Another reported that snorting six 50-mg doses over 5–6 h each resulted in onset of a euphoric effect after 10 min, with side-effects including tachycardia and craving *(22)*. Some people who used 3-CMC reported that 3-CMC was neurotoxic *(23)*, and one reported a painful ulcer in the mouth after use *(24)*. These reports are difficult to assess, not least because people who use the substance might be unable to confirm the actual substance or the amount used. Given the difficulty of collecting accurate self-reported data, these reports should be interpreted with caution.

B. Pharmacokinetics

No information was available on the absorption and distribution of 3-CMC. The metabolism of 3-CMC in human biological samples (Fig. 1) has been reported to include dihydro-3-CMC, *N*-desmethyl-3-CMC and *N*-desmethyl-dihydro-3-CMC *(25)*.

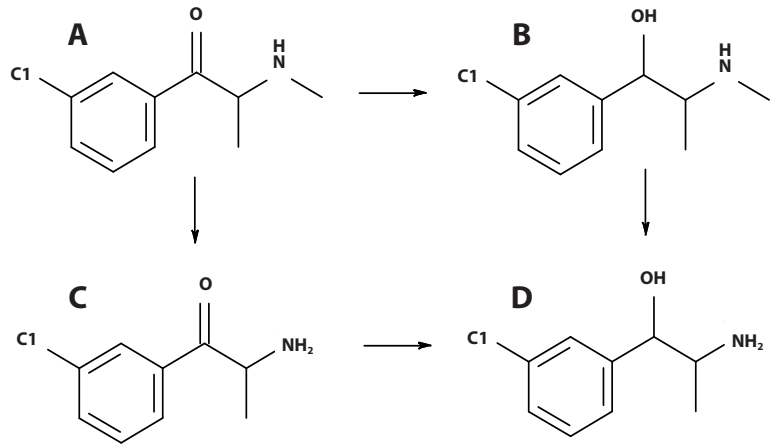


Fig. 1. Reported human metabolism of 3-CMC (A) to dihydro-3-CMC (B), *N*-desmethyl-3-CMC (C) and *N*-desmethyl-dihydro-3-CMC (D)

C. Pharmacodynamics

Little information was available on the pharmacodynamics of 3-CMC. 3-CMC has psychoactive effects in both humans and animals, including dose-dependent increases in horizontal spontaneous locomotor activity in mice *(26)*. Walter et al. *(27)* showed that 3-CMC is an active stimulant and releasing agent at dopamine, serotonin and norepinephrine transporters. The effects of the isomer 4-CMC were similar to those of 4-methylmethcathione (mephedrone), with nearly identical potency *(28)*.

5. Toxicology

No information was found on the acute or chronic preclinical toxicology of 3-CMC.

6. Adverse reactions in humans

Between 2018 and 2022, eight deaths involving 3-CMC were reported in Sweden, in seven of which the drug was considered to be the cause of death and one in which the drug was listed as contributing to death *(29)*. In 38 cases of drug-impaired driving, 3-CMC was confirmed in blood and/or urine. Physiological and adverse effects reported after cases of poisoning included vomiting, headache, large pupils, hyperventilation, agitation, motor restlessness, sweating, increased pulse, high blood pressure, chest pain and seizures *(29)*.

Wonderen et al. *(30)* reported two clinical cases of prolonged excited delirium after exposure to CMC; however, the isomer configuration was not determined. Both patients showed aggressive behaviour and anxiety at hospital admission. Their Glasgow Coma Scale was 4-6-1 and 3-6-5. Clinical signs were blood pressure of 129/100 and 129/60 mm Hg, heart rate of 110 and 110 beats per min, body temperature of 37.1 °C and 36.7 °C, respiration rate of 18 and 16 breaths per min, and oxygen saturation of 97% and 97% in room air. The pupils of one patient were normal in size but unresponsive to light. Both patients survived and were discharged from hospital after about 2 days.

3-CMC was reported in one medicolegal death investigation case after suspected poisoning *(25)*. Internal autopsy revealed pulmonary oedema, hyperaemia of internal organs, enlargement of the heart cavities, slight atherosclerosis of the coronary arteries, signs of hepatic steatosis and scars in the kidney cortex. 3-CMC and its metabolites were confirmed in biological samples.

A person who used 3-CMC described in an online report short-term neurological adverse effects after prolonged use of 3-CMC *(24)*.

3-CMC was reported in an acute non-fatal case in Spain in one individual *(5)*. The case report described "chemsex" practices, and additional drugs were detected during testing of biological samples. No further details were provided.

No additional studies of human exposure to 3-CMC were found, except for a case report involving 4-CMC, which is mentioned because the two isomers are expected to have similar effects. Tomczak et al. *(31)* reported 15 forensic cases involving 4-CMC, including both fatal and non-fatal drug overdoses and exposure. Autopsy of the decedents revealed acute cardiac failures, vomit in the respiratory tract and passive congestion of internal organs; however, 4-CMC might not have been the sole drug taken.

7. Dependence potential

A. Studies in experimental animals

No studies on the dependence potential of 3-CMC in experimental animals were found.

B. Studies in humans

No studies on the dependence potential of 3-CMC in humans were found.

8. Abuse potential

A. Studies in experimental animals

No studies on the abuse potential of 3-CMC in experimental animals were found.

B. Studies in humans

No studies on the avuse potential of 3-CMC in humans were found.

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

No information was found on therapeutic use.

10. Listing on the WHO Model List of Essential Medicines

3-CMC is not listed on the 23rd List of Essential Medicines List or the 9th List of Essential Medicines for Children as of July 2023.

11. Marketing authorizations (as a medicinal product)

No information was found on marketing authorization of 3-CMC as a medicinal product.

12. Industrial use

No information was found on industrial use of 3-CMC.

13. Non-medical use, abuse and dependence

3-CMC was first reported on the European drug market in 2014 by Sweden *(32)*. Since 2014, 3-CMC has been reported annually in Europe and other countries.

According to the UNODC Early Warning Advisory on New Psychoactive Substances, 3-CMC was detected in 31 countries in four regions between 2019 and 2022. Cases involving 3-CMC were reported in 21 countries in 2019, 17 in 2020, 20 in 2021 and 15 in 2022 *(33)*. A total of 161 cases involving 3-CMC were reported between 2015 and up to August 2023 (Table 1).

Table 1. Numbers of cases involving 3-CMC reported to the UNODC Early Warning Advisory on New Psychoactive Substances, by year

Year	No. of cases	Countries
2015	19	Belgium, Czechia, Estonia, Finland, France, Hungary, Kazakhstan, Netherlands (Kingdom of the), Norway, Poland, Romania, Russian Federation, Singapore, Slovakia, Slovenia, Sweden, Ukraine, USA
2016	13	Germany, Hungary, Kazakhstan, Netherlands (Kingdom of the), Norway, Poland, Slovakia, Spain, Sweden, Ukraine, USA
2017	13	Denmark, Estonia, France, Hungary, Italy, Netherlands (Kingdom of the), Norway, Poland, Slovakia, Spain, Sweden, United Kingdom, USA
2018	14	Austria, Belgium, Denmark, Finland, France, Lithuania, Luxembourg, Netherlands (Kingdom of the), Poland, Portugal, Slovenia, Spain, Switzerland, United Kingdom
2019	27	Austria, Belgium, Czechia, Denmark, Estonia, France, Germany, Greece, Hungary, Latvia, Lithuania, Netherlands (Kingdom of), Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom, USA
2020	21	Belgium, Denmark, Estonia, Finland, France, Germany, Hungary Italy, Malta, Netherlands (Kingdom of the), New Zealand, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom
2021	22	Austria, Bulgaria, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Netherlands (Kingdom of the), Norway, Poland, Slovakia, Spain, Sweden, Switzerland, United Kingdom, USA
2022	30	Argentina, Austria, Chile, Czechia, France, Germany, Hungary, Ireland, Italy, New Zealand, Panama, Poland, Romania, Spain, Switzerland, United Kingdom, USA
2023 (to August)	2	Austria, Switzerland

According to the UNODC, 3-CMC has been reported in the USA about once a year since 2015 *(33)*. 3-CMC has not been detected by toxicological investigations and seized drugs in the laboratory for New Psychoactive Drugs Discovery at the Center for Forensic Science Research and Education in the USA since 2018 *(34)*. According to the Drug Enforcement Administration National Forensic Laboratory Information System Drug Query System, 3-CMC was reported one to eight times a year between 2015 and 2021 by all participating crime laboratories *(35)*.

No epidemiological evidence for use of 3-CMC was found. It may be used in combination (intentionally or unintentionally) with other drugs, and people using the substance may be unaware of the exact dose or drug(s) being ingested. 3-CMC has been reported in products with 4-CMC and other drugs; however, the frequency and/or prevalence of use are not well understood *(33)*. 3-CMC is also available alone.

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

3-CMC has been offered for sale by numerous Internet retailers. As people who use drugs are likely to obtain 3-CMC from unregulated sources, its purity and dose are not assured, presenting an additional risk of adverse reactions. Currently, 3-CMC has only a small impact on public health, as its presence on the drug market is minimal. Given its pharmacological profile, however, 3-CMC appears to present a moderate risk for recreational use, physiological dependence and overdose.

15. Licit production, consumption and international trade

3-CMC is used as reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic use. Some Internet retailers have advertised it for sale as a "research chemical" or for similar use.

16. Illicit manufacture and traffic and related information

It was reported from Sweden that the amount of 3-CMC seized by customs increased in 2021 and 2022 to approximately 50 kg and 68 kg, respectively *(29)*.

The European Monitoring Centre for Drugs and Drug Addiction has received reports of seizures of 3-CMC totalling more than 2700 kg. Between 2020 and 2021, 2500 kg were seized, most seizures occurring in 2021. In the seizures reported, 3-CMC was found mainly as a powder and less frequently as tablets and capsules *(5)*.

17. Current international controls and their impact

3-CMC is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

See Annex 1.

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

Detection of 3-CMC may be under-reported if it is not included in routine screening in all laboratories that receive samples for analysis.

References

1. 3-Chloromethcathinone (hydrochloride) (Item No. 17394). Ann Arbo (MI): Cayman Chemicals; 2019 (https://www.caymanchem.com/product/17394, accessed 3 July 2023).
2. Blough BE, Landavazo A, Partilla JS, Baumann MH, Decker AM, Page KM et al. Hybrid dopamine uptake blocker–serotonin releaser ligands: a new twist on transporter-focused therapeutics. ACS Med Chem Lett. 2014;5:623–7. doi:10.1021/ml500113s.
3. Shalabi AR, Walther D, Baumann MH, Glennon RA. Deconstructed analogues of bupropion reveal structural requirements for transporter inhibition versus substrate-induced neurotransmitter release. ACS Chem Neurosci. 2017;8:1397-403. doi:10.1021/acschemneuro.7b00055.
4. Analytical report 3-CMC (C10H12ClNO) 1-(3-chlorophenyl)-2-(methylamino)propan-1-one. In: Novel psychoactive substances and related compounds – analytical reports European project RESPONSE to challenges in forensic drugs analyses. Ljubljana: National Forensic Laboratory; 2015 (https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/3-CMC-ID-1152-report_final.pdf).
5. Report on the risk assessment of 1-(3-chlorophenyl)-2-(methylamino)propan-1-one (3-chloromethcathinone, 3-CMC) in accordance with Article 5c of Regulation (EC) No. 1920/2006 (as amended). Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2022 (https://www.emcdda.europa.eu/publications/risk-assessments/3-cmc_en, accessed 4 July 2023).
6. Critical review report: 3-Methylmethcathinone (3-MMC). Geneva: World Health Organization, Expert Committee On Drug Dependance; 2022 (https://cdn.who.int/media/docs/default-source/controlled-substances/45th-ecdd/3-mmc_draft.pdf?sfvrsn=f046b91f_1, accessed 4 July 2023).
7. Romańczuk A, Rojek S, Synowiec K, Maciów-Głąb M, Kula K, Rzepecka-Woźniak E. The stability of synthetic cathinones and the study of potential intake biomarkers in the biological material from a case of 3-CMC poisoning. J Anal Toxicol. 2023;47:470–80. doi:10.1093/jat/bkad010.
8. Recommended methods for the identification and analysis of synthetic cathinones in seized materials. Vienna: United Nations Office on Drugs and Crime; 2020 (https://www.unodc.org/documents/scientific/Recommended_methods_for_the_Identification_and_Analysis_of_Synthetic_Cathinones_in_Seized_Materials-Rev..pdf.
9. Hägele JS, Hubner EM, Schmid MG. Chiral separation of cathinone derivatives using β-cyclodextrin-assisted capillary electrophoresis – comparison of four different β-cyclodextrin derivatives used as chiral selectors. Electrophoresis. 2019;40:1787–94. doi:10.1002/elps.201900085.
10. Hägele JS, Basrak M, Schmid MG. Enantioselective separation of novel psychoactive substances using a Lux® AMP 3 µm column and HPLC-UV. J Pharm Biomed Anal. 2020;179:112967. doi:10.1016/j.jpba.2019.112967.
11. Kadkhodaei K, Forcher L, Schmid MG. Separation of enantiomers of new psychoactive substances by high-performance liquid chromatography. J Sep Sci. 2018;41:1274–86. doi:10.1002/jssc.201701239.
12. Kadkhodaei K, Kadisch M, Schmid MG. Successful use of a novel lux® i-Amylose-1 chiral column for enantioseparation of "legal highs" by HPLC. Chirality. 2020;32:42–52. doi:10.1002/chir.23135.
13. Woźniak MK, Banaszkiewicz L, Wiergowski M, Tomczak E, Kata M, Szpiech B et al. Development and validation of a GC–MS/MS method for the determination of 11 amphetamines and 34 synthetic cathinones in whole blood. Forensic Toxicol. 2020;38:42–58. doi:10.1007/s11419-019-00485-y.
14. Synowiec K, Rojek S, Maciów-Głąb M, Kula K, Romańczuk A, Kłys M. The role of GC-EI-MS and derivatization in the detection of new psychoactive substances exemplified by 49 synthetic cathinones. J Anal Chem. 2022;77:1315–24. doi:10.1134/S106193482210015X.
15. 2-Chloromethcathinone (hydrochloride) (item No. 17744). Ann Arbor (MI): Cayman Chemicals; 2017 (https://www.caymanchem.com/product/17744/2-chloromethcathinone-(hydrochloride, accessed 4 July 2023).
16. 4-Chloromethcathinone (hydrochloride) (item No. 16436). Ann Arbor (MI): Cayman Chemicals; 2023 (https://www.caymanchem.com/product/16436/4-chloromethcathinone-(hydrochloride), accessed 4 July 2023).

17. Tusiewicz K, Chłopaś-Konowałek A, Wachełko O, Zawadzki M, Szpot P. A fatal case involving the highest ever reported 4-CMC concentration. J Forensic Sci. 2023;68:349–54. doi:10.1111/1556-4029.15162.

18. Axelsson MAB, Lövgren H, Kronstrand R, Green H, Bergström MA. Retrospective identification of new psychoactive substances in patient samples submitted for clinical drug analysis. Basic Clin Pharmacol Toxicol. 2022;131:420–34. doi:10.1111/bcpt.13786.

19. Bergström MA, Lövgren H, Abrahamsson A, Eriksson EK, Andersson ML, Komorowska M, Axelsson MAB. Rethinking drug analysis in health care: high-throughput analysis of 71 drugs of abuse in oral fluid using ion mobility–high-resolution mass spectrometry. J Anal Toxicol. 2022;46:765–75. doi:10.1093/jat/bkab114.

20. Ji J, Zhang Y, Wang J. Rapid detection of nine synthetic cathinones in blood and urine by direct analysis in real-time-tandem mass spectrometry. Rapid Commun Mass Spectrom. 2021;35:e9136. doi:10.1002/rcm.9136.

21. I feel like 3-MMC is not getting enough hype. Bluelight.org (https://bluelight.org/xf/threads/i-feel-like-3-mmc-is-not-getting-enough-hype.932027/).

22. 3-CMC (3-chloromethcathinone). San Francisco (CA): Reddit (https://www.reddit.com/r/researchchemicals/comments/dfw57f/3cmc_3chloromethcathinone/).

23. Risk analysis: cathinones 3-chloromethcathinone and alpha-pyrrolidinoisohexaphenone (3CMC vs α-PHiP). San Francisco (CA): Reddit (https://www.reddit.com/r/researchchemicals/comments/15b0c7n/risk_analysis_cathinones_3chloromethcathinone_and/).

24. 3-CMC short term neurological adverse effects – anecdotal report. Bluelight.org (https://bluelight.org/xf/threads/3-cmc-short-term-neurological-adverse-effects-anecdotal-report.927574/).

25. Romańczuk A, Rojek S, Synowiec K, Maciów-Głąb M, Kula K, Rzepecka-Woźniak E. The stability of synthetic cathinones and the study of potential intake biomarkers in the biological material from a case of 3-CMC poisoning. J Anal Toxicol. 2023;47:470–80. doi:10.1093/jat/bkad010.

26. Wojcieszak J, Kuczyńska K, Zawilska JB. Four synthetic cathinones: 3-chloromethcathinone, 4-chloromethcathinone, 4-fluoro-α-pyrrolidinopentiophenone, and 4-methoxy-α-pyrrolidinopentiophenone produce changes in the spontaneous locomotor activity and motor performance in mice with varied profiles. Neurotoxicity Res. 2020;38:536-51. doi:10.1007/s12640-020-00227-8.

27. Walther D, Shalabi AR, Baumann MH, Glennon RA. Systematic structure-activity studies on selected 2-, 3-, and 4-monosubstituted synthetic methcathinone analogs as monoamine transporter releasing agents. ACS Chem Neurosci. 2019;10:740–5. doi:10.1021/acschemneuro.8b00524.

28. Chojnacki MR, Thorndike EB, Partilla JS, Rice KC, Schindler CW, Baumann MH. Neurochemical and cardiovascular effects of 4-chloro ring-substituted synthetic cathinones in rats. J Pharmacol Exp Ther. 2023;385:162–70. doi:10.1124/jpet.122.001478.

29. Official communication – 3-CMC. Stockholm: Public Health Agency; 2023.

30. van Wonderen K, Jongbloed-de Hoon M, Meinders A, Harmsze A. Two cases of a prolonged excited delirium syndrome after chloromethcathinone ingestion. Neth J Med. 2020;78(5):300–2. PMID:33093258.

31. Tomczak E, Woźniak MK, Kata M, Wiergowski M, Szpiech B, Biziuk M. Blood concentrations of a new psychoactive substance 4-chloromethcathinone (4-CMC) determined in 15 forensic cases. Forensic Toxicol. 2018;36:476–85. doi:10.1007/s11419-018-0427-8.

32. EMCDDA–Europol 2014 Annual Report on the implementation of Council Decision 2005/387/JHA. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2014 (https://www.emcdda.europa.eu/publications/edr/trends-developments/2014_en).

33. UNODC Early Warning Advisory (EWA) on New Psychoactive Substances (NPS). Vienna: United Nations Office on Drugs and Crime; 2023 (https://www.unodc.org/LSS/Home/NPS, accessed 8 January 2023).

34. New psychoactive substances discovery. UNODC Early Warning Advisory (EWA) on NPS), accessed 8 March 2023).

35. The NFLIS Public Data Query System. Springfield (VA): National Forensic Laboratory Information System; 2023 (https://www.nflis.deadiversion.usdoj.gov/publicDQSinfo.xhtml, accessed 28 August 2023).

3.1.5 Dipentylone

1. Substance identification

A. International Nonproprietary Name (INN)

Not assigned

B. Chemical Abstract Service (CAS) registry number

803614-36-0 (free base)

17763-13-2 (hydrochloride salt)

2304915-61-3 ((S)-enantiomer)

2304915-25-9 ((R)-enantiomer)

C. Other chemical names

1-(1,3-Benzodioxol-5-yl)-2-(dimethylamino)-1-pentanone (ACI)

Valerophenone, 2-(dimethylamino)-3′,4′-(methylenedioxy)- (8CI)

Dipentylone

N,N-Dimethylpentylone

D. Trade names

Dipentylone hydrochloride is sold under the name N,N-Dimethylpentylone (hydrochloride) as analytical reference standard *(1)*.

E. Street names

Chemical names mentioned above may be encountered as street names. Other code names include DMBDP, Bk-dmbdp, betaK-Dmbdp BU crystal *(2)*.

F. Physical appearance

Dipentylone hydrochloride is described as a neat solid; for recreational use, dipentylone is mostly distributed as crystals or tablets *(1)*.

G. WHO review history

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

1. Chemistry

A. Chemical name

IUPAC name: 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one

CA index name: 1-Pentanone, 1-(1,3-benzodioxol-5-yl)-2-(dimethylamino)-(ACI)

Free base:
Canonical SMILES
O=C(C1=CC=C2OCOC2=C1)C(N(C)C)CCC

InChI
InChI=1S/C14H19NO3/c1-4-5-11(15(2)3)14(16)10-6-7-12-13(8-10)18-9-17-12/h6-8,11H,4-5,9H2,1-3H3

InChI Key
PQTJKFUXRBKONZ-UHFFFAOYSA-N

Hydrochloride salt
Canonical SMILES
Cl.O=C(C1=CC=C2OCOC2=C1)C(N(C)C)CCC

InChI
InChI=1S/C14H19NO3.ClH/c1-4-5-11(15(2)3)14(16)10-6-7-12-13(8-10)18-9-17-12;/h6-8,11H,4-5,9H2,1-3H3;1H

InChI Key
LSDMAZIZKMMYTB-UHFFFAOYSA-N

(2R)-enantiomer
Canonical SMILES
O=C(C1=CC=C2OCOC2=C1)C(N(C)C)CCC

Isomeric SMILES
C([C@@H](CCC)N(C)C)(=O)C=1C=C2C(=CC1)OCO2

InChI
InChI=1S/C14H19NO3/c1-4-5-11(15(2)3)14(16)10-6-7-12-13(8-10)18-9-17-12/h6-8,11H,4-5,9H2,1-3H3/t11-/m1/s1

InChI Key
PQTJKFUXRBKONZ-LLVKDONJSA-N

(2S)-enantiomer
Canonical SMILES
O=C(C1=CC=C2OCOC2=C1)C(N(C)C)CCC

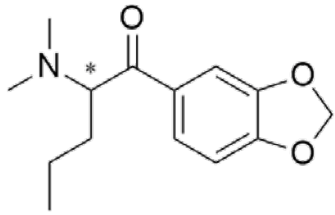
Isomeric SMILES
C([C@H](CCC)N(C)C)(=O)C=1C=C2C(=CC1)OCO2

InChI
InChI=1S/C14H19NO3/c1-4-5-11(15(2)3)14(16)10-6-7-12-13(8-10)18-9-17-12/h6-8,11H,4-5,9H2,1-3H3/t11-/m0/s1

InChI Key
PQTJKFUXRBKONZ-NSHDSACASA-N

B. Chemical structure

Free base:

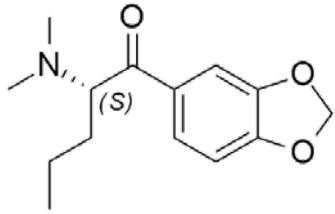


Molecular formula: $C_{14}H_{19}NO_3$

Molecular weight: 249.31 g/mol

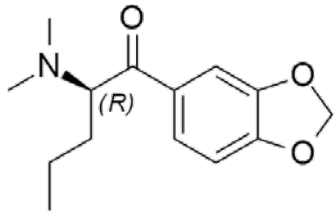
C. Stereoisomers

Dipentylone contains a chiral centre, thus two enantiomers may exist: (R)-dipentylone and (S)-dipentylone. No information is available on the enantiomeric composition of dipentylone circulating on the drug market but it is most likely available as a racemic mixture of the (R)- and (S)-enantiomers, though the appearance of individual stereoisomers cannot be excluded.



(2S)-1-(1,3-Benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one

CAS RN 2304915-61-3



(2R)-1-(1,3-Benzodioxol-5-yl)-2-(dimethylamino)pentan-1-one

CAS RN 2304915-25-9

D. Methods and ease of illicit manufacturing

There is no specific information available about the routes of synthesis employed for the dipentylone products circulating on the market. The first synthesis of dipentylone was described in 1967 in a patent *(3)*. However, the chemical synthesis of cathinones is facile and usually follows a two-step process. An α-bromoketone ((1-(1,3-Benzodioxol-5-yl)-2-bromo-1-pentanone), is obtained from the appropriate arylketone (1-(benzo[*d*][1,3]dioxol-5-yl)pentan-1-one, followed by nucleophilic substitution with an appropriate amine (dimethylamine) to give the corresponding cathinone (dipentylone,). Cathinones are generally isolated as their salts due to the instability of the freebase *(4)*. This procedure has been also employed for the preparation of dipentylone analogs. The ketone species (1-(1,3-Benzodioxol-5-yl)-2-bromo-1-pentanone) is accessible by various routes and is commercially available.

Whilst the total synthesis of dipentylone requires qualified personnel and well-equipped synthetic laboratory, the preparation requires simple equipment, and can be performed by unqualified personnel.

E. Chemical properties

Melting point
Dipentylone hydrochloride 225 °C-228 °C *(3)*

Boiling point
No information could be identified

Solubility
Dipentylone hydrochloride: 5 mg/mL in methanol (MeOH), 1 mg/mL in PBS (pH 7.2) *(1)*

F. Identification and analysis

Dipentylone hydrochloride salt and the deuterated species dipentylone-d_6 hydrochloride salt are available as reference material from commercial suppliers to assist with the implementation of routine methods of analysis associated with forensic and clinical investigations *(1)*.

Identification and quantification of dipentylone in seized material can be carried out according to the general procedure described for cathinones by the UNODC, where presumptive colour tests and confirmation methods by GC-MS and GC-FT-IR *(4)*.

As a pure compound, dipentylone hydrochloride has been fully characterized by proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NM), Fourier Transform-InfraRed (FT-IR) spectroscopy, and GC-MS *(5, 6)*.

Dipentylone was also detected in some wastewaters samples and quantified by both UHPLC and μLC coupled to MS/MS in Italy in 2019 for the first time *(7)* and by LC-MS/MS in Spain in 2018 *(8)*.

The enantiomers of dipentylone (purchased online) were separated by chiral LC-UV *(9)*.

Analytical methods were developed for the determination of dipentylone in urine samples by either LC-QqQ *(10)* or LC-HRMS *(11)*. Dipentylone was determined in oral fluid by LC-MS/MS with a limit of detection of 0.1 ng/mL *(12)*. In the same work, stability studies showed that dipentylone is stable at ambient temperature for 15 days, at 4 °C for 60 days, and at -20 °C for 90 days *(12)*.

3. Ease of convertibility into controlled substances

It is not known from the literature whether dipentylone can be converted into a controlled substance or how easy it would be.

4. General Pharmacology

A. Routes of administration and dosage

Unverified media reports describe that people are buying dipentylone in 'chunks' and then cutting it into powders to snort, inject, or smoke *(13)*. People posting on online forums (e.g., BlueLight) and reports to Wedinos indicate dipentylone may be smoked *(14)* or taken orally *(15)*.

No reports on dosage were found.

B. Pharmacokinetics

No data on the absorption, distribution, metabolism, and excretion of dipentylone could be found.

Pentylone is suspected to be a metabolite of dipentylone, as it was detected in the blood of a series of 18 post-mortem cases in which dipentylone was identified, but at a lower concentration than the detected concentration of dipentylone *(16)*. Similarly, data from the Center for Forensic Science Research and Education (CFSRE) indicated the presence of pentylone at lower concentrations (120 ± 170, range: 10 – 420) than dipentylone (270 ± 400, range: 33–970) in a series of 32 toxicological cases, further supporting pentylone as a metabolite of dipentylone *(17)*. However, co-ingestion of pentylone and dipentylone cannot be ruled out, and laboratories should always ascertain the presence of dipentylone whenever pentylone is detected.

C. Pharmacodynamics

The interaction of dipentylone with monoamine transporters was determined by testing the effects of dipentylone on radioligand ([^{125}I]RTI-55) binding and [^{3}H]neurotransmitter (i.e., dopamine, serotonin, norepinephrine) uptake by HEK cells expressing cDNA for the human dopamine transporter (HEK-hDAT cells), the human serotonin transporter (HEK-hSERT cells), and the human norepinephrine transporter (HEK-hNET cells). Dipentylone presented higher affinity for DAT (Ki = 0.354 ± 0.073 μM) than NET (Ki = 2.00 ± 0.34 μM) or SERT (Ki = 2.27 ± 0.30 μM), being equipotent at inhibiting NET (IC50 = 0.212 ± 0.068 μM) and DAT (IC50 = 0.233 ± 0.066 μM), and being about 10-fold more selective at inhibiting DAT and NET than SERT (IC50 = 2.57 ± 0.55 μM) (Table 1). As also shown in Table 1, comparison of the effects of dipentylone on binding and uptake with other stimulants indicated that dipentylone presented an affinity to DAT more similar to cocaine than to methamphetamine (METH) or MDMA (about 12- and 88-fold higher, respectively). Dipentylone further showed to be about 2-fold more potent in inhibiting dopamine uptake than cocaine or MDMA, but less potent (about 2.4-fold) than METH. It also showed much higher affinity to SERT than METH or MDMA (about 66- and 8-fold higher, respectively), but lower (about 4.5-fold) than cocaine, as well as higher potency (about 3.6-fold) than METH, and lower than cocaine and MDMA (about 7- and 22-fold, respectively) in inhibiting serotonin uptake. Dipentylone also showed a similar binding affinity to NET as cocaine and METH, but lower than MDMA (about 8-fold), and about 2- and 3-fold higher potency in inhibiting norepinephrine uptake than cocaine and MDMA, respectively, but about 10-fold less potent than METH in inhibiting the uptake of this neurotransmitter.

Table 1. Effects of dipentylone, in comparison with cocaine, methamphetamine (METH) and MDMA on [^{125}I]RTI-55 binding and [3H]neurotransmitter uptake by HEK-hDAT, HEK-hSERT, and HEK-hNET cells (mean ± SEM)
Adapted from Eshleman et al., 2019, (18)

	Dipentylone	Cocaine	METH	MDMA
HEK-hDAT				
[^{125}I]RTI-55 binding: Ki ± SEM (μM) (*n*)	0.354 ± 0.073 (3)	0.495 ± 0.049 (22)	4.41 ± 0.43 (20)	31.0 ± 4.9 (6)
[^{3}H]DA uptake: IC50 ± SEM (μM) (*n*)	0.233 ± 0.066 (3)	0.425 ± 0.036 (23)	0.097 ± 0.013 (21)	0.479 ± 0.070 (4)
HEK-hSERT				
[^{125}I]RTI-55 binding: Ki ± SEM (μM) (*n*)	2.27 ± 0.30 (3)	0.495 ± 0.034 (20)	150 ± 17 (20)	17.5 ± 3.3 (6)
[^{3}H]5-HT uptake: IC50 ± SEM (μM) (*n*)	2.57 ± 0.55 (5)	0.364 ± 0.040 (24)	9.3 ± 1.1 (18)	0.118 ± 0.019 (4)
HEK-hNET				
[^{125}I]RTI-55 binding: Ki ± SEM (μM) (*n*)	2.00 ± 0.34 (3)	1.95 ± 0.15 (18)	2.51 ± 0.24 (16)	15.8 ± 4.1 (7)
[^{3}H]NE uptake: IC50 ± SEM (μM) (*n*)	0.212 ± 0.068 (4)	0.382 ± 0.037 (23)	0.0258 ± 0.0030 (19)	0.63 ± 0.14 (3)

Dipentylone (administered at 2.5, 5, 10, 25, and 50 mg/kg immediately prior to locomotor activity testing) time- and dose-dependently stimulated locomotor activity, assessed by measuring horizontal activity, i.e., the interruption of photocell beams located in the horizontal direction along the sides of each activity chamber, for 8h, within 10-min periods, in a group of male Swiss-Webster mice *(19)*. Increases in locomotor activity were observed following 10 and 25 mg/kg, with peak effects observed after the administration of 25 mg/kg. Peak effects occurred within 10 min and lasted 360 min. A higher dose of 50 mg/kg returned locomotor activity to baseline levels. Dipentylone presented a locomotor activity potency similar to cocaine (ED50 = 5.29 ± 0.09 mg/kg vs 5.03 ± 0.06 mg/kg, for dipentylone and cocaine, respectively), but it was less potent than methamphetamine (ED50 = 0.41 ± 0.05 mg/kg) *(19)*.

Similar data were also previously obtained by Sumien et al., (2018) *(20)*, who showed that intraperitoneal injection of male Swiss-Webster mice with 1, 2.5, 5, 10, 25 or 50 mg/kg dipentylone immediately prior to locomotor activity testing, also stimulated locomotor activity (measurement of horizontal activity) in a time- and dose-dependent manner following 5 to 50 mg/kg.

Stimulant effects of 5 to 25 mg/kg occurred within 10 min following injection and lasted 80-220 minutes. Based on the 30-minute time period in which maximal stimulant effects occurred, the ED50 was estimated at 6.4 mg/kg and the peak effect was estimated to be 6539 counts/10 min at 14.2 mg/kg.

The maximum locomotor activity in mice administered cocaine was estimated to be 5593 counts/10 min at 12.7 mg/kg, with a potency (ED50) estimated at 2.5 mg/kg. For mice injected with methamphetamine, maximum locomotor activity was estimated at 6653 counts/10 min at 1.2 mg/kg, with an ED50 calculated at 0.51 mg/kg *(20)*.

5. Toxicology

The Center for Forensic Science Research and Education (CFSRE) reported that dipentylone was first identified in toxicology samples in the U.S. in the third quarter of 2021. Up to April 2022, dipentylone had been identified in 32 toxicology cases, including antemortem and postmortem investigations, in addition to drug material cases *(17)*.

A recent publication reported that dipentylone was detected in 18 post-mortem cases with a resulting concentration range of 3.3 to 970 ng/mL (median: 145 ng/mL, mean 277 ± 283 ng/mL). In all cases, dipentylone was found in combination with other substances, namely fentanyl (n=7), eutylone (n=6), and methamphetamine/amphetamine (n=5). Sixty-two additional cases were pending analysis *(16)*.

A recent paper confirmed the presence of dipentylone in a postmortem sample (using GC-MS/MS) in New Zealand in 2021 *(21)*. Also in New Zealand, "serious harm" was recently linked to the consumption of dipentylone, in combination with bromazolam, which was misrepresented as MDMA *(22)*.

Two fatal cases involving dipentylone were analyzed by DEA-Tox in 2023: 1) dipentylone was detected in the toxicological analysis of a 58-year-old male from Sevier County, with a past medical history including past intravenous drug use and cocaine use, at a concentration of 83.4 ng/mL. Methamphetamine (2500 ng/mL), fentanyl (36.6 ng/mL), and pentylone (10.7 ng/mL) were also detected. 2) Dipentylone (0.3 ng/mL) was also confirmed in the toxicological analysis of a 34-year-old male in Tennessee, with a history of tobacco and alcohol use, and previous reports from the Controlled Substances Monitoring Database positive for hydrocodone (Oct 2022) and oxycodone (on Nov 2022).

No reports were found on the toxic doses of dipentylone for humans.

6. Adverse reactions in humans

A media report described dipentylone's effects as similar to the effects of other narcotic stimulants *(13)*.

An individual who brought a sample to KnowYourStuffNZ for checking shared they had taken the substance and described the experience as "very unenjoyable". They also experienced a bad comedown, during which they felt anxious *(23)*.

A participant in the Bluelight forum reported smoking dipentylone was "very bad for the lungs" and it produced a bad taste (described as "resembling diesel fuel") and "nasty burning" *(14)*.

Reports to Wedinos indicate that adverse reactions following oral intake of dipentylone include: increased energy (5), enhanced senses (4), relaxation (5), increased confidence (5), euphoria (3), empathy (3), insomnia (3), memory loss (3), paranoia (2), confusion (2), hallucinations (1), panic attack (1), agitation (1), breathlessness (1), irregular heartbeat (1), depression (1), suicidal ideation (1) *(15)*.

7. Dependence potential

A. Animal studies

No studies were identified.

B. Human studies

No studies were identified.

8. Abuse potential

A. Animal studies

Using a two-lever choice methodology, dipentylone (2.5, 5, 10, and 25 mg/kg) was tested for substitution in Sprague-Dawley rats trained to discriminate either methamphetamine (1 mg/kg), cocaine (10 mg/kg), or MDMA (1.5 mg/kg) from saline *(19)*. Dipentylone fully substituted for the discriminative stimulus effects of methamphetamine (ED50 = 8.70 ± 0.12 mg/kg), and cocaine (ED50 = 8.27 ± 0.12 mg/kg), demonstrating abuse potential *(19, 20)*. In the methamphetamine-trained rats, dipentylone increased the response rate after injection with 5 and 10 mg/kg, with the maximum effect (152% of vehicle control) being reached at 10 mg/kg. This effect decreased to 52% of the vehicle control following 25 mg/kg. In the cocaine-treated rats, dipentylone (1 to 25 mg/kg) did not change the response rate, compared to the vehicle control *(19, 20)*. Dipentylone only partially substituted for the discriminative

stimulus of MDMA, producing a maximum of 60% MDMA-appropriate responding following 25 mg/kg. The response rate was increased to 155% of vehicle control following 10 mg/kg and decreased to 18% of vehicle control following 50 mg/kg, such that only two of six rats earned a reinforcer *(19, 24)*.

B. Human studies

No studies on the abuse potential of dipentylone were identified in humans.

One person who reported dipentylone use in an online forum described the inability to stop taking it *(14)*.

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

Dipentylone is not known to have any medical use.

10. Listing on the WHO Model List of Essential Medicines

Dipentylone 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)

Dipentylone is not known to be authorized for marketing in any country.

12. Industrial use

Dipentylone is not known to have any industrial use.

13. Non-medical use, abuse and dependence

In a 2019 study aimed at simultaneously determining the presence of illicit drugs and new psychoactive substances in sewage, dipentylone was detected in wastewater for the very first time. It was detected at a concentration of 6.4 ng/L in one out of the eight wastewater treatment plants analyzed. Further information about the characteristics of the wastewater treatment plants (i.e., location, area/population that they represent) was not disclosed *(7)*. More recently, in a study analyzing wastewater samples collected from 13 Spanish cities (covering 6 million inhabitants, which corresponds to 12.8% of the Spanish population), the same authors also reported the presence of dipentylone in samples taken from the wastewater in Valencia *(8)*.

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

No specific information on the nature and magnitude of public health problems associated with the use of dipentylone was identified.

However, it should be noted that dipentylone has been confirmed in biological fluids from postmortem cases.

Notably, dipentylone has been frequently detected in products mislabeled and/or thought to be sold as other substances (e.g., MDMA, 2c-B, alprazolam, 4-MMC, or mephedrone), suggesting that most people who use dipentylone may be unaware that they are using it.

15. Licit production, consumption and international trade

Dipentylone is used as reference material in scientific research and forensic applications.

16. Illicit manufacture and traffic and related information

Dipentylone was first detected in Sweden in 2014 *(25)*. Reports from the US National Forensic Laboratory Information System (NFLIS-Drug) indicate that dipentylone was also first detected in the USA in 2014, in Kansas *(26)*. Since then, dipentylone has been detected in 33 US states, with a total of 6,169 reports submitted to NFLIS-Drug. Of those states, Florida (4662) and Virginia (577) have contributed with most reports on dipentylone *(26)*.

In 2022, there were 4,901 reports to NFLIS-Drug. Only 2,880 of these encounters reported weights, totaling 64,586.71 grams. Data collected between August 2021, and March 2022, from Arkansas (1), District of Columbia (1), Florida (17), Georgia (1), New Jersey (1), New York (2), Pennsylvania (1), Virginia (5), and West Virginia (2), indicated that dipentylone was found in at least one Driving under the influence of drugs (DUID) case, and at least 26 fatal poisonings or deaths. Five other toxicology cases had unknown outcomes. Aegis Sciences Corporation detected 15 cases in 2021 and 45 cases in the first half of 2022 (Jan-June). The Center for Forensic Science Research & Education (CSFRE) with NPS Discovery reported 166 positive cases from Q1 2020 to Q1 2023 *(26)*.

A 45-year-old man in Syracuse (NY, USA) plead guilty to distributing controlled substances, including, on March 10, 2022, giving another individual approximately 770 grams of dipentylone, to deliver to a customer in Oswego (NY, USA). This individual further admitted that on the same date, he possessed at his residence approximately 7 kg of dipentylone, which he intended to distribute to others *(27)*.

The US Customs and Border Protection recently (June 2023) seized 32.2 kilograms of dipentylone, labeled as "beauty products", sent from China and mailed to an address in Washington, D.C. *(28)*.

On July 2023, an Assistant Special Agent from the Drug Enforcement Administration gave an interview reporting that dipentylone was found in possession by people attending nightclubs and bars in the Jacksonville, Florida (USA) area *(13)*. Dipentylone was reported to be very cheap ($150–$200 per ounce).

Dipentylone was first detected in New Zealand in 2017. During 2022 and 2023, this substance was detected at border seizures (43 border seizures, totaling 29.9 Kg) and drug checking samples (volumes and number of detections were not quantified). The presence of dipentylone was confirmed in 2 coronial cases in New Zealand *(21)*. An alert about the detection of dipentylone for the first time in New Zealand was issued by the drug early warning website High Alert. DIpentylone was found in two samples tested by KnowYourStuffNZ in Dunedin, including in a pink 'Playboy' tablet that was sold as MDMA *(23)*.

Dipentylone was first detected in Canada in 2022, having been identified in 11 cases in Ontario, by the Health Canada's Drug Analysis Service *(29)*.

17. Current international controls and their impact

Dipentylone is not currently controlled under the 1961, 1971, or 1988 United Nations Conventions.

18. Current and past national controls

Dipentylone is not explicitly scheduled in the U.S. However, it could be considered an isomer of the Schedule I substance N-ethyl pentylone.

Dipentylone is controlled as Class B by the United Kingdom Misuse of Drugs Act.

In Germany, dipentylone is classified as "Neue-psychoaktive-Stoffe-Gesetz (NpSG)", which authorizes its use only for industrial and scientific purposes.

In New Zealand, dipentylone is regulated as a Class C7 controlled drug under the Misuse of Drugs Act 1975, as an analogue of MDMA.

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

Dipentylone seems to be commonly sold as cocaine, MDMA, and Ecstasy in the US and New Zealand *(17, 23)*, hence individuals that use it may be unaware of what they are consuming.

Moreover, for all of the 16 sample analyses reported by Wedinos in which dipentylone was confirmed, the purchaser intended to buy other substances, including MDMA (7 cases), 2c-B (6 cases), alprazolam (1 case), 4-MMC (1 case), or mephedrone (1 case).

References

1. Cayman. (2021). N,N-Dimethylpentylone (hydrochloride) (Item No. 9001933). Available at: https://www.caymanchem.com/product/9001933/n%2Cn-dimethylpentylone-(hydrochloride). Accessed on 04/07/2023.
2. Cornish S. (2022). The new drug arriving at our borders posing a significant risk. Available at: https://www.stuff.co.nz/national/128753223/the-new-drug-arriving-at-our-borders-posing-a-significant-risk. Accessed on 04/07/2023.
3. Substituted phenyl-α-amino ketones. (1967). Koeppe H, Ludwig G, Zeile K.
4. United Nations Office on Drugs and Crime (UNODC). (2020). Recommended methods for the Identification and Analysis of Synthetic Cathinones in Seized Materials. United Nations, Office of Drugs and Crime.
5. Hungarian Institute for Forensic Science, Hungary (HIFS). (2016). Analytical data for Dipentylone. Hungarian Institute for Forensic Science, Hungary.
6. Sisco E, Burns A, Moorthy AS (2021). Development and evaluation of a synthetic cathinone targeted gas chromatography mass spectrometry (GC-MS) method. Journal of Forensic Sciences. 66 (5):1919-1928. doi: 10.1111/1556-4029.14789
7. Celma A, Sancho JV, Salgueiro-González N, Castiglioni S, Zuccato E, Hernández F, Bijlsma L (2019). Simultaneous determination of new psychoactive substances and illicit drugs in sewage: Potential of micro-liquid chromatography tandem mass spectrometry in wastewater-based epidemiology. Journal of Chromatography A. 1602 300-309. doi: 10.1016/j.chroma.2019.05.051
8. Bijlsma L, Picó Y, Andreu V, Celma A, Estévez-Danta A, González-Mariño I, Hernández F, López de Alda M, López-García E, Marcé RM, Miró M, Montes R, Pérez de San Román-Landa U, Pitarch E, Pocurull E, Postigo C, Prieto A, Rico A, Rodil R, Valcárcel Y, Ventura M, Quintana JB (2021). The embodiment of wastewater data for the estimation of illicit drug consumption in Spain. Science of the Total Environment. 772 144794. doi: 10.1016/j.scitotenv.2020.144794
9. Kadkhodaei K, Forcher L, Schmid MG (2018). Separation of enantiomers of new psychoactive substances by high-performance liquid chromatography. J Sep Sci. 41 (6):1274-1286. doi: 10.1002/jssc.201701239
10. Chen JY, Chen GY, Wang SY, Fang CC, Chen LY, Weng TI (2022). Development of an analytical method to detect simultaneously 219 new psychoactive substances and 65 other substances in urine specimens using LC-QqQ MS/MS with CriticalPairFinder and TransitionFinder. Talanta. 238 (Pt 1):122979. doi: 10.1016/j.talanta.2021.122979
11. Stephanson NN, Signell P, Helander A, Beck O (2017). Use of LC-HRMS in full scan-XIC mode for multi-analyte urine drug testing - a step towards a 'black-box' solution? Journal of Mass Spectrometry. 52 (8):497-506. doi: 10.1002/jms.3946
12. da Cunha KF, Oliveira KD, Huestis MA, Costa JL (2020). Screening of 104 New Psychoactive Substances (NPS) and Other Drugs of Abuse in Oral Fluid by LC-MS-MS. Journal of Analytical Toxicology. 44 (7):697-707. doi: 10.1093/jat/bkaa089
13. News4JAX. (2023). Newest drug to hit the streets makes its way to Northeast Florida nightclubs, bars. Available at: https://www.news4jax.com/news/local/2023/07/11/newest-drug-to-hits-the-streets-makes-its-way-to-northeast-florida-nightclubs-bars/. Accessed on 28/07/2023.

14. Bluelight. (2023). Available at: http://www.bluelight.org. Accessed on 29/07/2023.

15. Wedinos. (2023). Sample results for dipentlyone. Available at: https://www.wedinos.org/sample-results#mylocation. Accessed on 24/07/2023.

16. Fogarty MF, Krotulski AJ, Papsun DM, Walton SE, Lamb M, Truver MT, Chronister CW, Goldberger BA, Logan BK (2023). N,N-Dimethylpentylone (dipentylone)—A new synthetic cathinone identified in a postmortem forensic toxicology case series. Journal of Analytical Toxicology. doi: 10.1093/jat/bkad037

17. Center for Forensic Science Research and Education (CFSRE). (2022). Synthetic Stimulant Market Rapidly Changing as N,N-Dimethylpentylone Replaces Eutylone in Drug Supply Typically Sold as "Ecstasy" or "Molly".

18. Eshleman AJ, Nagarajan S, Wolfrum KM, Reed JF, Swanson TL, Nilsen A, Janowsky A (2019). Structure-activity relationships of bath salt components: substituted cathinones and benzofurans at biogenic amine transporters. Psychopharmacology. 236 (3):939-952. doi: 10.1007/s00213-018-5059-5

19. Gatch MB, Shetty RA, Sumien N, Forster MJ (2021). Behavioral effects of four novel synthetic cathinone analogs in rodents. Addiction Biology. 26 (4):e12987. doi: 10.1111/adb.12987

20. Sumien N, Shetty RA, Forster MJ. (2018). Time-course (8-h) mouse locomotor activity test vs cocaine and (+)-Methamphetamine time courses. Contract Nr. N01DA-13-8908 (HHSN271201300001).

21. Fearn D, Kappatos D, Russell S, Murray A, Johnson C, McCarthy M-J (2022). First confirmation of synthetic cathinone N,N-dimethylpentylone in postmortem sample in New Zealand using GC-MS/MS. Toxicologie Analytique et Clinique. 34 (3, Supplement):S111-S112. doi: 10.1016/j.toxac.2022.06.177

22. High Alert. (2023). Misrepresented MDMA linked to serious harm in Hawke's Bay. Available at: https://highalert.org.nz/alerts-and-notifications/misrepresented-mdma-linked-to-serious-harm-in-hawkes-bay/. Accessed on: 21/08/2023

23. High Alert. (2021). New synthetic cathinone dimethylpentylone detected in NZ. Available at: https://highalert.org.nz/alerts-and-notifications/new-synthetic-cathinone-dimethylpentylone-detected-in-nz. Accessed on 28/07/20223.

24. Gatch MB, Forster MJ. (2019). Test of substitution for the discriminative stimulus effects of 3,4-methylenedioxymethamphetamine. Contract Nr. N01DA-18-8936 (HHSN271201800031).

25. European Monitoring Centre for Drugs and Drug Addiction – Europol. (2014). Europol 2014 Annual Report on the implementation of Council Decision 2005/387/JHA. Publications Office of the European Union, Luxembourg.

26. National Forensic Laboratory Information System (NFLIS-Drug). (2023). DIpentylone summary.

27. Drug Enforcement Administration. (2022). Syracuse Man Pleads Guilty to Distribution of "Molly". Available at: https://www.dea.gov/press-releases/2022/07/15/syracuse-man-pleads-guilty-distribution-molly. Accessed on 28/07/2023.

28. US Customs and Border Protection. (2023). Dulles CBP Officers Seize 70 Pounds of a Dangerous, Newer Cathinone Analogue Destined to D.C. Available at: https://www.cbp.gov/newsroom/local-media-release/dulles-cbp-officers-seize-70-pounds-dangerous-newer-cathinone-analogue. Accessed on 28/07/2023.

29. Health Canada's Drug Analysis Service. (2023). Canada - dipentylone.

3.1.6 2-Fluorodeschloroketamine

1. Substance identification

A. International nonproprietary name

Not assigned

B. Chemical Abstracts Service (CAS) registry number

111982-50-4 (free base)

2657761-05-0 ((2S)-enantiomer)

2657761-04-9 ((2R)-enantiomer)

111982-49-1 (hydrochloride salt)

C. Other chemical names

2-(2-Fluorophenyl)-2-(methylamino)cyclohexanone (ACI)

2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one

Cyclohexanone, 2-(2-fluorophenyl)-2-(methylamino)-

2-Fluorodeschloroketamine

2-Fluoroketamine

Fluoroketamine

2-FDCK

2F-DCK

2-FL-2′-OXO-PCM

D. Trade names

2-Fluorodeschloroketamine is sold under its own chemical names.

E. Street names

2-Fluorodeschloroketamine is available on the Internet, sold under various names, including "2-fluoroketamine", "2FDCK" and "2-FK", or as "ketamine" *(1)*.

F. Physical appearance

The free base pure has been described as a brown oil *(2)*. The hydrochloride salt is described as a crystalline solid *(3)* or a white powder *(4)*.

2-Fluorodeschloroketamine for recreational use is distributed mainly as crystals or powder. Recently, chocolates containing 2-fluorodeschloroketamine and other new psychoactive substances (NPS) were seized in China *(5)*.

G. WHO review history

2-Fluorodeschloroketamine has not been formally reviewed by WHO and is not currently under international control.

2. Chemistry

A. Chemical name

IUPAC name:
2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one

Chemical Abstracts index name:
Cyclohexanone, 2-(2-fluorophenyl)-2-(methylamino)- (9CI, ACI)

Free base
Canonical SMILES
O=C1CCCCC1(NC)C=2C=CC=CC2F

InChI
InChI=1S/C13H16FNO/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14/h2-3,6-7,15H,4-5,8-9H2,1H3

InChI key
PHFAGYYTDLITTB-UHFFFAOYSA-N

Hydrochloride salt
Canonical SMILES
Cl.O=C1CCCCC1(NC)C=2C=CC=CC2F

InChI
InChI=1S/C13H16FNO.ClH/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14;/h2-3,6-7,15H,4-5,8-9H2,1H3;1H

InChI key
FQOFLBNEXJTBJE-UHFFFAOYSA-N

(2R)-enantiomer
Canonical SMILES
O=C1CCCCC1(NC)C=2C=CC=CC2F

Isomeric SMILES
N(C)[C@@]1(C(=O)CCCC1)C2=C(F)C=CC=C2

InChI
InChI=1S/C13H16FNO/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14/h2-3,6-7,15H,4-5,8-9H2,1H3/t13-/m1/s1

InChI key
PHFAGYYTDLITTB-CYBMUJFWSA-N

(2S)-enantiomer
Canonical SMILES
O=C1CCCCC1(NC)C=2C=CC=CC2F

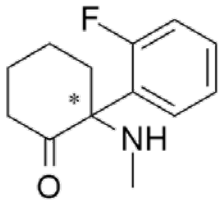
Isomeric SMILES
N(C)[C@]1(C(=O)CCCC1)C2=C(F)C=CC=C2

InChI
InChI=1S/C13H16FNO/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14/h2-3,6-7,15H,4-5,8-9H2,1H3/t13-/m0/s1

InChI Key
PHFAGYYTDLITTB-ZDUSSCGKSA-N

B. Chemical structure

Free base:

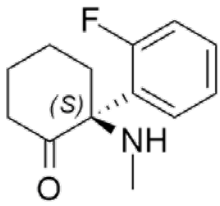


Molecular formula: $C_{13}H_{16}FNO$

Molecular weight: 221.27 g/mol

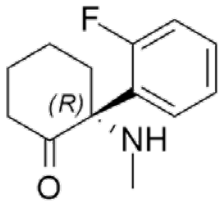
C. Stereoisomers

2-Fluorodeschloroketamine contains a chiral centre; therefore, two enantiomers may exist: (*R*)-2-Fluorodeschloroketamine and (*S*)-2-Fluorodeschloroketamine. No information is available on the enantiomeric composition of 2-fluorodeschloroketamine circulating on the drug market but it is probably available as a racemic mixture of the (*R*)- and (*S*)-enantiomers. Individual stereoisomers cannot be excluded.



2657761-05-0

(2S)-2-(2-Fluorophenyl)-2-(methylamino)cyclohexan-1-one



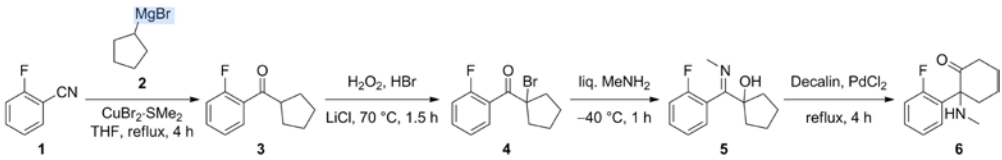
2657761-04-9

(2R)-2-(2-Fluorophenyl)-2-(methylamino)cyclohexan-1-one

D. Methods and ease of illicit manufacture

2-Fluorodeschloroketamine is an analogue of ketamine in which the chlorine atom is replaced by a fluorine atom. The first synthesis was reported in 1987 by Dimitrov et al. *(6)*, who prepared the material in several steps, starting from 2-fluorobenzoyl chloride; however, no details were given.

Later, 2-fluorodeschloroketamine was synthesized by Moghimi et al. *(2)*, who reported the reaction conditions shown in scheme 1. Synthesis started with reaction of 2-fluorobenzonitrile (**1**) and the Grignard reagent cyclopentylmagnesium bromide (**2**) to give 2-fluorophenyl-cyclopentyl ketone (**3**), which was brominated in the α position. The resulting α-bromo ketone (**4**) reacted with methylamine to form the α-hydroxy imine (**5**). Thermal rearrangement of the imine hydroxide to 2-fluorodeschloroketamine (**6**) was obtained by heating at high temperature in decalin with the addition of $PdCl_2$ as a catalyst.



Scheme 1. Synthesis of 2-fluorodeschloroketamine

No information was available on the routes of synthesis used for the 2-fluorodeschloroketamine products circulating on the market, although (2′′-fluorophenyl)(methylimino) methyl]cyclopentan-1-ol was reported to have been seized at a production site as a suspected chemical precursor of 2-fluorodeschloroketamine *(7)*. This suggests that the synthetic route used is that shown in scheme 1. The procedure leads to the formation of the racemic mixture of 2-fluorodeschloroketamine.

Although the synthesis is simple and does not require controlled precursors, it must be carried out in a synthetic chemistry laboratory by qualified personnel.

E. Chemical properties

Melting-point
Hydrochloride salt
258–260 °C *(2)*

Boiling-point
No information was found.

Solubility
Hydrochloride salt
Soluble in dimethylformamide (10 mg/mL), dimethylsulfoxide (5 mg/mL), ethanol (5 mg/mL), methanol (1 mg/mL), and phosphate-buffered saline (pH 7.2, 10 mg/mL) *(3)*.

Partially soluble in dichloromethane and soluble in methanol and water *(10)*.

F. Identification and analysis

Reference material and pure compound
2-Fluorodeschloroketamine hydrochloride salt and its urinary metabolite 2-fluorodeschloronorketamine hydrochloride are available as reference materials from commercial suppliers for use in routine methods of analysis for forensic and clinical investigations *(3, 9)*.

2-Fluorodeschloroketamine hydrochloride as a pure compound was fully characterized by gas chromatography coupled to mass spectrometry (GC-MS) (electron ionization), liquid chromatography (LC) coupled to high-resolution mass spectrometry (quadrupole time-of-flight [QToF]), Fourier-transform infrared and nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectroscopy *(2, 10)*.

Separation of the two enantiomers of 2-fluorodeschloroketamine has been reported by LC–ultraviolet in a chiral stationary phase *(11)*.

Seized material

Seized material has been analysed for 2-fluorodeschloroketamine with several techniques, including direct analysis in real-time MS (DART-MS) and GC-MS, specifically on two powders (white crystals) purchased on the Internet and sold as bucinnazine. One sample was identified as 2-fluorodeschloroketamine *(12)*. Gao et al. *(13)* analysed 78 seized samples in China by LC-high-resolution MS (HRMS) and confirmed the identification by NMR.

GC-MS and quantitative NMR were used for determination of 2-fluorodeschloroketamine in seized chocolate samples *(5)*.

Trace residues of 2-fluorodeschloroketamine were found in an analysis by DART-MS and MS/MS of over 1000 discarded drug packaging samples taken at large public events *(14)*.

2-Fluorodeschloroketamine has been identified and quantified in wastewater by GC-MS and was found to be stable in wastewater for 15 days at room temperature and pH 7 and pH 2 *(15)*. Li et al. *(16)* reported quantification of 2-fluorodeschloroketamine and its urinary metabolite 2-fluorodeschloronorketamine by LC coupled with triple quadrupole MS (LC-QqQ) in wastewater.

Biological samples

Several analytical methods based on the LC-HRMS technique, particularly QToF and Orbitrap, have been reported for the identification and quantification of 2-fluorodeschloroketamine in biological samples, including blood from people driving under the influence of drugs and forensic hair samples *(17)*, one patient's urine *(1)* and post-mortem blood and hair samples from a forensic case of suicide *(18)*. The authors of the last study presumptively identified the nor-, dihydro- and nor-dihydro metabolites and reported that the parent compound in blood and hair was stable in an autosampler for at least 48 h *(18)*. Hair samples from a cohort of pregnant women in Mexico were tested for various NPS by LC-HRMS and found to contain 2-fluorodeschloroketamine *(19)*. LC-QToF was used for forensic toxicology testing of over 3000 biological samples, including blood, urine, serum/plasma and tissue matrices *(20)*.

LC coupled to low-resolution MS, particularly tandem MS with-QqQ was used to quantify 2-fluorodeschloroketamine in nail samples from nearly 300 people who used drugs in China *(21)*. LC-MS-MS in dynamic multiple reaction monitoring mode was fully validated for simultaneous detection of 163 substances in blood (120 NPS and 43 other drugs) *(22)*. In this work, 2-fluorodeschloroketamine was reported to be stable in blood for 1 month

at –25 °C. An LC-MS/MS method was validated for the analysis of 11 drugs of abuse, 2-fluorodeschloroketamine, in urine *(23)*.

3. Ease of conversion to controlled substances

No information was found on whether 2-fluorodeschloroketamine can be converted into a controlled substance.

4. General pharmacology

A. Routes of administration and dosage

The available data, including reports from people who used 2-fluorodeschloroketamines and law enforcement seizures, 2-fluorodeschloroketamine is usually purchased in the form of crystals or powder. The crystals may be crushed or the powder may be placed in capsules, and both may be solubilized. Common routes of administration include insufflation (direct snorting of powder or crushed crystals or solubilization into a nasal spray) and oral; less commonly mentioned routes are intramuscular injection, sublingual and rectal insertion *(24–26)*.

No studies were found on human dosages; however, one informational website has categorized doses according to their intoxicating effects after insufflation as "light" (20–50 mg), "common" (50–100 mg) and "strong" (100–≥ 175 mg) *(27)*. The website also listed the following doses of ketamine: "light" (20–50 mg), "common" (50–125 mg) and "strong" (125–175 mg) *(28)*. The onset of effects is estimated to occur 20–40 min after insufflation; the duration of action is 1–3 h; and the after-effects last for 1–3 h *(27)*. The basis for this information is not clear, and, given its anecdotal nature, caution is suggested in interpreting these data.

B. Pharmacokinetics

No information was available on the absorption and distribution of 2-fluorodeschloroketamine. Several studies have been conducted of its metabolism in vitro (human liver microsomes or human hepatocytes) and in vivo (analysis of biological samples). The results show that 2-fluorodeschloroketamine undergoes extensive hepatic biotransformation in the body. The number of identified phase-I and -II metabolites ranged from 3 to 26, depending on the assay. N-Dealkylation, oxidation and reduction are the primary phase-I reactions, and N-glucuronidation of the N-dealkylated metabolites are the primary phase-II reactions *(29)*. The main metabolites in several studies and assays were nor-2-fluorodeschloroketamine, dihydro-2-fluorodeschloroketamine, dihydro-nor-2-fluorodeschloroketamine and

dehydroamine-nor-2-fluorodeschloroketamine *(18, 30–33)*. It is not known whether these metabolites are psychoactive.

While the time course of 2-fluorodeschloroketamine has not been assessed in humans, its estimated in-vitro half-life after exposure to human liver microsomes was 69.1 ± 13.1 min, with an intrinsic clearance rate of 9.2 ± 1.7 mL/min per kg *(17)*. 2-Fluorodeschloroketamine showed less protein binding than ketamine, with measured unbound fractions (f_u) of 0.54 and 0.79 for the two compounds, respectively *(17)*. Similarly, the predicted lipophilicity of 2-fluorodeschloroketamine was less than that of ketamine (predicted logP = 2.89 and 3.35, respectively). Protein binding and lipophilicity would be expected to affect the absorption and distribution of these substances as well as their time courses.

C. Pharmacodynamics

Little information is available on the pharmacodynamics of 2-fluorodeschloroketamine. No in-vitro binding or functional data are available. Two published studies examined the effects of the compound in several preclinical procedures designed to evaluate the abuse potential of psychoactive drugs. The results are described in section 8A of this report.

5. Toxicology

No studies of the preclinical toxicology of 2-fluorodeschloroketamine were available.

6. Adverse reactions in humans

Measurable concentrations of 2-fluorodeschloroketamine have been reported in post-mortem blood samples and in biological samples from impaired drivers and clinical admissions by several sources *(17, 30–38)*. In some cases, other drugs were also detected (including ketamine and other ketamine analogues). 2-Fluorodeschloroketamine was the only substance detected in at least one fatality in Finland *(39)*, and the likelihood of causality was high according to the system used to rate the contribution of a substance to the outcome; further details were lacking. Several case reports provide additional information on the disposition of patients observed by medical or law enforcement personnel while under the influence of 2-fluorodeschloroketamine. The symptoms tend to cluster into three categories: CNS, cardiovascular and other. The reported CNS and behavioural effects included dissociation, confusion, agitation, combativeness, nystagmus, hallucinations and impaired or loss of consciousness; the reported cardiovascular effects were tachycardia and hypertension; other effects included nausea and vomiting *(30, 33, 34)*. The

extent to which 2-fluorodeschloroketamine contributed directly to these observed or reported effects is uncertain, as the presence of other substances in the biological samples of most of the patients was confirmed by laboratory analysis.

The predominant effects of 2-fluorodeschloroketamine described by people who have used it include dissociation, tranquility, happiness and numbness and tingling in the periphery *(24–26)*. Lost sense of time, loss of motor control and colourful visual or vivid auditory hallucinations have also been mentioned. Similarities to the subjective effects of ketamine were noted by several people who had used both drugs. Other subjective experiences reported by people who have used 2-fluorodeschloroketamine include confusion, agitation and memory loss *(40)*. Posts on online forums of self-reported experience of use of 2-fluorodeschloroketamine should be considered as 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

2-Fluorodeschloroketamine has been examined in several preclinical procedures designed to evaluate the abuse potential of psychoactive drugs. In each model, its potency was roughly equivalent to that of ketamine.

In a conditioned place preference procedure, which is sometimes used to assess the rewarding effects of a drug according to the principles of classical conditioning, 2-fluorodeschloroketamine dose-dependently induced conditioned place preference (as compared with vehicle) in male ICR mice in a three-compartment procedure *(41)*. The minimum effective dose of both 2-fluorodeschloroketamine and ketamine was 3 mg/kg (intraperitoneally [i.p.]). At this dose, neither drug affected locomotor activity in mice.

Locomotor sensitization is a phenomenon whereby, rodents show enhanced sensitivity to the locomotor stimulant effects of a drug after repeated

dosing and a period of drug withdrawal. When tested acutely in male Sprague-Dawley rats, a 30 mg/kg (i.p.) dose of 2-fluorodeschloroketamine significantly increased locomotor activity. During repeated dosing with 2-fluorodeschloroketamine (1–30 mg/kg, i.p.), locomotor activity remained constant; however, during a challenge test conducted after 2 weeks of abstinence, 30 mg/kg (i.p.) 2-fluorodeschloroketamine increased locomotion *(41)*. Ketamine had similar effects at the same doses. These findings suggest induction of locomotor sensitization, a pharmacological effect that is characteristic of psychomotor stimulants.

Drug discrimination is a pharmacologically selective animal model of the subjective effects of psychoactive drugs in humans. In a study using male Sprague-Dawley rats trained to discriminate ketamine (5 mg/kg, i.p.) from vehicle in a standard two-nose-poke procedure, 2-fluorodeschloroketamine produced full dose-dependent substitution for the ketamine training dose, with an ED_{50} of 1.605 mg/kg (i.p.) and a maximum percentage of responding on the ketamine-associated aperture of 97.25% at a 2.5 mg/kg dose *(41)*. The ED_{50} of ketamine in this procedure was 2.185 mg/kg. These results suggest that 2-fluorodeschloroketamine has subjective effects in humans similar to those of ketamine.

In the same study, 2-fluorodeschloroketamine and ketamine were assessed in separate groups of male Sprague-Dawley rats trained to self-administer the respective training drug at an intravenous dose of 0.5 mg/kg per infusion *(41)*. Rats self-administered both drugs, with an inverted U-shaped dose–effect function. The peak number of infusions of both drugs occurred at 1 mg/kg/infusion. In a study using a behavioural economics strategy, 2-fluorodeschloroketamine and ketamine showed similar reinforcing efficacy in male Sprague-Dawley rats trained to self-administer the drugs (0.5 mg/kg/infusion) *(42)*. In further tests, 2-fluorodeschloroketamine resulted in reinstatement after extinction induced by previous cues paired with drug delivery and when primed by a pre-session i.p. injection of the drug. Western blot analysis of the nucleus accumbens of the rats showed downregulation of CREB/BDNF and upregulation of phosphorylation of the Akt/mTOR/GSK-3β signalling pathway, suggesting mechanisms for the observed reinstatement.

B. Studies in humans

No information was found.

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

2-Fluorodeschloroketamine has no known therapeutic uses.

10. Listing on the WHO Model List of Essential Medicines

2-Fluorodeschloroketamine 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)

2-Fluorodeschloroketamine has no known marketing authorization.

12. Industrial use

2-Fluorodeschloroketamine has no known industrial use.

13. Non-medical use, abuse and dependence

2-Fluorodeschloroketamine is a ketamine analogue that was synthesized in 2014 *(2)* and appeared on the European illicit drug market in Spain in 2016 *(43)*. Reports on online forums by people who use drugs provide evidence that 2-fluorodeschloroketamine has been used intentionally for its intoxicating effects (see section 6). This substance has been detected in seized and biological samples in at least 11 countries (see section 16 for list). The prevalence of chronic use of and dependence on 2-fluorodeschloroketamine 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 2016, 2-fluorodeschloroketamine has been confirmed analytically in post-mortem samples as well as in samples collected from impaired drivers and emergency department admissions in several countries, including Australia *(39)*, Canada *(39)*, China *(33, 38)*, Denmark *(17)*, Finland *(39)*, France *(39)*, Italy *(18, 44)* and the USA *(34, 39)*.

Between July 2019 and May 2022, 11 cases (five post-mortem) including analytically confirmed 2-fluorodeschloroketamine were reported to the Early Warning System Tox-Portal *(39)*. 2-Fluorodeschloroketamine was the only listed substance detected in four cases. In three of the nonfatal cases and two of the fatalities, 2-fluorodeschloroketamine was designated as contributory (medium) on the causality scale used in the system. In two fatalities (in Finland and in France), the effects of 2-fluorodeschloroketamine were determined to

be causal (high), and this drug was the only substance listed in the case in Finland. Between January and April 2020, 2-fluorodeschloroketamine was the sole (or one of only a few) substance(s) detected in six samples analysed by Welsh authorities *(40)* and in 35 samples analysed in a laboratory based in the USA *(45)*.

15. Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

In China, where ketamine has been a prominent drug of abuse since the early 2000s, at least 60 cases of analytically confirmed exposure to 2-fluorodeschloroketamine have been reported recently *(33, 37, 38)*. In 19 of 20 cases involving 2-fluorodeschloroketamine reported in one study, use with ketamine or another ketamine analogue was found by analysis of biological samples *(33)*. A trend of increasing use by young females in China was noted, although use by males predominated *(38)*. Analysis of wastewater in several cities in southern China confirmed continuous use of 2-fluorodeschloroketamine over a 2-year sampling period (2018–2020) *(15)*.

In Europe, 2-fluorodeschloroketamine was first reported in 2016 *(29)*, and its presence was analytically verified in biological samples collected in the USA in 2019 *(34)*. Samples containing 2-fluorodeschloroketamine submitted to an anonymous testing site (between 2017 and the present) were received from Austria (n=7), Canada (n=1), China (n=8), Netherlands (Kingdom of the, n=1), the United Kingdom (n=1) and the USA (n=5) *(45)*. As submission of samples was voluntary, the distribution of sites of origin may not represent the global distribution or trafficking of 2-fluorodeschloroketamine. Other countries in which 2-fluorodeschloroketamine has been detected as a product sample or measured in biological samples include Australia *(39)*, Denmark *(17)*, Finland *(39)*, France *(39)* and Italy *(18, 44)*.

17. Current international controls and their impact

2-Fluorodeschloroketamine is not currently under international control.

18. Current and past national controls

2-Fluorodeschloroketamine is regulated under national psychoactive drug control regulations in Austria, Canada, China, Germany, Italy, Latvia, Switzerland, Turkey, and the United Kingdom *(32, 46)*. 2-Fluorodeschloroketamine does not appear to be controlled under national regulations in other countries.

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

One of 65 chocolate samples submitted to the National Anti-Drug Laboratory of China for analysis was found to contain 2-fluorodeschloroketamine *(5)*. No information was provided on the source of the chocolate samples or on the prevalence. The presence of 2-fluorodeschloroketamine and other novel psychoactive substances in food may increase the risk of unintentional exposure (including paediatric).

References

1. Tang MHY, Li TC, Lai CK, Chong YK, Ching CK, Mak TWL. Emergence of new psychoactive substance 2-fluorodeschloroketamine: Toxicology and urinary analysis in a cluster of patients exposed to ketamine and multiple analogues. Forensic Sci Int. 2020;12:110327.
2. Moghimi A, Rahmani S, Zare R, Sadeghzadeh M. Synthesis of 2-(2-fluorophenyl)-2-methylamino-cyclohexanone as a new ketamine derivative. Synthet Communications. 2014;44:2021–8.
3. 2-Fluoro deschloroketamine (hydrochloride) (Item No. 19786) [Online]. Ann Arbor (MI): Cayman Chemicals; 2017 (https://www.caymanchem.com/product/19786/2-fluoro-deschloroketamine-(hydrochloride, accessed 10 July 2023).
4. Analytical report: 2-fluoro deschloroketamine (C13H16FNO) (2-(2-fluorophenyl)-2-(methylamino) cyclohexan-1-one). Ljubljana: Slovenian National Forensic Laboratory; 2017 (https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/2-fluoro%20Deschloroketamine-ID-1847-17_report.pdf).
5. Song CH, Jia W, Liu CM, Hua ZD, Meng X, Zhao YB et al. New trends of new psychoactive substances (NPS)-infused chocolate: Identification and quantification of trace level of NPS in complex matrix by GC-MS and NMR. Talanta. 2023;255:124257.
6. Dimitrov I, Denny WA, Jose J. Syntheses of ketamine and related analogues: a mini review. Synthesis. 2018;50:4201–15.
7. Luo X, Zhang D, Luo Q, Huang K, Liu X, Yang N et al. Structure identification and analysis of the suspected chemical precursor of 2-fluorodeschloroketamine and its decomposition products. Drug Test Anal. 2022;14:1065–78.
9. 2-Fluoro deschloronorketamine (hydrochloride) (Item No. 29118) [Online]. Ann Arbor (MI): Cayman Chemicals; 2019 (https://www.caymanchem.com/product/29118/2-fluoro-deschloronorketamine-(hydrochloride, accessed 10 July 2023).
10. Analytical report: 2F-ketamine (C13H16FNO) 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one. Ljubljana: Slovenian National Forensic Laboratory; 2017 (https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/2-fluoro%20Deschloroketamine-ID-1847-17_report.pdf).
11. Hägele JS, Basrak M, Schmid MG Enantioselective separation of novel psychoactive substances using a Lux® AMP 3 µm column and HPLC-UV. J Pharmaceut Biomed Anal. 2020;179:112967.
12. Resnik KN, Babb KN, Bekenstein LW, Moeller FG, Peace MR, Alves EA. Case report: Identification of AP-238 and 2-fluorodeschloroketamine in internet available powder samples sold as bucinnazine. Forensic Sci Int. 2023;348:111732.
13. Gao J, Xu B, Yang R, Zhang H Screening strategy for ketamine-based new psychoactive substances using fragmentation characteristics from high resolution mass spectrometry. Forensic Sci Int. 2023;347:111677.

14. West H, Fitzgerald J, Hopkins K, Li E, Clark N, Tzanetis S et al. Early warning system for illicit drug use at large public events: trace residue analysis of discarded drug packaging samples. J Am Soc Mass Spectrom. 2021;32:2604–14.

15. Shao XT, Yu H, Lin JG, Kong XP, Wang Z, Wang DG. Presence of the ketamine analog of 2-fluorodeschloroketamine residues in wastewater. Drug Test Anal. 2021;13:1650–7.

16. Li X, Feng L, Fan X, Huang J, Du Y. Wastewater-based monitoring of 2-fluoro-deschloroketamine abuse from 2019 to 2021 in a southern Chinese province. Sci Total Environ. 2022;826:154191.

17. Davidsen AB, Mardal M, Holm NB, Andreasen AK, Johansen SS, Noble C et al. Ketamine analogues: comparative toxicokinetic in vitro-in vivo extrapolation and quantification of 2-fluorodeschloroketamine in forensic blood and hair samples. J Pharm Biomed Anal. 2020;180:113049.

18. Mestria S, Odoardi S, Biosa G, Valentini V, Di Masi G, Cittadini F et al. Method development for the identification of methoxpropamine, 2-fluoro-deschloroketamine and deschloroketamine and their main metabolites in blood and hair and forensic application. Forensic Sci Int. 2021;323:110817.

19. Marchei E, Rotolo MC, Mannocchi G, Capomassi A, Gómez-Ruiz LM, Acosta-López A et al. Assessment of licit and illicit drugs consumption during pregnancy by ultra-high performance liquid chromatography–high resolution mass spectrometry (UHPLC-HRMS) target screening in Mexican women hair. J Pharm Biomed Anal. 2022;211:114607.

20. Krotulski AJ, Varnum SJ, Logan BK. Sample mining and data mining: combined real-time and retrospective approaches for the identification of emerging novel psychoactive substances. J Forens Sci. 2020;65:550–62.

21. Liu P, Liu W, Qiao H, Jiang S, Wang Y, Chen J et al. Simultaneous quantification of 106 drugs or their metabolites in nail samples by UPLC-MS/MS with high-throughput sample preparation: Application to 294 real cases. Anal Chim Acta. 2022;1226:340170.

22. Vaiano F, Bertol E, Mineo M, Pietrosemoli L, Rubicondo J, Supuran CT et al. Development of a new LC-MS/MS screening method for detection of 120 NPS and 43 drugs in blood. Separations. 2021;8:221.

23. Wong GF, Lee WM, Li CK. Qualitative screening of amphetamine- and ketamine-type abuse drugs in urine employing dual mode extraction column by liquid chromatography–tandem mass spectrometry (LC-MS-MS). J Anal Toxicol. 2023;46:1045–52.

24. The Big and Dandy 2-fluorodeschloroketamine (2fk/2fdck) thread. Bluelight; 2023 (https://bluelight.org/xf/threads/the-big-dandy-2-fluorodeschloroketamine-2fk-2fdck-thread.776753/, accessed 29 July 2023).

25. 2-Fluorodeschloroketamine reports. Grass Valley (CA): Erowid Center (https://www.erowid.org/experiences/subs/exp_2Fluorodeschloroketamine.shtml#General, accessed 29 July 2023).

26. 2-Fluorodeschloroketamine. San Francisco (CA): Reddit Inc; 2023 (https://www.reddit.com/r/researchchemicals/search/?q=2-fluorodeschloroketamine&restrict_sr=1, accessed 29 July 2023).

27. 2-FDCK. Springfield (PA): Tripsit; 2023 (https://drugs.tripsit.me/2-fdck, accessed 28 July 2023).

28. Ketamine. Springfield (PA): Tripsit; 2023 (https://drugs.tripsit.me/ketamine, accessed 28 July 2023).

29. Joseph D, Lesueur C, Zerizer F, Fenot A, Alvarez JC, Larabi IA. Characterization of extensive 2-fluorodeschloroketamine (2F-DCK) metabolism in pooled human liver microsomes (pHLM), urine, and hair from an addicted patient using high-resolution accurate mass (HRAM) spectrometry. J Anal Toxicol. 2023;47(6):504–16.

30. Domanski K, Fleming SW, Maag H, Bouso Raley E, Debord J, Wright B et al. A psychonaut's experience of intoxication with multiple classes of drugs including novel psychoactive substance 2-fluorodeschloroketamine: case report and urinary analysis. J Psychoactive Drugs. 2022 ;54:319–23.

31. Gicquel T, Pelletier R, Richeval C, Gish A, Hakim F, Ferron P et al. Metabolite elucidation of 2-fluoro-deschloroketamine (2F-DCK) using molecular networking across three complementary in vitro and in vivo models. Drug Test Anal. 2022;14:144–53.

32 Luo X, Zhang D, Zhang F, Luo Q, Huang K, Liu X et al. Comparative analysis and structure identification of oxidative metabolites and hydrogenation metabolite enantiomers for 2-fluorodeschloroketamine. J Anal Toxicol. 2023;47:436–47.

33. Tang MHY, Li TC, Lai CK, Chong YK, Ching CK, Mak TWL. Emergence of new psychoactive substance 2-fluorodeschloroketamine: toxicology and urinary analysis in a cluster of patients exposed to ketamine and multiple analogues. Forensic Sci Int. 2020;312:110327.

34. Arango E, Toriello A, Rodario Z, Cooper G. Increasing prevalence of ketamine in drivers in New York City including the identification of 2-fluoro-deschloroketamine. J Anal Toxicol. 2021;45:799–806.

35. Pelletier R, Le Daré B, Grandin L, Couette A, Ferron P, Morel I et al. New psychoactive substance cocktail in an intensive care intoxication case elucidated by molecular networking. Clin Toxicol (Phila). 2022;60:122–5.

36. Pelletier R, Le Daré B, Le Bouëdec D, Kernalléguen A, Ferron PJ, Morel I et al. Arylcyclohexylamine derivatives: pharmacokinetic, pharmacodynamic, clinical and forensic aspects. Int J Mol Sci. 2022;23:15574.

37. Li C, Lai CK, Tang MHY, Chan CCK, Chong YK, Mak TWL. Ketamine analogues multiplying in Hong Kong. Hong Kong Med J. 2019;25:169.

38. Li Z, Li Z, Xie W, Liu J, Li B, Liu W et al. Hair-based rapid UPLC-MS/MS analysis of 36 phencyclidine-type substances in forensic cases. J Pharm Biomed Anal. 2023;234:115577.

39. 2-Fluorodeschloroketamine. Vienna: United Nations Office on Drugs and Crime; 2023 (https://www.unodc.org/tox/#/admin/search/detailed/%7B%22textQuery%22:%222-fluorodeschloroketamine%22%7D).

40. 2-Fluorodeschloroketamine. Cardiff: Welsh Emerging Drugs and Identification of Novel Substances Project; 2023 (https://www.wedinos.org/sample-results#mylocation, accessed 31 July 2023).

41. Li F, Du H, Wu B, Wei J, Qiao Y, Lai M et al. 2-Fluorodeschloroketamine has similar abuse potential as ketamine. Addict Biol. 2022;27:e13171.

42. Du H, Lai M, Zhuang D, Fu D, Zhou Y, Chen S et al. A comparison of reinforcing effectiveness and drug-seeking reinstatement of 2-fluorodeschloroketamine and ketamine in self-administered rats. Front Mol Neurosci. 2022;15:972798.

43. EMCDDA–Europol 2016 annual report on the implementation of Council Decision 2005/387/JHA. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2016 (https://www.emcdda.europa.eu/publications/implementation-reports/2016_en, accessed 31 July 2023).

44. Vincenti F, Gregori A, Flammini M, di Rosa F, Salamone A. Seizures of new psychoactive substances on the Italian territory during the COVID-19 pandemic. Forensic Sci Int. 2021;326:110904.

45. 2-Fluorodeschloroketamine. Grass Valley (CA): Erowid Center, DrugsData.org; 2023 (https://drugsdata.org/results.php?search_field=all&s=2-fluorodeschloroketamine, accessed 31 July 2023).

46. 2-Fluorodeschloroketamine. Psychonaut Wiki; 2023 (https://psychonautwiki.org/wiki/2-Fluorodeschloroketamine, accessed 30 July 2023).

3.2 Pre-review reports

3.2.1 Nitrous oxide

1. Substance identification

A. International nonproprietary name

Not assigned

B. Chemical Abstracts Service (CAS) registry number

100024-97-2

C. Other chemical names

Canonical SMILES
N#N=O

InChI
InChI=1S/N2O/c1-2-3

InChI key
GQPLMRYTRLFLPF-UHFFFAOYSA-N

Other names
Dinitrogen monoxide

Dinitrogen oxide

Dinitrogen oxide (N2O)

Hyponitrous acid anhydride

Nitrogen protoxide

Nitrous-oxide

2-Oxodiazen-2-ium-1-ide

1,2-Diazaethyne1-oxide

Diazyne 1-oxide

Nitrogen hypoxide

Nitrogen oxide

Nitrogenium oxydulatum

Oxodiazen-2-ium-1-ide

Oxidodinitrogen(N-N

Diazooxidane

Laughing gas

Factitious air

R 744A

D. Trade names

Nitrous oxide is used as a food additive (aerosol propellant to make whipped cream), a refrigerant, a leak detecting agent, an oxidizing agent, a chemical reagent and as an additive to fuels for racing cars under several trade names.

Medical nitrous oxide is sold as single ingredient in several countries under the trade name NIONTIX (Belgium, Czechia, Denmark, Finland, Germany, Netherlands [Kingdom of the], Norway and Sweden) or MAXICOOL (Israel). Medical nitrous oxide is also sold in multi-ingredient preparations under the trade names Entonox and Equanox in Australia; Livopan in Austria; Actynox, Kalinox and Relivopan in Belgium; Alnox, Entonax and Liquid-Med in Canada; Entonox in Czechia; Kalinox, Latox, Livopan and Medimix in Denmark; Livopan in Finland; Antasol, Entonox, Kalinox and Oxynox in France; Livopan in Germany; Livopan and Nitralgin in Hungary; Donopa and Entonox in Ireland; Protoxan in Italy; Actynox, Donopa, Kalinox, Protoxan and Relivopan in Netherlands (Kingdom of the); Livopan in Norway; Entonox in New Zealand; Entomix, Entonox and Kalinox in Poland; Kalinox, Livopan and Protoxan in Portugal; Entonox in South Africa; Actynox, Entonox, Kalinox, Nodolox and Protoxan in Spain; Livopan and Medimix in Sweden; Entonox and Kalinox in Switzerland; and Entonox and Equanox in the United Kingdom *(1)*.

E. Street names

Bulb; Buzz bomb; Cartridges; Fall down; Gas; Going to the dentist; Grocery store high; Hippy crack; Hysteria; Laughing gas; Nang; Nie; Nigh; Nitro; Nitrogen; Nitrous; Noss; Pan; Shoot the breeze; Tanks; Whippet; Whippets; and Wippets *(1)*. The name Nox is used when nitrous oxide is combined with other substances, such as 3,4-methylenedioxymethamphetamione (MDMA) *(2)*.

F. Physical appearance

The European Pharmacopoeia describes nitrous oxide as a colourless gas *(3)* and the United States Pharmacopeia describes it as a colourless gas with no appreciable odour or taste *(4)*. It has also been reported as a colourless gas under ambient conditions, with a slightly sweet odour and taste *(5, 6)*.

The British Pharmacopeia 2019 *(3)* states that nitrous oxide should be kept in approved metal cylinders painted blue and carry a label stating "nitrous oxide". Furthermore, "nitrous oxide" or "N_2O" should be stenciled in paint on the shoulder of the cylinder.

G. WHO review history

Nitrous oxide has not previously been reviewed by the WHO Expert Committee on Drug Dependence.

2. Chemistry

A. Chemical name

IUPAC name: Nitrous oxide

Chemical Abstracts index name: Nitrogen oxide (N_2O) (7CI, 8CI, 9CI, ACI)

B. Chemical structure

Free base:

$^{-}N{=}\overset{+}{N}{=}O$

Molecular formula: N_2O

Molecular weight: 44.013 g/mol

C. Stereoisomers

No stereoisomers of nitrous oxide have been described.

D. Methods and ease of illicit manufacture

Nitrous oxide was first isolated by Joseph Priestley in 1772 and was synthesized by Humphry Davy in the late 1790s. The synthesis of nitrous oxide has remained relatively unchanged, as it is widely used in industrial preparation of the gas *(7)*. The synthesis consists of thermal decomposition of a 92–94% hot solution of ammonium nitrate in reaction (1):

$$NH_4NO_3 \rightarrow N_2O + 2H_2O \text{ (1)}.$$

The ideal temperature of the reaction for the maximum yield is 265–278 °C. Higher and lower temperatures result in undesired side-products, such as nitrogen (N_2), nitrogen dioxide (NO_2), dinotrogen trioxide (N_2O_3), nitric oxide (NO), ammonia (NH_3) and nitric acid (HNO_3). The presence of impurities such as chlorides, carbonates, nitric acid, iron, organic substances and especially oil in a hot solution of ammonium nitrate can disturb the

decomposition reaction. For instance, in the presence of 0.1% chlorides (w/w) the formation of nitrous oxide is slower and the formation of impurities is faster. Additionally, the presence of oil traces leads to formation of carbon monoxide as a gaseous impurity, while the presence of iron traces increases the formation of impurities *(8)*. As the reaction is exothermal, a large increase in the reaction temperature can cause an explosion *(7)*. The gas obtained from the reaction undergoes a series of processes to achieve the desired purity.

Another synthesis reported in a US patent *(9)* involves reaction of urea in sulfuric acid with nitric acid and subsequent purification with an aqueous alkaline solution.

Clandestine and home production of nitrous oxide are possible but expensive and dangerous because of the risks of explosions and formation of noxious side products such as NO and NO_2 *(5)*. Other methods have been developed for producing nitrous oxide at home. For example, mixing sodium nitrate and ammonium sulfate according to reaction (2) minimizes the formation of side products; however, the procedure is unsafe *(10)*.

$$2NaNO_3 + (NH_4)_2SO_4 \rightarrow Na_2SO_4 + 2N_2O + 4H_2O \quad (2).$$

E. Chemical properties

Melting-point
–90.83 °C *(11)*

Boiling-point
-88.57 °C *(11)*

Solubility
In water: 1 volume of nitrous oxide dissolves in about 1.5 volumes of water at 20 °C and at a pressure of 101 kPa *(3)*.

1 volume of nitrous oxide dissolves in about 1.4 volumes of water at 20 °C and at a pressure of 760 mmHg *(4)*.

It is also freely soluble in alcohol and soluble in ether and oils *(4)*.

F. Identification and analysis

Chromatographic, optical and amperometric techniques are currently used to measure nitrous oxide *(12)*. There are portable devices to measure nitrous oxide in gaseous media *(13)*, but they apparently have not been used to detect nitrous oxide in exhaled breath at the site of motor vehicle accidents or in cases of apparent intoxication. There is no portable device for detecting nitrous oxide in blood or other liquid matrices.

Chromatographic techniques

The most widely used analytical technique is gas chromatography (GC) coupled to an electron-capture detector with manual or automated sampling. The limit of detection is about 30 ppb, and the precision ranges from 0.18 to 0.4. The cost of this instrumental platform is low *(12)*, the methods are readily available, and the data are comparable to those previously collected *(14)*. As the presence of water vapour and carbon dioxide can result in inaccurate results, samples must be pre-treated *(12)*. High accuracy and precision can also be obtained with GC coupled to an isotope-ratio mass spectrometer for isotopic analysis of nitrous oxide *(15)*.

Optical techniques

The advantage of optical techniques is the short analysis time – fractions of a second – which makes them the techniques of choice for measuring trace gas fluxes *(12)*. Two optical techniques are used preferentially for measuring nitrous oxide: Fourier-transform infra-red spectroscopy and laser-adsorption spectroscopy *(16)*. The limit of detection is about 1 ppb, and the precision may reach 0.1 ppb *(17)*. An indirect optical technique is photoacoustic spectroscopy, which measures the effect on the absorbing medium rather that direct light absorption. This technique is attractive because portable devices can be set up that work at atmospheric pressure, allowing measurements in situ *(18)*.

Amperometric techniques

The current produced by reduction of nitrous oxide at an electrode can be used to measure its concentration. Electrochemical amperometric sensors are sensitive, simple, easy to use and cheap *(19)*. Such instrumentation can reach a limit of detection of 22 ppb but cannot be used for prolonged monitoring *(20)*.

Nitrous oxide in biological specimens

Few methods have been reported for the determination of nitrous oxide in biological samples. Those reported are based on either GC-electron capture detection (ECD) or GC-mass spectrometry (MS) *(21–23)*. Brugnone et al. *(21)* determined nitrous oxide concentrations in plasma and urine of physicians exposed to the gas during anaesthesia of patients and reported concentrations far higher than in controls. Poli et al. *(22)* examined post-mortem samples from eight cases of intoxication due to erroneous replacement of the oxygen gas line with one containing nitrous oxide. Nitrous oxide levels were detected even 1 month after death by head-space GC-ECD. Abnormal amounts of nitrous oxide were found in all post-mortem tissues (blood, urine, liver, bile, kidney, fat and brain) by HS-GC-MS in toxicological studies of a death suspected to be due to nitrous oxide intoxication *(23)*.

Because of its short half-life, nitrous oxide is more difficult to detect in biological samples from living people than in post-mortem specimens. Levels can be measured in blood and urine immediately after exposure *(21)*, but routine analysis is more difficult. Mariller et al. *(24)* attempted to detect nitrous oxide in urine and exhaled air but found sampling and interpretation of the results to be difficult. They recommended early sampling, use of entirely filled airtight containers and freezing if immediate analysis is not possible.

3. Ease of conversion into controlled substances

Although nitrous oxide is used in a wide variety of chemical reactions, especially as an oxidizing agent, it is not known whether it can be converted into a controlled substance.

4. General pharmacology

A. Routes of administration and dosage

Nitrous oxide is an inert, colourless, slightly sweet smelling, non-irritating gas that is administered via inhalation through the nose and/or mouth *(25)*. For non-medical use, nitrous oxide is typically inhaled from small metal canisters or bulbs used to generate whipped cream ("whippets", "nangs" [in Australia]) or from balloons filled with gas from other sources *(26)*. Bulbs typically contain 10–50 mL of pure nitrous oxide. Balloons may be filled from cylinders ("smart whips") or large tanks containing up to 10 kg of nitrous oxide that are sold legally for industrial or medical use. This is readily done with a "cracker", a device screwed onto the cylinder, and turning the cap to release nitrous oxide into the attached balloon *(5)*.

Cross-sectional, online, anonymous international surveys of convenience samples of self-selected individuals who use psychoactive substances (global drug surveys in 2014–2016) identified 17 325 respondents who had used nitrous oxide for non-medical reasons in the past year *(27)*. The vast majority (82%) had inhaled nitrous oxide from balloons, which they had filled from bulbs (87.2%) or large tanks (6.8%). The remainder inhaled nitrous oxide from whipped cream dispensers (12.8%), plastic bags (0.7%) or gas bulbs (0.9%). Among 4883 respondents in the 2014 global drug survey (data collected in late 2013) who reported use of nitrous oxide in the past year, 80.6% had inhaled nitrous oxide from a balloon, 15.9% from a whipped cream dispenser, 0.8% from a plastic bag and 0.8% from a gas bulb *(28)*. The gas was almost always inhaled by mouth (98.3%) and rarely via the nose (0.7%) or both (1.0%).

Respondents in the global drug surveys in both 2014 (data collected in late 2013) and 2014–2016 reported taking a median (interquartile range, IQR) of 5 (3–10) "hits" each time they used nitrous oxide *(27, 28)*. Respondents in the Australian Ecstasy and Related Drug Reporting System in Sydney, Australia (about 100 each year) (see section 13) reported using nitrous oxide on a median of 7 days (IQR 2–14), 5 days (2–10) and 5 days (2–10) over the previous 6 months in 2018, 2019 and 2020, respectively *(9, 10)*. Respondents reported using a median of seven bulbs (IQR 4–10), five bulbs (3–10) and eight bulbs (4–20) at a typical session in 2018, 2019 and 2020, respectively. In 2018, 17% of respondents reporting using at least 15 bulbs at their most recent session *(29)*.

Among 158 people wo reported lifetime "recreational" nitrous oxide use self-identified in a 2002 in-class survey of first-year students at the University of Auckland, New Zealand, the typical use pattern was two to five bulbs per session; 5% used more than 10 bulbs *(30)*.

B. Pharmacokinetics

Nitrous oxide is rapidly absorbed via inhalation. It is poorly soluble in blood and adipose tissue and does not bind to blood constituents, resulting in rapid onset (15–30 s) and offset (10–15 min) of effects *(31)*. Nitrous oxide is not metabolized and is eliminated unchanged in exhaled breath.

C. Pharmacodynamics

Two neuropharmacological mechanisms have been proposed for the abuse potential and other behavioural effects of nitrous oxide: activation of opioid receptors and blockade of the NMDA-type glutamate receptor *(26)*. Evidence for the role of opioid receptors is suggestive but not consistent. In mice, pharmacological blockage of κ-opioid receptors consistently blocks nitrous oxide-induced analgesia, while pharmacological blockage of μ-opioid receptors is inconsistent *(32–36)*. Administration of a κ-receptor agonist with the antagonist restored the analgesic effect *(35)*. In some studies, a μ-opioid receptor antagonist (usually naloxone) did not alter the analgesic effect of nitrous oxide *(32–37)*, while in others it reduced the analgesic effect *(38–40)*. The discrepancy may be due partly to differences in the type and dose of μ-opioid receptor antagonist used. Naloxone was not selective for the μ-opioid receptor at the higher doses used in some studies. In a study in which a wide range of naloxone doses were injected into the cerebral ventricles, higher doses blocked the analgesic effect, while lower doses potentiated the effect *(40)*. Deletion of the gene for the μ-opioid receptor did not influence the analgesic effect *(41)*. In one study in mice *(42)* and one in rats *(43)*, injection of a μ-opioid receptor antagonist directly into

the periaqueductal gray area of the brain reduced nitrous oxide-induced analgesia. These studies suggest that the periaqueductal gray area, known to be an important site for pain perception, plays a role in the analgesic effect of nitrous oxide. In two studies, naloxone reduced nitrous oxide-induced hyperlocomotion *(44, 45)*. Three studies in rats showed that μ-opioid receptor antagonists (naloxone, naltrexone) reduced nitrous-oxide induced analgesia *(46–48)*, while κ- and δ-opioid receptor antagonists had no effect *(47)*. In another study in rats, naloxone had no effect on nitrous oxide-induced analgesia *(49)*. A study in cats also showed no effect of naloxone on nitrous oxide-induced analgesia *(50)*. A study in mice indicated that naloxone had no effect on nitrous oxide-induced anesthesia *(51)*. In rats, naltrexone (an opioid receptor antagonist selective for the μ-opioid receptor at lower doses) had no effect by itself but exacerbated nitrous oxide-induced impairment of performance in a visual vigilance task *(52)*.

Studies in humans on the influence of naloxone on nitrous oxide-induced analgesia, in a variety of pain models, had mixed results. Two showed a decreased analgesic effect, four showed no influence, and two (by the same research group) showed a reduction or increase in the analgesic effect depending on the participant (Table 1). Although a different experimental pain model was used in each study, there were no other methodological issues that would explain the different results. In one study, naloxone (0.1–10 mg/kg intravenously) had no significant effect on the subjective effects or psychomotor impairment induced by nitrous oxide (30% for 90 min) *(53)*.

Table 1. Studies on the influence of intravenous naloxone on the analgesic effect of nitrous oxide

Dose	No. of participants	Age (years)	Pain model	Effect	Reference
4, 8 mg	Unclear	"Young"	Arm ischaemia	↓	*54*
0.4 mg/kg	12	18–32	Tooth pulp shock	↓	*55*
1.4 mg	7	27–41	Eyelid muscle stimulation	No change	*56*
10 mg	30	18–32	Tooth extraction	No change	*57*
0.01 mg	6	22–23	Skin heat	No change	*58*
30 mg/70 kg	14	21–39	Cold pressor test	No change	*59*
0.8–1.2 mg	15	21–30	Skin pressure	4 ↑ 7 ↓	*60*
0.8 mg	6	28–40	Chronic musculo-skeletal pain	2 ↑ 4 ↓	*61*

No change, no effect of naloxone on nitrous oxide-induced analgesia; ↓ = reduced analgesia; ↑ = increased analgesia.

The second proposed neuropharmacological mechanism for the abuse liability of nitrous oxide is noncompetitive antagonism at the NMDA receptor *(26, 62)*. This has also been proposed as the mechanism for the rapid antidepressant action of nitrous oxide, which resembles that of ketamine *(63)*. There is no direct evidence for this mechanism in humans. Mice that lack the gene for the epsilon1 subunit of the NMDA receptor show reduced anaesthetic response to nitrous oxide *(64)*. Nitrous oxide, like ketamine, enhances glutamatergic neurotransmission in the rat hippocampus *(63)*.

Flumazenil (an antagonist at the benzodiazepine site of the γ-aminobutyric acid receptor) significantly reduced self-ratings of "high" during exposure to nitrous oxide (30% for 35 min), but only at the highest dose (5 mg/70 kg intravenously) *(65)*. Flumazenil had no effect on other subjective effects ("drunk", "high", "drug liking") nor on psychomotor impairment (Digit Symbol Substitution Test) due to nitrous oxide. In mice exposed to nitrous oxide (50% or 75%), pretreatment with flumazenil (10 mg/kg subcutaneously) attenuated the effect of nitrous oxide on reducing rearing (a putative model of anxiolytic action) *(66)* (Quock et al., 1992).

Nitrous oxide has other weak neuropharmacological actions in rodents, the relevance of which to its effects in humans is unknown *(67)*. They include activation of α-adrenergic receptors in the brain stem and spinal cord, weak antagonism at 5-HT_3 receptors, and partial inhibition of certain nicotinic acetylcholine receptors.

5. Toxicology

Nitrous oxide, an inert gas, does not cause acute biochemical or cellular toxicity. Deaths associated with nitrous oxide use are due to asphyxiation when the inhaled substance prevents inhalation of sufficient oxygen (see section 14).

The main toxic action of nitrous oxide is irreversible oxidation of the cobalt ion in cobalamin (vitamin B12), which renders the vitamin functionless *(26)*. This is considered to be the mechanism by which chronic use of nitrous oxide causes major neurological and haematological toxicity. Cobalamin plays a major role in enzymatic formation of methionine and tetrahydrofolate, which are essential for formation of the myelin sheath surrounding neuronal axons and for formation of red blood cells. Thus, chronic nitrous oxide use and cobalamin deficiency are associated with several generalized demyelinating polyneuropathies, such as peripheral neuropathy, progressive spinal cord degeneration, subacute combined spinal cord degeneration and megaloblastic anaemia ("pernicious anemia"). A causal association is suggested by functional vitamin B12 deficiency with chronic, heavy use of

nitrous oxide and by recovery with abstinence from nitrous oxide use and/or treatment with cobalamin, although only about two thirds of patients have low blood concentrations of cobalamin and/or holotranscobalamin (the transporter for cobalamin) *(68)*. Another possible mechanism of nitrous oxide-induced neurotoxicity may be elevated levels of homocysteine and methylmalonic acid, which are found in about 75% of chronic users of nitrous oxide (68). Both compounds are neurotoxic in rodents *(26)*.

6. Adverse reactions in humans

The true prevalence of adverse reactions due to use of nitrous oxide is unknown, as no population-based or systematic unbiased surveys appear to have been conducted. Among 4883 respondents with non-medical nitrous oxide use in the past year who participated in the anonymous, online global drug survey in 2014 (data collected in late 2013), the most common adverse effects associated with nitrous oxide use were hallucinations (lifetime prevalence, 36.3%; prevalence in the past year, 27.8%), confusion (31.5%/24.0%), fainting (10.4%/4.4%), nausea (9.7%/5.8%), persistent numbness (5.2%/4.3%) and accidents (3.2%/1.2%) *(28)*. Among 16 239 respondents to the global drug surveys in 2014–2016 who answered a question about paraesthesia (a proxy for peripheral neuropathy), a dose-dependent relation was found between the amount of nitrous oxide used per session and the prevalence of paraesthesia. The prevalence was 1.86% (95% CI 1.8 ; 2.5) for people who took one per session, 5.0% (4.4 ; 5.6) among those who took 20 doses per session, and 8.48% (6.6 ; 10.4) among those who took 100 doses per session *(69)*.

The adverse reactions seen most commonly in people who use chronic nitrous oxide presenting for medical attention are neurological (usually related to demyelinization) and haematological. In a case series of 110 patients (52% men; mean age, 21.4 years [range, 14–33 years]; mean duration of nitrous oxide use, 12.5 months [0.5–72 months]) who had used nitrous oxide non-medically and were treated in Shengjing Hospital of China Medical University between 2018 and 2020, the most common symptoms were limb weakness or numbness (97%), difficulty in walking (12%), headache or dizziness (8%), involuntary movements (6%) and constipation (5%) *(70)*. Among about 4000 cases reported to two toxicology units in the Sydney, Australia, area in 2017–2020, 22 involved individuals (50% women; 68% post-secondary students; median age, 22, IQR 20–28) who had used nitrous oxide daily for more than 1 week *(71)*. All reported heavy use, with a median (IQR) peak use of nitrous oxide 300 (200–370) bulbs daily for 6 (3–24) months. Only four (18%) reported use of illicit drugs, including ketamine, cannabis, MDMA ("ecstasy") and/or cocaine. The most common

presenting symptoms were gait disturbance (68%) and psychiatric symptoms (23%), including hallucinations, paranoia and/or depression. Two patients each had urinary retention, urinary incontinence and confusion. Ten (45%) patients had low serum cobalamin concentrations, 8 of 10 patients (80%) had elevated homocysteine concentrations, 5 (23%) had anaemia, and 3 (14%) had neutropenia. Of the 18 patients who underwent magnetic resonance imaging, 10 (45%) had spinal cord abnormalities consistent with subacute combined degeneration due to cobalamin deficiency. All seven patients who underwent nerve conduction studies had abnormalities consistent with sensory peripheral neuropathy.

Nitrous oxide produced psychotic-like subjective effects similar to those of ketamine in some laboratory studies. They included both positive symptoms (e.g. perceptual distortion, paranoia, delusions) and negative symptoms (e.g. anhedonia, cognitive disorganization) *(72)*. At least 32 cases presenting for medical care with psychosis related to non-medical use of nitrous oxide have been reported in the published literature *(73, 74)*. About half of the patients did not have concurrent neurological symptoms, suggesting that their psychosis was not due to neurological factors such as vitamin B12 deficiency. The most common psychotic symptoms were hallucinations, delusions and paranoia *(73)*.

Nitrous oxide causes dose-dependent cognitive and psychomotor impairment in healthy adults at concentrations that have positive subjective effects. Impairment resolves within 5–20 min of cessation of exposure *(75, 76)*. For example, exposure to 15% and 30% nitrous oxide for 40 min impaired performance on the DSST by 10–20% and on a test of logical reasoning by 15% (only at 30%) *(77)*. No significant impairment was found in eye–hand coordination or auditory reaction time. Among 12 healthy adults exposed to nitrous oxide (at 0%, 3%, 5%, 7%, 10% or 15%) for 55 min, cognitive and psychomotor function was impaired only at 15% (DSST, continuous attention, choice reaction time, block pattern recognition, short-term memory recall), with one exception *(78)*. Long-term memory recall was impaired at all concentrations. Subjective effects (e.g., "drowsy", "feel well", "energetic", "drunk") were generated only at 15%, with one exception: "dizzy" was generated at 7% and higher concentrations.

Twelve healthy young adults exposed to nitrous oxide (0%, 5%, 10%, 20% and 40%) for 1 h experienced dose-dependent impairment of cognitive and psychomotor function *(79)*. At 5% nitrous oxide, no impairment was seen on any test. At 10%, DSST, finger-tapping rate and continuous attention were impaired. At 20%, choice reaction time, body sway, decision-making and visual vigilance were also impaired. At 40%, Gibson spiral maze (a test

of visuo-motor coordination) and paired word learning were also impaired. Critical flicker fusion was not impaired at any concentration. In 12 healthy young adults exposed to nitrous oxide (0%, 10%, 20% and 40%) for 30 min, DSST performance was impaired in a dose-dependent manner: by 9% at 10%, 6% at 20% and by 20% at 40% *(75)*. No significant change was found in auditory reaction time at any concentration.

Even brief exposure to nitrous oxide can impair cognition. In 12 healthy young adults who took four deep inhalations of nitrous oxide (0%, 40%, 60% and 80%), verbal recall and DSST performance were significantly, albeit modestly (10%), impaired only at the highest concentration *(80)*. Performance was normal 3 min after inhalation.

Use of nitrous oxide has been associated with motor vehicle accidents, although the true prevalence is unknown due to lack of onsite tests for the substance. The number of driving incidents involving nitrous oxide in Netherlands (Kingdom of the) increased from 2652 in 2019 to 4860 in 2021 *(5)*. The incidents included both driving while intoxicated and while filling a balloon. Dutch police estimated that nitrous oxide use was a contributing factor in almost 1800 motor vehicle accidents between 2019 and 2021, with 362 injuries and 63 deaths *(81)*. Nitrous oxide (50% or 70% for 5 min) significantly impaired performance in a driving simulator in 10 healthy young male dental students *(82)*.

Use of nitrous oxide from metal cannisters has occasionally been associated with frostbite injury, usually to the inner thighs (from holding a large tank between the legs), hands or lips and face. Frostbite can result from either direct skin contact with pressurized liquified nitrous oxide released from the container because of its boiling-point of – 55 °C to –88.5 °C or by touching the cold metal, which can be cooled to – 40 °C by release of the gas *(83–85)*.

The number of calls to poison centres related to nitrous oxide have increased substantially during the past decade in several European countries: from 16 (2015) to 73 (2021) in Denmark, 10 (2017) to 134 (2020) in France and 13 (2015) to 98 (2021) in Netherlands (Kingdom of the) *(5)*.

7. Dependence potential

A. Studies in experimental animals

Nitrous oxide generates acute and chronic tolerance to many, but not all, of its effects in rodents, including anaesthesia, analgesia, hypolocomotion, hypothermia and electrophysiological responses. Partial acute tolerance to the anaesthetic effect developed in mice after 60 min of continuous exposure

(86). Development of tolerance was blocked by concomitant treatment with nitrendipine, a calcium channel blocker. Tolerance to the analgesic effect occurred in rats within 45 min of > 16 h of exposure to 75% nitrous oxide *(80, 87)*; however, development of tolerance was blocked by pretreatment with an enkephalinase inhibitor *(88)*, which presumably increased enkephalinergic activity in the brain. No tolerance developed to the anaesthetic effect over 3 h *(88)*, and there was no cross-tolerance with morphine-induced analgesia *(80)*. In mice exposed to 80% nitrous oxide for up to 30 h, naloxone did not elicit signs of withdrawal (as would have been seen in mice tolerant to morphine) *(89)*. In another study in rats, no tolerance to analgesia developed during 2 h of exposure to 75% nitrous oxide *(90)*. Mice became tolerant to analgesia after exposure to 75% nitrous oxide for 16 h *(78)*, to 50% or 70% for one week or to 40% for 3 weeks *(95)*, with partial cross-tolerance to ethanol *(91)* but no cross-tolerance to barbiturates *(92)*. Tolerance resolved within 6 days.

Tolerant mice had normal synaptic membrane fatty acid, phospholipid and cholesterol content *(87)*. Acute tolerance to analgesia occurred in mice within 41 min of continuous exposure *(93)*. Adolescent rats developed significant tolerance to nitrous oxide-induced hypothermia after three 90-min exposures to 60%, while adult rats developed minimal tolerance *(94)*. Mice developed partial tolerance to the hypolocomotor effects of 70% nitrous oxide during 48 h of exposure *(95)*, and rats developed partial tolerance to the suppression of cortical evoked potential amplitude during exposure to 70% nitrous oxide, within 2–10 min for somatosensory evoked potentials *(96)* and within 15 min for visual evoked potentials *(95)*. Exposure to nitrous oxide had no effect on spinal cord evoked potentials *(96)*. Rats developed partial tolerance to the aversive effect of 80% nitrous oxide (conditioned taste aversion) after four 60-min exposures *(97)*.

Rodents exposed to nitrous oxide experienced signs of withdrawal when exposure was ended abruptly. Mice exposed continuously to nitrous oxide (0.9–1.5 atmospheric pressure or 50–80% mixture) for 30–60 min at 34 or 68 h developed handling seizures (tonic–clonic) for 2 min to 6 h after the end of exposure *(86, 89, 98–101)*. The occurrence of handling seizures was significantly reduced in mice treated concomitantly with nitrendipine *(86)* or treated before nitrous oxide exposure with cholinesterase inhibitors (physostigmine or galantamine) *(100)*. Withdrawal seizures were suppressed by nitrous oxide or ethanol treatment; however, nitrous oxide suppressed handling seizures that occurred during withdrawal from ethanol *(101)*. Tolerance did not occur to nitrous oxide-induced impairment of performance on a visual vigilance task over 7 days of exposure to 60% concentration for 7 h daily *(51)*.

μ-Opioid receptor ligands influence seizures in mice during withdrawal from nitrous oxide, the effects depending on when they are administered. Pretreatment with naloxone (μ-opioid receptor antagonist) just before exposure to nitrous oxide reduced withdrawal seizures *(100)*, while treatment 5 min before the end of exposure increased the occurrence of seizures *(89)*, and treatment with naloxone or naltrexone (another μ-opioid receptor antagonist) after exposure had no effect *(99, 100)*. Conversely, treatment with morphine (μ-opioid receptor agonist) 5 min before the end of exposure decreased the occurrence of seizures *(89)*. Rats exposed for 48 h to 70% nitrous oxide had decreased levels of β-endorphin immunoreactivity in the brainstem and subcortex (but not the cortex) 30 min into withdrawal *(102)*. Brain β-endorphin immunoreactivity was unchanged during withdrawal from acute exposure (25 min) to 70% nitrous oxide or during exposure to 70% nitrous oxide.

B. Studies in humans

Tolerance to the analgesic effects of nitrous oxide was observed in several laboratory studies, but no tolerance was seen to its subjective or psychomotor effects. Three of seven healthy adult men exposed continuously to 33% nitrous oxide showed complete tolerance after 1 h *(103)*. In a study with healthy young adults, continuous exposure to 35% nitrous oxide led to about 33% tolerance after 30 min and about 50% tolerance after five 30-min exposures spaced at least one half-day apart *(104)*. In a study of eight healthy young adult men who were exposed continuously to 60–80% nitrous oxide for 3 h, tolerance was observed after 30 min, which was complete by 150 min *(105)*. In a study with 10 healthy young adults who were exposed continuously to 2–40% nitrous oxide for 2 h, partial tolerance developed to analgesia and to rewarding subjective effects (e.g. "like drug effect", "feel elated"); no tolerance developed to other subjective effects (e.g. "feel drug effect", "dizzy", "sedated") or to cognitive or psychomotor impairment *(106)*. In another study by the same research group, 11 healthy young adults who were exposed continuously to 20–40% nitrous oxide for 2 h showed no tolerance to rewarding subjective effects or to cognitive or psychomotor impairment *(107)*.

Among 190 medical students at the University of Paris, France, who met the DSM-5 diagnostic criteria for nitrous oxide use disorder and participated in an anonymous online survey in March–October 2021, 45% reported tolerance *(108)*.

For 525 cases of non-medical nitrous oxide use reported to the French national addictovigiliance system between 2012 and 2021 (mean age,

21.9 years, median 21 years, range 13–53 years; 38.3% women), there was sufficient clinical information to evaluate the individual DSM-5 diagnostic criteria for (nitrous oxide) use disorder in 111 cases. Of these, 27.9% reported tolerance *(109)*.

Among 10 individuals (median age, 23 years, range 18–26 years; 80% women) reported to the Dutch Poisons Information Centre between 16 January 2021 and 15 January 2022 who had nitrous oxide "intoxication" and neuropathy, eight reported tolerance to the effects of nitrous oxide and nine reported withdrawal effects, including insomnia, anxiety, restlessness, sweating or shaking *(110)*. Eight participants used nitrous oxide at least weekly; nine were "heavy" users (more than 50 balloons at a session).

Of 73 published cases of non-medical nitrous oxide use that resulted in "major side effects", identified in a recent systematic electronic literature search (in English and French), only one report in each language provided sufficient clinical information to evaluate tolerance to nitrous oxide or withdrawal effects *(111)*. The case did meet DSM-5 diagnostic criteria for tolerance, but the other case did not meet the criteria for withdrawal effects.

VigiBase is the World Health Organization (WHO) global database of reported adverse events of medicinal products. It is the largest database of its kind in the world, with Individual Case Safety Reports (ICSRs) submitted since 1968, by Members of the WHO Programme for International Drug Monitoring (PIDM) (website). The WHO PIDM is a global network aiming to ensure safety of medicines and vaccines and it consists of more than 177 Members contributing to the database.

VigiLyze, a signal detection and signal management tool with integration of VigiBase data, was used to conduct this assessment. The data search was conducted on 28 June 2023 on ICSRs associated with nitrous oxide (as suspected drug) reporting drug abuse and dependence submitted in VigiBase in 2018–2023. The search retrieved 368 reports. The peak of reporting was in 2021. Most patients (about 80%) were aged 18–44 years, and 60% were male; 63.9% of the reports were from France, 19.8% from the USA, and 6.8% from the United Kingdom of Great Britain and Northern Ireland. 75.0% of reports were classified as serious defined with the following criteria: Death, Life threatening, Caused/prolonged hospitalization, Disabling/incapacitating and Other medically important condition. When reports were classified by reported MedDRA terms *(112)*, drug abuse was identified in 158 (42.9%), drug dependence in 37 (10.1%), drug abuser in 35 (9.5%) and substance use in 35 (9.5%). The activity ingredients which were most frequently reported in combination were ethanol (14.7%) and cannabis sativa (13.0%). Most co-

reported preferred terms included: Subacute combined cord degeneration (40; 10.9%), Paraesthesia (34; 9.2%), Myelopathy (29; 7.9%), Vitamin B12 deficiency (25; 6.8%) and Euphoric mood (21; 5.7%).

Tentative and variable nature of the data in VigiBase should be carefully considered due to uncertainty, variability of source, contingent influences, no prevalence data and time to VigiBase. For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account *(113)*.

8. Abuse potential

A. Studies in experimental animals

In the four widely used animal models of substance abuse liability, nitrous oxide had clear rewarding properties in two (self-administration, drug discrimination) and mixed results in two (ICSS, conditioned place preference) *(26)*, although the evidence is sparse. Of four rats offered 60% nitrous oxide, two self-administered it, one avoided it, and one showed no preference *(114)*. Squirrel monkeys readily learnt to self-administer 60% nitrous oxide in 15-s bursts, even when 20 lever presses were required to receive one dose *(115)*. Mice discriminated between 60% nitrous oxide and pure oxygen, suggesting that nitrous oxide has distinctive stimulus effects *(116)*. Of other inhalants, toluene almost fully substituted for nitrous oxide in discrimination tests from pure oxygen, while 1,1,1-trichloroethane and ethanol only partially substituted and 2-butanol did not substitute.

Nitrous oxide alters the response rate in mice trained to self-administer ICSS, but with no clear dose–response pattern: 40% increased responding (at two of the electrical frequencies used), while 80% decreased responding (at a broader range of frequencies), 20% showed no effect, and 60% decreased responding only at the highest frequency *(117)*. Nitrous oxide at 40% and 60% reduced the effort (lever presses) mice made before stopping self-administration of ICSS. In comparison, cocaine (at 3, 10, 18 mg/kg intraperitoneally) increased the response at all doses and frequencies used and increased the effort made before stopping ICSS self-administration. Diazepam and toluene facilitated the ICSS response more strongly than nitrous oxide, but only at intermediate doses; higher doses suppressed the response.

Nitrous oxide generates a dose-dependent conditioned place preference in rats but not in mice. In rats, 8% nitrous oxide induced conditioned place preference, 15% had no effect, and 30% and 60% induced conditioned place

avoidance, suggesting an aversive effect *(114)*. Nitrous oxide at 70% and 80% induced a conditioned taste aversion in rats, also suggesting an aversive effect *(97, 118)*. In mice, 50% nitrous oxide for 20 min did not generate a conditioned place preference and it blocked development of morphine- or cocaine-elicited conditioned place preference *(119, 120)*.

B. Studies in humans

The abuse potential of nitrous oxide was noted immediately after its synthesis by Joseph Priestly in 1772. Humphrey Davy reported that inhalation of nitrous oxide produced a pleasurable euphoria and giddiness, which he likened to alcohol intoxication, with pleasant thrilling sensations in the body and auditory and visual distortions *(121)*. He promoted recreational use of nitrous oxide, including at "laughing gas" parties, which became popular in England.

Modern laboratory studies with healthy young adults have confirmed that inhaled nitrous oxide produces robust, dose-dependent, pleasurable, rewarding subjective effects at sub-anaesthetic concentrations (10–50%) but does not consistently generate preference to oxygen in discrete choice procedures.

Inhaling nitrous oxide at 10–50% for 2–30 min under blinded conditions (when participants did not know whether they were inhaling nitrous oxide or oxygen) generated a dose-dependent pleasurable subjective experience commonly described by participants as having one of three main characteristics: dreamy, detached reverie (e.g. "floating", "coasting", "spaced out"); a happy, euphoric mood (e.g. "happy", "high", "elated", "stimulated") or psychedelic-like (e.g. "pleasant bodily sensations", changed body awareness and image, altered time perception, dissociative state) *(72, 122–124)*. The subjective effects resolved substantially within 15 min of the end of exposure *(124)* and resolved completely within 1 h *(74)*. Adults who took a single deep inhalation of 100% nitrous oxide *(121, 125)* or four consecutive deep inhalations of 40%, 60% or 80% nitrous oxide *(126)* experienced positive subjective effects within 15–30 s, peaking at 2–3 min and subsiding within 15–20 min. Subjective effects were rated by participants as more similar to those of ketamine and alcohol than to those of cannabis or cocaine *(72, 124)*. In comparison with equipotent (strength of drug effect, psychomotor impairment) concentrations of other inhalational anaesthetics (e.g. isoflurane, sevoflurane), nitrous oxide (15% or 30% for 40 min) produced less sedation and more pleasant psychedelic-like subjective effects *(77)*.

Substantial individual differences have been found in the quality and intensity of the subjective effects of nitrous oxide *(123)*. Among 12 participants

exposed to 30% or 40% nitrous oxide for 30 min, one "liked" the 30% concentration, while seven were neutral and four "disliked" it *(69)*. Four "liked" the 40% concentration, while three were neutral and five "disliked" it. Among 12 participants exposed to 30% nitrous oxide for 10 min in nine sessions daily on 5 days, the mean within-participant rating on a 100-mm visual analogue scale ranged from 1–84 mm for "high" *(127)*. Substantial inter-participant variation was also observed for self-ratings of "dreamy", "coasting" and "having pleasant thoughts". The ratings for placebo were consistently low (< 10 mm).

Considerable inter-individual variation was also seen among among healthy young adults in their preference for inhaling nitrous oxide rather than placebo (100% oxygen or room air), even when they reported positive subjective effects. In these studies, participants first sampled the two gases double-blinded and then chose which gas to inhale. Among 19 participants given the choice between 10–40% nitrous oxide for 17 min and 100% oxygen, 84% preferred nitrous oxide at 10%, 47% at 20%, 42% at 30% and 40% at 40% *(128)*. Among 12 participants given two or three single-blind discrete choices between 30% or 40% and placebo (100% oxygen), 41.6% chose nitrous oxide at 30% and 20% chose it at 40% *(69)*. A positive association was found between choice of nitrous oxide and degree of positive subjective effects. Among 16 participants given 18 discrete choices between 30% nitrous oxide for 5 min and 100% oxygen, seven chosen nitrous oxide at least two thirds of the time, three chose oxygen at least two thirds of the time, and six were neutral *(129)*. A significant positive association was found between choice of nitrous oxide and "liking" a drug (Spearman $r = 0.42$) or wanting to take the drug again ($r = 0.27$). Among 12 participants each given 45 discrete single-blind free choices (nine daily on 5 days) between 30% nitrous oxide and 100% oxygen or open-label "drug-free air" (100% oxygen) each for 10 min, 41% of the choices were for nitrous oxygen, 11% for placebo and 48% for "drug-free air" *(127)*. The choice of nitrous oxide was relatively consistent among participants during the 45 sessions. Five participants chose nitrous oxide more than two thirds of the time, five chose nitrous oxide less than 10% of the time, and two were neutral (40% and 51% of the time). The choice of nitrous oxide was significantly associated with several subjective effects, including "drunk" (Pearson $r = 0.60$), "dreamy" ($r = 062$) and "floating" ($r = 0.59$).

In a separate group of 20 participants given the same choice with four nitrous oxide concentrations, 25% preferred (chose more than half the time) placebo, 45% preferred 10% nitrous oxide, 65% preferred 20% nitrous oxide, and 65% preferred 30% nitrous oxide *(130)*. At all doses (including placebo), at least one participant never chose nitrous oxide and at least one always chose

nitrous oxide. Significant associations were found between choosing nitrous oxide and subjective effects, although these did not occur at all nitrous oxide concentrations or at all times. The choice of nitrous oxide was significantly associated with "liking" at the end of inhalation of all concentrations (Pearson r = +0.44 at 10%, +0.68 at 20%, +0.46 at 30% and +0.59 at 40%) and with "inhale again" at 20% (r = +0.71), 30% (+0.48) and 40% (+0.60). Among 14 participants each given 27 single-blind opportunities to choose among nitrous oxide (10%, 30% or 50%), placebo (100% oxygen) or neither, the cumulative choices were 27% for nitrous oxide, 16% for placebo and 57% for neither *(131)*. Eight participants showed a significant preference for nitrous oxide, but the preference was not always monotonically dependent on dose. Three participants showed an increasing preference with increasing dose, three showed decreased preference at the highest dose, and 2 showed no change with increasing dose.

Little is known about the reasons for individual differences in response to nitrous oxide. In a study of 80 psychologically healthy young adults exposed to 50% nitrous oxide for 30 min, participants with high trait impulsivity (assessed on an eight-item version of the Barratt Impulsiveness Scale-11) had a significantly greater liking for nitrous oxide than those with low impulsivity *(124)*. Depressed mood during the previous week was inconsistently associated with the nitrous oxide response, but a history of bipolar traits was not *(124)*. Gender did not appear to influence the abuse potential of nitrous oxide significantly. When 38 women and 72 men were exposed to 30% nitrous oxide for 15 min, no significant difference was seen between the two groups in the quality or intensity of positive subjective effects (e.g. "elated", "high", "pleasant thoughts") *(132)*.

Personal or family use of other psychoactive substances, such as alcohol or cannabis, influenced the positive subjective and rewarding effects of nitrous oxide in human laboratory studies. Among 32 participants exposed to 20%, 30% and 40% nitrous oxide for 10 min, only the 16 who were considered moderate drinkers (at least seven standard drinks weekly and drinking on at least 4 days per week) experienced positive subjective effects (e.g. "drug liking", "inhale again"), while light drinkers (no more than four drinks per month) did not *(133)*. Participants who were moderate drinkers were also more likely to choose nitrous oxide over placebo (100% oxygen), while light drinkers made equal choices. Among 19 healthy young adults exposed to 0–40% nitrous oxide for 30 min, those who drank alcohol moderately (mean [standard deviation] 11.4 [4.7] drinks per week; 40% were current cannabis smokers) chose nitrous oxide over placebo significantly more often than those who drank alcohol lightly (0.8 [0.2]; no current cannabis

smokers) *(128)*. The groups did not differ significantly in positive subjective effects or psychomotor impairment. Among 60 healthy adults who drank heavily (112 and 168 g/week for women and men, respectively) but did not have alcohol use disorder, those with a family history of alcohol use disorder experienced significant "stimulation" from exposure to 50% nitrous oxide for 30 min, while those without such a history did not *(134)*.

Among 18 healthy young adults exposed to 40% nitrous oxide or placebo for 30 min, those who used cannabis (mean [SD] 1.28 [1.02] joints per week), two thirds of whom also used hallucinogens), experienced stronger positive subjective effects than non-users of cannabis (none of whom used hallucinogens), but there was no difference in psychomotor impairment *(135)*. Of 24 healthy adults exposed to a single inhalation of 100% nitrous oxide, those who used cannabis and/or hallucinogens experienced less psychomotor impairment and were less likely to have an adverse experience than those who did not (8% and 58%, respectively) *(121)*. People who use cannabis and/or hallucinogens compared intoxication with nitrous oxide to a psychedelic experience, while those who did use these substances compared it to alcohol intoxication. Among 60 healthy young men exposed to 40% nitrous oxide for 20 min, those who had used cannabis in the previous 12 months experienced more positive mood and less anxiety or depression than those who had not *(136)*. Among 80 healthy young adults exposed to 40% nitrous oxide for 20 min, those who were experienced users of cannabis (at least 100 times; most had also used psychedelics) compared the experience to cannabis or LSD intoxication; those who had used cannabis no more than 10 times (and never used psychedelics) compared the experience to alcohol intoxication *(137)*. These findings suggest that use of cannabis or psychedelics enhances the abuse potential of nitrous oxide. Thus, human laboratory studies in which only participants who have not used other substances are enrolled are likely to result in underestimates of the abuse potential of nitrous oxide.

Nitrous oxide is more rewarding than the potent inhalational anaesthetic sevoflurane. Among 14 participants given a choice between placebo (100% oxygen) and either 30% nitrous oxide or 0.2%, 0.4% or 0.6% sevoflurane, 71% chose nitrous oxide over placebo, while 50%, 57% and 50% chose the sevoflurane concentration over placebo, respectively *(138)*.

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

The first medical use of nitrous oxide was as a dental anesthetic, in 1844 *(25)*. Nitrous oxide is now used as a supplement in inhalational anaesthesia (as it is not potent enough to be used alone) and for analgesia and sedation

during childbirth and painful short procedures in dentistry, paediatrics and emergency medicine *(139, 140)*. Use of nitrous oxide for inhalational analgesia appears to have decreased during the past few decades, in part because of concern about adverse effects (e.g. nausea and vomiting) after exposure for more than 1 h *(141)* and environmental damage due to its greenhouse gas properties *(140)*. The advantages of nitrous oxide over other inhalational anaesthetics include its analgesic and sedative effects (also present at subanaesthetic doses), its very rapid onset (within seconds) and the offset of effects (due to the very low blood:gas partition coefficient of 0.47), which allows more rapid induction and emergence from effects; it also has no adverse haemodynamic or pulmonary effects *(31, 140)*. The advantages of nitrous oxide over other analgesics (e.g. opioids) and sedatives (e.g. benzodiazepines) include all of the above and also the fact that it is eliminated unchanged in exhaled breath, such that its pharmacokinetics is not affected by liver or kidney function. Furthermore, it has apparently less abuse potential than opioids and can be administered by inhalation, which allows intravenous catheter placement or avoids the need for such placement, both of which are advantages for infants and children *(142)*, and allows patient self-administration (self-titration). The advantages of its use during childbirth include lack of interference with labour and no significant retention by the neonate, as it is rapidly exhaled, or during breastfeeding *(143)*.

The number of patients who receive nitrous oxide for medical purposes is unknown. In an online survey conducted in November 2019–March 2020 of 171 paediatric emergency departments in 17 European countries plus Israel and Türkiye, which serve about 5 million children annually, 54% used nitrous oxide for sedation and/or analgesia *(144)*. It was estimated recently that more than 500 hospitals and birthing centres in the USA were using nitrous oxide for analgesia during labour in 2018 *(145)*.

Nitrous oxide has been proposed as a treatment for depression (especially treatment-resistant depression) on the basis of a limited number of favourable randomized, double-blind, placebo-controlled clinical trials, although it is not approved for this condition by any national regulatory authority. The interest is due partly to the rapid onset of anti-depressant effects seen in some studies (within 24 h, similar to the action of ketamine), whereas weeks are required with conventional antidepressants. At least eight clinical trials of treatment-resistant and other forms of depression are currently under way *(146)*. Three controlled clinical trials involving a total of 88 adult patients with major treatment-resistant depression found that a single treatment with nitrous oxide (50% for 1 h) significantly reduced depressive symptoms as

compared with placebo (oxygen only) *(147–149)*. Significant anti-depressant effects appeared after 2 and 24 h in two studies (but not after 1 and 2 weeks in the study in which those periods were evaluated) and after 1 and 2 weeks (but not after 2 or 24 h) in a third study *(148)*. Cognitive performance was improved throughout the 2 weeks of the study in which anti-depressive effects lasted only 24 h *(150)*. The anti-depressant effect was accompanied by increased brain cortical connectivity assessed by electroencephalogram *(151)*. A fourth controlled clinical trial involving 23 adults with major depression (not necessarily treatment-resistant) who remained on their prescribed anti-depressant medication found that nitrous oxide at 50% for 1 h twice weekly for 4 weeks significantly reduced depressive symptoms by 4 weeks *(152)*. Of the patients who received nitrous oxide, 91.7% showed a clinically significant response (at least 50% reduction in their score on the Hamilton Depression Rating Scale), and 75% achieved remission, as compared with 44.4% and 11.1%, respectively, in the placebo group. A controlled clinical trial involving 25 adults with bipolar disorder and current treatment-resistant depression found that nitrous oxide (25% for 20 min) resulted in a significantly larger proportion of patients with a clinically significant anti-depressant response (at least 50% reduction in scores on the Montgomery-Asberg Depression Rating Scale [MADRS]) 2 h after treatment (92% vs 38%) as compared with a group who received active placebo (medical air + 2 mg midazolam intravenously), but there was no significant difference 4 or 24 h after treatment *(153)*. There was no significant difference in the mean MADRS scores of the treatment groups at any time. The nitrous oxide-induced reduction in MADRS score at 24 h was significantly associated with a lower baseline cerebral blood flow (assessed by magnetic resonance imaging arterial spin labelling) in the frontal, ventral prefrontal and anterior cingulate cortical regions.

A systematic literature review conducted in 2005 identified five controlled clinical trials conducted by the same research group in South Africa, involving 212 participants, to evaluate the influence of nitrous oxide on acute alcohol withdrawal *(154)*. All five studies found that nitrous oxide (titrated to achieve mild sedation, "psychotropic analgesic nitrous oxide") was non-inferior to standard dosing with oral benzodiazepines in reducing the signs and symptoms of acute alcohol withdrawal. A controlled clinical trial conducted in Finland of 105 adults admitted for inpatient alcohol detoxification (not included in the systematic review) found that nitrous oxide (30–70% titrated to achieve an end-tidal concentration of 30%, duration not reported) had no significant effect on the signs and symptoms of acute alcohol withdrawal or dosing with benzodiazepines during 42 h after treatment *(155)*.

10. Listing on the WHO Model List of Essential Medicines

Nitrous oxide is listed on the 23rd WHO Model List of Essential Medicines *(156)* and on the 9th WHO Model List of Essential Medicines for Children as an inhalational anaesthetic *(157)*.

11. Marketing authorizations (as a medicinal product)

Nitrous oxide is approved by national regulatory authorities as a medical gas in the European Union, North America and many other countries. It is marketed as an equimolar mixture (50%/50%) of oxygen and nitrous oxide in France (known as EMONO) and the United Kingdom (Entonox). In other countries, nitrous oxide is marketed as the pure gas and mixed with the appropriate amount of oxygen at the site of clinical administration.

12. Industrial use

Nitrous oxide is widely used commercially in the food and beverage, electronics and motor fuel industries *(25, 158)*. Nitrous oxide is used as a mixing, aerating and foaming agent in food and beverage preparation and as a propellent for dispensing whipped cream and other toppings. It is preferred to other inert gases (e.g. nitrogen, carbon dioxide) for such culinary uses because it is tasteless, colourless, non-irritating, does not promote oxidation or bacterial growth, and is highly fat soluble *(159–161)*. It is approved for use as a food additive by most national regulatory authorities *(162)*. Nitrous oxide is used as an oxidizing agent to increase the efficiency of fuels for racing cars and some rocket engines. It is preferred to other oxidizing agents because it is nonflammable and condenses under relatively low pressure at room temperature, making it easier to handle *(163)*. Nitrous oxide is used in the manufacture of semi-conductor chips *(139)*.

13. Non-medical use, abuse and dependence

The true prevalence of non-medical use of nitrous oxide or of nitrous oxide use disorder is unknown. Data on the use of nitrous oxide are not included in the United Nations Office on Drugs and Crime annual World Drug Report. As nitrous oxide is not a novel psychoactive substance, events are not reported to its ToxPortal, nor is its use monitored systematically in Europe in the European Monitoring Centre on Drugs and Drug Addiction Early Warning System. Few population-based surveys of psychoactive substance use include nitrous oxide, and those that do group it with other inhalants (e.g. alkyl nitrites, volatile organic compounds) *(164)*. Surveys on non-medical use of nitrous oxide do not include data on use disorder.

The global prevalence of non-medical use of nitrous oxide appears to be low but may be increasing in some countries and population groups (e.g. in Lithuania, Netherlands (Kingdom of the), see Table 2). The lifetime prevalence of use was 0.6–7.6% in four countries that have conducted nationally representative, population-based cross-sectional surveys (Lithuania, Netherlands (Kingdom of the), New Zealand, USA) (Table 2). The median age at first use was 19 years in New Zealand (2007–2008) *(165)*, and the prevalence in the past year was 0.8–3.2% in England and Wales, Netherlands (Kingdom of the) and New Zealand; the prevalence in the past month was 1.1% in Netherlands (Kingdom of the). The lifetime prevalence of use in the USA has been relatively stable in the past decade, ranging from 4.4% to 4.8% (see Table 2). The prevalence in Netherlands (Kingdom of the) was 3.2% in 2019 and decreased to 1.6% in 2021 (see Table 2).

Table 2. Prevalence of non-medical use of nitrous oxide in population-based surveys

Country or region	Year	Age range (years)	Population	Prevalence (%)		
				Lifetime	Past year	Past month
Denmark	2019	15–18	High-school students	15	7	
Denmark	2019	19–25	Vocational school students	12	6	
England and Wales	2022	16–59	National		1.3	
England and Wales	2020	16–59	National		2.4	
England and Wales	2013–2014	16–59	National		2	
England and Wales	2022	16–24	National		3.9	
England and Wales	2020	16–24	National		8.7	
England and Wales	2013–2014	16–24	National		8	
England	2021	11–15	Students	3.0	1.6	0.9
Lithuania	2021		National	0.6		
Lithuania	2016		National	0.2		
Netherlands (Kingdom of the)	2021	≥ 18	National		1.6	
Netherlands (Kingdom of the)	2020	≥ 18	National	7.4	2.1	
Netherlands (Kingdom of the)	2019	≥ 18	National	7.6	3.2	1.1
Netherlands (Kingdom of the)	2018	≥ 18	National	6.9	2.7	
Netherlands (Kingdom of the)	2020	20–24			12.1	

Table 2. *continued*

Country or region	Year	Age range (years)	Population	Prevalence (%)		
				Lifetime	Past year	Past month
Netherlands (Kingdom of the)	2018	20–24	National		14.6	
Netherlands (Kingdom of the)	2017	20–24	National		9.4	
Netherlands (Kingdom of the)	2015	20–24	National		7.8	
New Zealand	2007–2008	16–65	National	4.6	0.8	
USA	2021	≥ 12	National	4,4		
USA	2020	≥ 12	National	4.7		
USA	2019	≥ 12	National	4.6		
USA	2018	≥ 12	National	4.6		
USA	2017	≥ 12	National	4.7		
USA	2014	≥ 12	National	4.8		
USA	2013	≥ 12	National	4.7		

Sources: European Monitoring Centre for Drugs and Drug Addiction *(5)*; Office for National Statistics, United Kingdom *(166)*; van Amsterdam et al. *(167)*; van Laar et al. *(168, 169)*; New Zealand Alcohol and Drug Use Survey *(163)*; Center for Behavioral Health Statistics and Quality *(170–173)*.

The prevalence of non-medical use of nitrous oxide was higher in men than in women in all three countries in which this variable was reported: 6.0% vs 3.3%, respectively, for lifetime use and 1.2% vs 0.6%, respectively, for use in the past year (2007–2008) in New Zealand *(165)*; 2.3% vs 1.9%, respectively, for use in the past year (2020) in Netherlands (Kingdom of the) *(169)* and 17% vs 10%, respectively, among high-school students (15–18 years) and 17% vs 8%, respectively, among vocational-school students (19–25 years) for lifetime use in Denmark *(163)*.

The prevalence of non-medical use of nitrous oxide varies by age. In most countries, the prevalence is greatest among adolescents and young adults *(165, 169)*. For example, in Netherlands (Kingdom of the), the highest prevalence in the past year (2020) was among those aged 18–19 years (14.5%), followed by those aged 20–24 years (12.1%), 25–29 years (4.0%), 30–39 years (1.8%), 40–49 years (0.3%), 50–64 years (0.2%) and ≥ 65 years (0%) *(176)*. The USA is an exception, as the highest lifetime prevalence (2021) was among people aged ≥ 26 years (5.1%) *(173)*.

Cross-sectional, online, anonymous international surveys of convenience samples of self-selected individuals who use psychoactive substances (global drug surveys) found a substantially higher prevalence of non-medical use

of nitrous oxide than in population-based studies, presumably because of the bias inherent in their sampling method. In these biased samples, the prevalence of nitrous oxide use was also highest among adolescents and young adults. The 2020–2021 Global Drug Survey (with more than 147 000 respondents in 35 countries) found that the prevalence of use of nitrous oxide in the past year was 21% *(174)*, as compared with 7.2% in the 2014–2016 global drug surveys (241 566 unique respondents) *(8)*. The highest prevalence in both studies was among adolescents and young adults. A majority (57%) of people who use nitrous oxide reported "clubbing" at least weekly, and 18% reported clubbing at least five times a week. In the 2021 Global Drug Survey, 22.5% of respondents reported lifetime nitrous oxide use, which is similar to the 23.6% reported lifetime use in 2019 *(172)*. The majority (89.2%) of participants in these surveys also used other psychoactive substances. The prevalence of nitrous oxide use in the past year was higher among men than women (7.2% vs 4.9%, respectively) and among "clubbers" than non-"clubbers" (9.4% vs 3.0%, respectively). Of the six countries with the highest number of respondents, New Zealand, the United Kingdom and the USA had the highest prevalence of lifetime or past-year nitrous oxide use: 26.6% (25.5 ; 27.8), 38.6% (95% CI, 37.5 ; 39.7)/20.5% (19.6 ; 21.5) and 29.4% (28.3 ; 30.5)/8.2% (7.6/8.9), respectively. Australia, the United Kingdom and the USA had the highest prevalence of past-month nitrous oxide use: 2.0% (1.0 ; 2.4), 7.7% (7.1 ; 8.3) and 2.9% (2.5 ; 3.3), respectively. Germany and Switzerland had the lowest prevalence of lifetime or past-year/past-month nitrous oxide use: 11.2% (10.8 ; 11.6)/1.5% (3.3 ; 3.7)/0.9% (0.8 ; 1.0) and 13.4% (12.5 ; 14.4)/3.6% (3.1 ; 4.1)/1.0% (0.7 ; 1.3), respectively.

An anonymous online survey (on a website targeted at adolescents and young adults) of a self-selected convenience sample of 6070 Dutch residents conducted in May–October 2020 found that 40.7% had used nitrous oxide before onset of the COVID-19 pandemic, which decreased to 20.7% during the pandemic (when the Netherlands [Kingdom of the] was in lockdown) *(175)*. Among those who used nitrous oxide during the pandemic, 22.6% decreased their use from the pre-pandemic levels, 28.0% did not change their use, and 36.0% increased their use.

The prevalence of non-medical use of nitrous oxide is relatively high in some population subgroups, including health profession students (perhaps because of easier access), high school (secondary) and university students, attendees at dance clubs and music festivals and adolescents in psychiatric treatment *(167)*. A questionnaire administered in class to 1360 (61.2% of eligible students) first-year engineering, law and health science students at the University of Auckland, New Zealand, in 2002 indicated a 11.1% lifetime

prevalence of "recreational" nitrous oxide use (56% men; median age, 20 years, range 17–48 years) *(30)*. Most (78%) used at least one other recreational drug, and 23% used another inhalational drug. An anonymous survey in 1976–1978 of a convenience sample of 351 medical students and 273 dental students at a university in the USA found that 10.3% and 17.9%, respectively, had ever used nitrous oxide in a social setting for recreational purposes *(176)*. In an anonymous online survey of a self-selected sample of 981 medical students at the University of Paris, France (29% of all eligible students), conducted in March–October 2021, 80.3% reported lifetime nitrous oxide use *(106)*. People who use nitrous oxide were significantly more likely than nonusers to be men (odds ratio [OR] = 1.63, $P = 0.006$), have an alcohol use disorder (1.83, $P = 0.017$) and be younger (0.90, $P = 0.0005$). Use of other psychoactive substances was significantly more common among people who use nitrous oxide than among nonusers: 96.6% (vs 58%) used alcohol, 62.8% (vs 2.6%) used alkyl nitrites ("poppers"), 47% (vs 9.3%) used cannabis, 43.9% (vs 9.3%) used tobacco, 11.8% (vs 1%) used MDMA and 5.6% (vs 0%) used cocaine. An anonymous online survey in 2021 of a convenience sample of 593 health profession students (medicine, dentistry, midwifery, pharmacy) at a French university found a 76.6% lifetime prevalence of non-medical use of nitrous oxide, ranging from 66.5% among pharmacy students to 80.0% among medical students *(177)*. Only 2.6% had "given up" nitrous oxide use at the time of the survey. Nitrous oxide use was slightly more prevalent among men than among women (81.7% vs 74.2%,). In an anonymous, online, cross-sectional survey of a self-selected convenience sample of 10 066 French university students aged at least 18 years conducted in 2015–2017, the reported prevalence of nitrous oxide use was 26% for lifetime and 12% for past-year use *(178)*. Half (50.6%) of the people who report past-year nitrous oxide use reported using only nitrous oxide; 23.7% also used cannabis, 20.2% also used MDMA, and 11.8% also used cocaine. A survey of a self-selected convenience sample of 140 young adults (18–25 years, 67% women, 95% university students) in southwest London, United Kingdom, in 2017 found that 77% had heard of nitrous oxide ("hippy crack") and 28% reported use in the past-year *(179)*. The prevalence of use was not significantly associated with age or gender. More than three quarters (83%) of people who reported use had used nitrous oxide no more than 10 times in the past year, 31% had used it only once and 10% more than 20 times. An anonymous online survey of 555 Dutch secondary school students (14–18 years, 47% girls) indicated a 13.6% prevalence of lifetime use of nitrous oxide *(180)*. More than one third had used it only once (40.7%) or two or three times (34.9%), 16.3% had used it 4–10 times and 8.1% had used it more than 10 times. Most people who used it (52.3%) reported that they would "definitely" use nitrous oxide again;

only 7.0% said they would "never" use nitrous oxide again. An in-person interview survey in 2004 of 723 adolescents (97.7% of all those in treatment) in residential psychiatric treatment in Missouri, USA (mean age, 15.5 years, 87.0% male) found a 15.8% prevalence of lifetime nitrous oxide use and a 12.2% prevalence of past-year use *(181)*. Of the people who reported nitrous oxide use, 80.1% also had a history of lifetime inhalation of volatile organic solvents. Most (77.7%) of those who had used both nitrous oxide and volatile organic solvents had a psychiatric diagnosis, while 36% of those who used only nitrous oxide had such a diagnosis. Among 106 adolescents and young adults (mean [standard deviation] age 17.25 [1.33] years, 19.8% > 18 years, 71.7% men) court-ordered into outpatient treatment for "illicit drug use" in Taiwan (China) between September 2016 and September 2021, 22.6% had used nitrous oxide as their main drug *(182)*.

For the Australian Ecstasy and Related Drug Reporting System, interviews are conducted annually with a convenience sample of people in each state capital city who are at least 16 years of age, resident in the city for at least 12 months and had used stimulants, hallucinogens or novel psychoactive substances at least six times in the past 6 months *(183)*. Respondents are recruited by advertisements and peer referral. Among respondents interviewed in Sydney, New South Wales (about 100 annually), the prevalence of use of nitrous oxide in the past 6 months was relatively stable (8–12%) in 2003–2011, increased to 20% in 2012–2013 and steadily increased to 55% in 2016–2017, 75% in 2018, 72% in 2019 and 67% in 2020. Among the 69 respondents in 2020 who answered a question about changes in their use of nitrous oxide in the past 6 months, 25% reported decreased use, 15% increased use, 10% stopped use, and the remainder had not changed their use. A review of the Rapid Emergency Department Data for Surveillance for New South Wales, Australia, for 2012–2018 identified 118 patients for whom nitrous oxide use was the presenting problem or mentioned in their diagnosis, of whom 24% reported chronic or heavy use *(184)*. More than half (56%) were men, 83% were aged 16–30 years, and 46% reported "polydrug" use. The number of patients who used nitrous oxide increased gradually from 2 in 2012 to 10 in 2015–2016 and then dramatically to 61 in 2018.

A systematic review of four electronic databases conducted in January 2022 identified 91 case reports and 24 case series comprising 355 people with chronic nitrous oxide "misuse" or "abuse", of whom 55.5% were men with a mean age of 24 years (range, 14–60 years) *(185)*. The duration of nitrous oxide use ranged from 1 month to 10 years, but most had used it for at least 1 year. All the patients used nitrous oxide at least weekly, using 15–900 bulbs per session. Most of the patients came to clinical attention because of

medical problems (most commonly sensory changes, weakness or autonomic dysfunction) rather than psychiatric problems.

The prevalence of nitrous oxide use disorder, of heavy nitrous oxide use (suggesting use disorder) and the proportion of people who report nitrous oxide use who develop a use disorder is unknown. This information has not been collected in large-scale, population-based or otherwise unbiased surveys. Surveys of convenience samples suggest that only a minority of people who use nitrous oxide develop a use disorder, while a high proportion of cases that come to medical attention or are reported to monitoring systems have a use disorder.

Among 876 cases of non-medical nitrous oxide use reported to the French national addictovigilance system between 2012 and 2022 (mean age, 22 years; median, 21 years; range, 13–53 years; more than one-third women (30.8% in 2020, 42.7% in 2021) 67.3% met the diagnostic criteria for nitrous oxide use disorder, and another 18% were considered to have "heavy" use patterns (daily use or at least 20 cartridges per use occasion) *(109)* (Prof. Caroline Vigneau Victorri, personal communication 12 October 2023).About one quarter of cases also used alcohol (23.4%) or cannabis (23.8%) (2002-2021). The number of cases reported annually was low and stable from 2012—2018 then increased from 40 in 2019 to 344 in 2021 and 351 in 2022. The proportion of cases with use disorder increased from 42.5% in 2020 to 76.6% in 2021 and 71.5% in 2022 (Prof. Caroline Vigneau Victorri, personal communication 10 October 2023). Compared to cases without nitrous oxide use disorder, those with a use disorder were significantly younger (22 vs. 23 years), using nitrous oxide for a longer period (about 1.5 years vs. < 1 year, respectively), more likely to inhale using large bottles (about 50% vs. 10%, respectively), experience serious adverse consequences (>80% vs. <30%, respectively) and neurological effects (>80% vs. about 70%, respectively), use tobacco (about 25% vs. 10%, respectively), and be referred for addiction treatment (about 20% vs. <10%, respectively), and less likely to experience psychological effects (about 10% vs. 20%, respectively). For 111 cases through 2021, sufficient clinical information was available to evaluate at least one individual DSM-5 diagnostic criterion for (nitrous oxide) use disorder *(109)*. Of these cases, 60.4% took nitrous oxide in larger amounts or for longer periods than initially intended, 40.1% had spent a great deal of time in obtaining nitrous oxide or recovering from its use, 35.1% continued use despite persistent health problems due to nitrous oxide, 30.1% had a persistent desire or had unsuccessfully attempted to reduce or stop their use, 27.9% showed tolerance, 23.4% had social, financial or vocational problems due to use, and 11.7% had withdrawal symptoms. Craving to use nitrous oxide was reported by 15.3% and risky behavior while using nitrous oxide by 2.7%.

Among 788 medical students at the University of Paris, France, with self-identified lifetime nitrous oxide use who participated in an anonymous online survey in March–October 2021, 24.1% met the DSM-5 diagnostic criteria for nitrous oxide use disorder: 79% of cases were mild (meeting 2–3 of 11 possible criteria), 17% moderate (4–5 criteria) and 4% severe (≥ 6 criteria) *(108)*. The most common criteria were a persistent desire or unsuccessful attempts to reduce or stop use (46%), tolerance (45%), continued use despite persistent health problems due to nitrous oxide (44%), and use in larger amounts or for longer periods than intended (18%). People who use nitrous oxide with a use disorder were significantly more likely than peoplewho use it without a use disorder to be men (36.8% vs 27.7%), to use nitrous oxide at least monthly (33.1% vs 12.9%) and to use it more than once a week (3.6% vs 0.8%). Use of other psychoactive substances was common with and without a use disorder, except that use of alkyl nitrites ("poppers") was more common in those with a use disorder (72.5% vs 59.7%).

In a systematic review of 73 published cases of non-medical nitrous oxide use that resulted in "major side effects", 62 provided sufficient clinical information to evaluate at least one of the DSM-5 diagnostic criteria for nitrous oxide use disorder *(111)*. Of the 73 cases, 55 (88.7%) met the criteria for taking nitrous oxide in larger amounts or over a longer period than intended and for spending time in obtaining nitrous oxide, using it or recovering from its effects (in all the cases for which these two criteria could be evaluated), qualifying as having mild use disorder. Eight cases met the criteria for use resulting in failure to fulfill major role obligations, interfering with important activities or continued use despite persistent social or interpersonal problems due to its use (88.9% of the cases for which these three criteria could be evaluated). Six cases met the criteria for persistent use when it was physically hazardous or despite physical or psychological problems due to use, representing 66.7% of all the cases for which these two criteria could be evaluated.

In a retrospective case series of seven adults (21–33 years, four women) who sought treatment for "severe nitrous oxide use disorder" at a psychiatric centre in Taiwan (China) between 2017 and 2018. the duration of nitrous oxide use varied from 4 months to 20 years; five used nitrous oxide daily, one two or three times weekly and one weekly *(186)*. All had used other psychoactive substances before initiating nitrous oxide use; and all but one had a comorbid psychiatric disorder (five major depressive disorder, one bipolar disorder).

Little is known about the time course of nitrous oxide use disorder. Only two published studies were found. A 5-month follow-up of 430 patients

(57% men, mean age 23.9 years, mean [SD] 2.2 [0.6] years of nitrous oxide use, mean daily dose 1800 [450] mL) who received 1 month of inpatient treatment (psychological therapy and vitamin B12) for nitrous oxide use disorder (diagnostic criteria not reported) at the Gaoxin Hospital in Beijing, China, found a non-linear relapse rate: 15.8% at 1 month, 38.6% at 2 months, 47% at 3 months, 51.2% at 5 months and 55.1% at 6 months *(187)*. Half the patients had relapsed by 108 days. Depressed or anxious mood at hospital discharge was associated with an increased risk of relapse.

A prospective, 3-month longitudinal study was conducted to follow 10 individuals (median age, 23 years, range 18–26 years; 80% women) who were reported to the Dutch Poisons Information Centre between 16 January 2021 and 15 January 2022 with nitrous oxide "intoxication" and neuropathy *(110)*. At baseline, all 10 participants met the DSM-5 diagnostic criteria for (nitrous oxide) use disorder: one mild, one moderate and eight severe. Eight participants used nitrous oxide at least weekly, and nine reported "heavy" use (> 50 balloons at a session). At 1-month follow-up, six of the remaining seven participants still met the criteria for severe nitrous oxide use disorder, as did the one participant at the 3-month follow-up. The external validity of this study is low because of the high drop-out rate (90%). In addition, the 10 participants were drawn from a pool of 75 individuals who met the eligibility criteria but 65 of whom refused to participate.

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

Deaths directly related to non-medical use of nitrous oxide appear to be rare. Coroners' inquests were conducted in England and Wales for 62 deaths associated with nitrous oxide use (both intentional and unintentional) between 2001 and 2021 *(188)*, for an average of three annually. The prevalence of nitrous oxide-associated deaths tripled, from 1.6 annually during the first decade to 4.5 annually during the last decade. A review of the Australian National Coronial Information System for 2000–2021 identified 20 fatalities related to nitrous oxide misuse, representing 12.2% of all fatalities related to inhalant misuse *(189)*. Nitrous oxide was detected in the blood in all five cases in which it was tested. More than 75% of all inhalant-related fatalities were considered to be unintended, about 10% were due to intentional self-harm and about 5% to unintended traumatic injury. A review of autopsies of cases of suicide in 2003–2017 in the files of Forensic Science South Australia identified only two cases associated with nitrous oxide use *(190)*.

The most common cause of death from non-medical use of nitrous oxide is asphyxia, either unintended or intended (in a suicide attempt). When nitrous

oxide is inhaled in a confined space, it displaces the available oxygen *(191)*, and the resulting hypoxia may lead to death if nitrous oxide inhalation is continued. This may occur when nitrous oxide is inhaled with the person's head in a plastic bag *(188)*, through a tight-fitting face mask or in a car or a small unventilated room *(192)*.

15. Licit production, consumption and international trade

Nitrous oxide is legally manufactured for industrial and medical use. The leading manufacturers are based in France, Japan, Netherlands (Kingdom of the), Singapore and the USA. The global market for nitrous oxide was estimated in 2016 to be US$ 805 million for both the medical (about 85% of the market) and the industrial sector *(193)*, which increased to US$ 1.2 billion in 2022 *(2)*. North America accounts for almost half the market, followed by Europe and Asia with about one-quarter each. The electronics industry used an estimated 10 000 tonnes of nitrous oxide in 2022 *(158)*.

16. Illicit manufacture and traffic and related information

Nitrous oxide is not known to be manufactured illicitly. Non-medical use is with nitrous oxide manufactured legally for legitimate medical or industrial use but then purchased for non-medical use online or in person. Among 4883 self-selected respondents to an anonymous online survey in late 2013 (2014 Global Drug Survey) who reported use of nitrous oxide in the past year, nitrous oxide was most commonly obtained from friends (38.8%), a supermarket (34.4%), over the Internet (29.3%) or at a festival (28.7%) and rarely from "head shops" (9.9%), a dealer (7.3%) or an adult store (6.1%) *(28)*.

17. Current international controls and their impact

Nitrous oxide is not currently controlled under any international treaty.

18. Current and past national controls

Nitrous oxide is sold legally in all countries; however, many countries have imposed controls to limit non-medical use *(5)*. Such restrictions include bans on sale to minors, banning sales during certain hours (e.g. 22:00–05:00) and from certain locations (e.g. shops that sell alcohol or tobacco), restrictions on retail display and advertisement in shops, warning labels on packaging, prohibiting concurrent sale of products that enable non-medical use (e.g. balloons, "crackers"), and limits on importation and production. In the United Kingdom, production or supply (but not possession) of nitrous oxide for its psychoactive effects is illegal under the Psychoactive Substances Act of 2016 *(194)*. Netherlands (Kingdom of the) banned the production, sale and possession of nitrous oxide effective 1 January 2023, with exceptions

for medical use and the food industry *(195)*. In South Australia, it is illegal to keep nitrous oxide visible in stores or to sell to minors or between 22:00 and 05:00 *(196)*.

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

No other medical and scientific matters were identified.

References

1. Nitrous oxide. In: Reynolds JEF, editor. Martindale, The Extra Pharmacopoeia. 29th edition. London: Pharmaceutical Press; 1989. ISBN 0 85369 210 6 El 10.00.
2. Nitrous oxide overdose: How much is too much? Newport Beach (CA): WindwardWay; 2023 (https://windwardway.com/prescription-drug-abuse/nitrous-oxide/overdose/, accessed 28 June 2023).
3. Nitrous oxide. In: European Pharmacopoeia. 11th edition. Strasbourg: Council of Europe: European Directorate for the Quality of Medicines and Health Care; 2023 (https://www.edqm.eu/en/european-pharmacopoeia-ph.-eur.-11th-edition).
4. Nitrous oxide. In: United States Pharmacopoeia – The National Formulary (USP42-NF37). 42nd edition. Rockville (MD): United States Pharmacopeial Convention; 2019 (usp.org).
5. Recreational use of nitrous oxide: a growing concern for Europe. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2022 (https://www.emcdda.europa.eu/publications/rapid-communication/recreational-use-nitrous-oxide-growing-concern-europe_en, accessed 9 July 2023).
6. Trogler WC. Physical properties and mechanisms of formation of nitrous oxide. Coordination Chem Rev. 1999;187:303–27. doi:10.1016/S0010-8545(98)00254-9.
7. Buslov A, Carroll M, Desai MS. 2018. Frozen in time: a history of the synthesis of nitrous oxide and how the process remained unchanged for over 2 centuries. Anesth Analg. 2018;127:65–70. doi:10.1213/ANE.0000000000003423.
8. Denisova KO, Ilyin AA, Rumyantsev RN, Ilyin AP, Volkova AV. Nitrous oxide: production, application, and protection of the environment. Russ J Gen Chem. 2019;89:1338–46. doi:10.1134/S107036321906032X.
9. Matuda H, Mishimura T, Tanaka T, Hatabu Y. 1981. Process for producing nitrous oxide. US patent US4376105A (https://patents.google.com/patent/US4376105A/en).
10. Helmenstine A. How to make nitrous oxide or laughing gas. Science Notes; 2020 (https://sciencenotes.org/how-to-make-nitrous-oxide-or-laughing-gas/, accessed 28 June 2023).
11. Blue RW, Giauque WF. The heat capacity and vapor pressure of solid and liquid nitrous oxide. The entropy from its band spectrum. J Am Chem Soc. 1935;57:991–7. doi:10.1021/ja01309a008.
12.. Rapson TD, Dacres H. Analytical techniques for measuring nitrous oxide. Trends Anal Chem. 2014;54:65–74. doi:10.1016/j.trac.2013.11.004.
13. Milam-Guerrero J, Yang B, To DT, Myung NV. Nitrous oxide is no laughing matter: a historical review of nitrous oxide gas-sensing capabilities highlighting the need for further exploration. ACS Sens. 2022;7(12):3598–610. doi:10.1021/acssensors.2c01275.
14. Kolb C, Wormhoudt JC, Zahniser MS. Recent advances in spectroscopic instrumentation for measuring stable gases in the natural environment. In: Matson PA, Harriss RC, editors. Biogenic trace gases: Measuring emissions from soil and water. Hoboken (NJ): Wiley-Blackwell; 1995:259–90 (https://www.wiley.com/en-sg/Biogenic+Trace+Gases:+Measuring+Emissions+from+Soil+and+Water-p-9780632036417).

15. Brenninkmeijer CAM, Janssen C, Kaiser J, Röckmann T, Rhee TS, Assonov SS. Isotope effects in the chemistry of atmospheric trace compounds. Chem Rev. 2003;103:5125–62. doi:10.1021/cr020644k.

16. Heard D, editor. Analytical techniques for atmospheric measurement. Hoboken (NJ): Wiley-Blackwell; 2008 (https://www.wiley.com/en-fr/Analytical+Techniques+for+Atmospheric+Measurement-p-9781405123570).

17. Griffith DWT, Deutscher NM, Caldow CGR, Kettlewell G, Riggenbach M, Hammer S. A Fourier transform infrared trace gas analyser for atmospheric applications. Atmos Meas Tech Discuss. 2012;5:3717–69. doi:10.5194/amtd-5-3717-2012.

18. Li J, Chen W, Yu B. Recent progress on infrared photoacoustic spectroscopy techniques. Appl Spectrosc Rev. 2011;46:440–71. doi:10.1080/05704928.2011.570835.

19. Compton RG, Northing RJ. Novel amperometric sensor for the detection of the anaesthetic gases isoflurane and nitrous oxide. J Chem Soc Faraday Trans. 1990;86:1077–81. doi:10.1039/FT9908601077

20. Andersen K, Kjær T, Revsbech NP. An oxygen insensitive microsensor for nitrous oxide. Sensors Actuators B Chem. 2001;81:42–8. doi:10.1016/S0925-4005(01)00924-8.

21. Brugnone F, Perbellini L, Cerpelloni M, Soave C, Cecco A, Giuliari C. Nitrous oxide in blood and urine of operating theatre personnel and the general population. Int Arch Occup Environ Health. 1995;68:22–6. doi:10.1007/BF01831629.

22. Poli D, Gagliano-Candela R, Strisciullo G, Colucci AP, Strada L, Laviola D et al. Nitrous oxide determination in postmortem biological aamples: a case of serial fatal poisoning in a public hospital. J Forensic Sci. 2010;55(1):258–64. doi:10.1111/j.1556-4029.01218.x.

23. Giuliani N, Beyer J, Augsberger M, Varlet V. Validation of an analytical method for nitrous oxide (N2O) laughing gas by headspace gas chromatography coupled to mass spectrometry (HS-GC-MS): forensic application to a lethal intoxication. J Chromatogr B Analyt Technol Biomed Life Sci. 2015;983-984:90-3. doi:10.1016/j.jchromb.2014.12.034.

24. Marillier M, Karila L, Miguet-Alfonsi C. Quand le protoxyde d'azote ne fait plus rire: épidémiologie, aspects analytiques, incidences clinique et médicojudiciaire [When nitrous oxide is no longer a laughing matter: epidemiology and analytical, clinical incidents and medicolegal aspects]. Toxicol Analyt Clin. 2020;32:278–90. doi:10.1016/j.toxac.2020.07.002.

25. Xiang Y, Li L, Ma X, Li S, Xue Y, Yan P et al. Recreational nitrous oxide abuse: prevalence, neurotoxicity, and treatment. Neurotoxicity Res. 2021;39:975–85. doi:10.1007/s12640-021-00352-y.

26. Brunt TM, van den Brink W, van Amsterdam J. Mechanisms involved in the neurotoxicity and abuse liability of nitrous oxide: a narrative review. Int J Mol Sci. 2022;23:14747. doi:10.3390/ijms232314747.

27. Winstock AR & Ferris JA. Nitrous oxide causes peripheral neuropathy in a dose dependent manner among recreational users. Journal Psychopharmacol. 2020;34(2):229-236.

28. Kaar SJ, Ferris J, Waldron J, Devaney M, Ramsey J, Winstock AR. Up: The rise of nitrous oxide abuse. An international survey of contemporary nitrous oxide use. J Psychopharmacol. 2016;30(4):395–401. doi:10.1177/0269881116632375.

29. Gibbs D, Peacock A. New South Wales Drug Trends 2018: Key findings from the Ecstasy and Related Drugs Reporting System (EDRS) interviews. Sydney: National Drug and Alcohol Research Centre, University of New South Wales; 2018 (https://ndarc.med.unsw.edu.au/sites/default/files/NSW%20EDRS%20Interview%20Report%202018_2.pdf).

30. Ng J, O'Grady G, Pettit T, Frith R. Nitrous oxide use in first-year students at Auckland University. Lancet. 2003;361:1349–50. doi:10.1016/S0140-6736(03)13045-0.

31. Becker DE, Rosenberg M. Nitrous oxide and the inhalation anesthetics. Anesthesia Progress. 2008;55:124–31. doi:10.2344/0003-3006-55.4.124.

32. Quock RM, Graczik LM. Influence of narcotic antagonist drugs upon nitrous oxide analgesia in mice. Brain Res. 1988;440: 35–41. doi:10.1016/0006-8993(88)91156-0.

33. Chen DC, Quock RM. A study of central opioid receptor involvement in nitrous oxide analgesia in mice. Anesthesia Progress. 1990;7:181–5. PMID:1965769.

34. Quock RM, Walczak CK, Henry RJ, Chan DC. Effect of subtype-selective opioid receptor blockers on nitrous oxide antinociception in rats. Pharmacol Res. 1990;22(3):351–7. doi:10.1016/1043-6618(90)90733-t.

35. Quock RM, Mueller J. Protection by U-50,388H against β-chlornaltrexamine antagonisms of nitrous oxide antinociception in mice. Brain Res. 1991;549:162–4. doi:10.1016/0006-8993(91)90615-3.

36. Koyama T, Fukuda K. Involvement of the k-opioid receptor in nitrous oxide-induced analgesia in mice. J Anesthesia. 2010;24:297–9. doi:10.1007/s00540-010-0886-5.

37. Kingery WS, Sawamura S, Agashe GS, et al. 2001. Enkephalin release and opioid receptor activation does not mediate the antinociceptive or sedative/hypnotic effects of nitrous oxide. European Journal of Pharmacology 427: 27–35.

38. Smith EH, Rees JM. The effects of naloxone on the analgesic activities of general anaesthetics. Experientia. 1981;37(3):289–90. doi:10.1007/BF01991660.

39. Moody EJ, Mattson M, Newman AH, Rice KC, Skolnick P. Stereospecific reversal of nitrous oxide analgesia by naloxone. Life Sci. 1989;44(11):703–9. doi:10.1016/0024-3205(89)90381-0.

40. Quock RM, Curtis BA, Reynolds BJ, Mueller JL. Dose-dependent antagonism and potentiation of nitrous oxide antinociception by naloxone in mice. J Pharmacol Exp Ther. 1993.;267(1):117–22. PMID:8229738.

41. Koyama T, Mayahara T, Wakamatsu T, Sora I, Fukuda K. Deletion of mu-opioid receptor in mice does not affect the minimum alveolar concentration of volatile anaesthetics and nitrous oxide-induced analgesia. Br J Anaesthesia. 2009;103(5):744–9. doi:10.1093/bja/aep246.

42. Emmanouil DE, Dickens AS, Heckert RW, Ohgami Y, Chung E, Han S et al. Nitrous oxide-antinociception is mediated by opioid receptors and nitric oxide in the periaqueductal gray region of the midbrain. Eur Neuropsychopharmacol. 2007;18:194–9. doi:10.1016/j.euroneuro.2007.06.008.

43. Fang F, Guo TZ, Davies MF, Maze M. Opiate receptors in the periaqueductal gray mediate analgesic effect of nitrous oxide in rats. Eur J Pharmacol. 1997;336:137–41. doi:10.1016/s0014-2999(97)01219-3.

44. Hynes MD, Berkowitz BA. Nitrous oxide stimulation of locomotor activity: evidence for an opiate-like behavioral effect. J Pharmacol Exp Ther. 1979;209:304–8.

45. Hynes MD, Berkowitz BA. Lack of an opiate response to nitrous oxide in mice resistant to the activity-stimulating effects of morphine. J Pharmacol Exp Ther. 1982;220:499–503. PMID:6278126.

46. Tulunay FC, Tulunay M, Akkartal B, ayhan IH. A study of analgesic and dependence producing actions of nitrous oxide in mice. Pharm Res Commun. 1982;14(2):13–9. doi:10.1016/s0031-6989(82)80094-5.

47. Hodges BL, Gagnon MJ, Gillespie TR, Breneisen JR, O'Leary DF, Hara S et al. Antagonism of nitrous oxide antinociception in the rat hot plate test by site-specific mu and epsilon opioid receptor blockade. J Pharmacol Exp Ther. 1994;269(2):596–600. PMID:8182525.

48. Guo TZ, Poree L, Golden W, Stein J, Fujinaga M, Maze M. Antinociceptive response to nitrous oxide is mediated by supraspinal opiate and spinal adrenergic α2 receptors in the rat. Anesthesiology. 1996;85:846–52. doi:10.1097/00000542-199610000-00020.

49. Fukihara N, Ishikawa T, Kinoshita H, Xiong L, Nakanishi O. Central noradrenergic mediation of nitrous oxide-induced analgesia in rats. Can J Anaesth. 1998;45:1123–9. doi:10.1007/BF03012404.

50. Shingu R, Osawa M, Omatsu Y, Komatsu T, Urabe N, Mori K. Naloxone does not antagonize the anesthetic-induced depression of nociceptor-driven spinal cord response in spinal cats. Acta anaesth scand. 1981;25:526–32. doi:10.1111/j.1399-6576.1981.tb01699.x.

51. Smith RA, Wilson M, Miller KW. Naloxone has no effect on nitrous oxide anesthesia. Anesthesiology. 1978;49:6–8. doi:10.1097/00000542-197807000-00003.

52. Courtière A, Hardouin J. Behavioural effects induced by nitrous oxide in rats performing a vigilance task. Behav Pharmacol. 1997;8:408–15. PMID:9832980.

53. Zacny JP, Coalson DW, Lichtor JL. Effects of naloxone on the subjective and psychomotor effects of nitrous oxide in humans. Pharmacol Biochem Behav. 1994;49(3):573–8. doi:10.1016/0091-3057(94)90071-x.

54. Yang JC, Clark WC, Ngai SH. Antagonism of nitrous oxide analgesia by naloxone in man. Anesthesiology. 1980;52:414-417.

55. Chapman CR, Benedetti C. Nitrous oxide effects on cerebral evoked potential to pain: Partial reversal with a narcotic antagonist. Anesthesiology. 1979;51:135–8. doi:10.1097/00000542-197908000-00009.

56. Willer JC, Bergeret S, Gaudy JH, Dauthier C. Failure of naloxone to reverse the nitrous oxide-induced depression of a brain stem reflex: an electrophysiologic and double-blind study in humans. Anesthesiology 1985;63(5):467-72.

57. Levine JD, Gordon NC, Fields HL. Naloxone fails to antagonize nitrous oxide analgesia for clinical pain. Pain. 1982;13:65-170. doi:10.1016/0304-3959(82)90026-4.

58. Yagi M, Mashimo T, Kawaguchi T, Yoshiya I. Analgesic and hypnotic effects of subanaesthetic concentrations of xenon in human volunteers: comparison with nitrous oxide. Br J Anaesth. 1995;74:670–3. doi:10.1093/bja/74.6.670.

59. Zacny JP, Conran A, Pardo H, Coalson DW, Black M, Klock AP et al. Effects of naloxone on nitrous oxide actions in healthy volunteers. Pain. 1999;83:411–8. doi:10.1016/S0304-3959(99)00127-X.

60. Gillman MA, Kok L, Lichtigfeld FJ. Paradoxical effect of naloxone on nitrous oxide analgesia in man. Eur J Pharmacol. 1980;61:175–7. doi:10.1016/0014-2999(80)90160-0.

61. Gillman MA, Lichtigfeld FJ. A comparison of the effects of morphine sulphate and nitrous oxide analgesia on chronic pain states in man. J Neurolog Sci. 1981;49:41–5. doi:10.1016/0022-510x(81)90186-6.

62. Jevtovic-Todorovic V, Todorovic SM, Mennerick S, Powell S, Dikranian K, Benshoff N et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1998;4(4):460–3. doi:10.1038/nm0498-460.

63. Izumi Y, Hsu FF, Conway CR, Nagele P, Mennerick SJ, Zorumski CF. Nitrous oxide, a rapid antidepressant, has ketamine-like effects on excitatory transmission in the adult hippocampus. Biol Psychiatry. 2022;92:964–72. doi:10.1016/j.biopsych.2022.06.016.

64. Sato Y, Kobayashi E, Murayama T, Mishina M, Seo N. Effect of N-methyl-D-aspartate receptor epsilon1 subunit gene disruption of the action of general anesthetic drugs in mice. Anesthesiology. 2005;102:557–61. doi:10.1097/00000542-200503000-00013.

65. Zacny JP, Yajnik S, Coalson D, Lichtor JL, Apfelbaum JL, Rupani G et al. Flumazenil may attenuate some subjective effects of nitrous oxide in humans: a preliminary report. Pharmacol Biochem Behav. 1995;51(4):815–9. doi:10.1016/0091-3057(95)00039-y.

66. Quock RM, Emmanouil DE, Vaughn LK, et al. 1992. Benzodiazepine mediation of behavioral effects of nitrous oxide in mice. Psychopharmacology. 107:310-314.

67. Kalmoe MC, Janski AM, Zorumski CF, Nagele P, Palanca BJ, Conway CR. Ketamine and nitrous oxide: the evolution of NMDA receptor antagonists as antidepressant agents. J Neurol Sci. 2020;412:116778. doi:10.1016/j.jns.2020.116778.

68. Menetrier T, Denimal D. Vitamin B12 status in recreational users of nitrous oxide: a systematic review focusing on the prevalence of laboratory abnormalities. Antioxidants. 2023;12:1191. doi:10.3390/antiox12061191.

69. Dohrn CS, Lichtor JL, Coalson DW, Uitvlugt A, de Wit H, Zacny JP. Reinforcing effects of extended inhalation of nitrous oxide in humans. Drug Alcohol Depend. 1993;31(3):265–80. doi:10.1016/0376-8716(93)90009-f.

70. Yu M, Qiao Y, Li W, Fang X, Gao H, Zheng D et al. Analysis of clinical characteristics and prognostic factors in 110 patients with nitrous oxide abuse. Brain Behav. 2021;12:e2533. doi:10.1002/brb3.2533.

71. Chiew AL, Raubenheimer JF, Berling I, Buckley I, Buckley NA, Becker T et al. Just "nanging" around – harmful nitrous oxide use: a retrospective case series and review of Internet searches, social media posts and the coroner's database. Intern Med J. 2022;52:1724–32. doi:10.1111/imj.15391.

72. Piazza GG, Iskandar G, Hennessy V, Zhao H, Walsh K, McDonnell J et al. Pharmacological modelling of dissociation and psychosis: an evaluation of the Clinician Administered Dissociative States Scale and Psychotomimetic States Inventory during nitrous oxide ("laughing gas")-induced anomalous states. Psychopharmacology. 2022;239:2317–29. doi:10.1007/s00213-022-06121-9.

73. Paulus MC, Wijnhoven AM, Maessen GC, Blankensteijn SR, van der Heyden MAG. Does vitamin B12 deficiency explain psychiatric symptoms in recreational nitrous oxide users? A narrative review. Clin Toxicol. 2021;59(11):947–55. doi:10.1080/15563650.2021.1938107.

74. Sood R, Parent T. Peripheral polyneuropathy and acute psychosis from chronic nitrous oxide poisoning. A case report with literature review. Medicine (Baltimore). 2022;101(31):e28611. doi:10.1097/MD.0000000000028611.

75. Dohrn CS, Lichtor JL, Finn RS, Uitvlugt A, Coalson DW, Rupani G et al. Subjective and psychomotor effects of nitrous oxide in healthy volunteers. Behav Pharmacol. 1992;3:19–30. doi:10.1097/00008877-199203010-00005.

76. Lichtor JL, Lane BS, Zimmerman MB. Residual sleepiness after N2O sedation: a randomized control trial [ISRCTN88442975]. BMC Anesthesiology. 2004;4:5. doi:10.1186/1471-2253-4-5.

77. Beckman NJ, Zacny JP, Walker DJ. Within-subject comparison of the subjective and psychomotor effects of a gaseous anesthetic and two volatile anesthetics in healthy volunteers. Drug Alcohol Depend. 2006;81:89–95. doi:10.1016/j.drugalcdep.2005.06.002.

78. Armstrong PJ, Morton C, Sinclair W, Tiplady B. Effects of nitrous oxide on psychological performance. A dose-response study using inhalation of concentrations up to 15%. Psychopharmacology (Berl). 1995;117:486–90. doi:10.1007/BF02246223.

79. Fagan D, Paul DL, Tiplady B, Scott DB. A dose–response study of the effects of inhaled nitrous oxide on psychological performance and mood. Psychopharmacology (Berl). 1994;115:333–8. doi:10.1007/BF02245337.

80. Berkowitz BA, Finck AD, Hynes MD, Ngai SH. Tolerance to nitrous oxide in rats and mice. Anesthesiology. 1979;51:309–12. doi:10.1097/00000542-197910000-00006.

81. Laughing gas implicated in growing number of fatal accidents: NOS. Dutch News, 2 December 2021. https://www.dutchnews.nl/2021/12/laughing-gas-implicated-in-growing-number-of-fatal-accidents-nos/, accessed 27 August 2023).

82. Moyes D, Cleaton-Jones P, Lelliot J. Evaluation of driving skills after brief exposure to nitrous oxide. S Afr Med J. 1979;56:1000–2. PMID:550424.

83. Baran KC, van Munster IG, Meij-de Vries A, Gardien KLM, van Trier T, Pijpe A et al. Severe nitrous-oxide frostbite injuries on the rise in The Netherlands; let's raise awareness. Burns. 2020;46(6):1472–9. doi:10.1016/j.burns.2020.04.016.

84. Quax MLJ, Van Der Steenhoven TJ, Bronkhorst MWGA, Emmink BL. Frostbite injury: an unknown risk when using nitrous oxide as a party drug. Acta Chir Belg. 2020;122(2):140–3. doi:10.1080/00015458.2020.1782160.

85. Chan JHK, Eriksson S, Mohamed H, Bhatti S, Frew Q, Barnes D. Experiences of frostbite injury from recreational use of nitrous oxide canisters in a United Kingdom burns center: Not a laughing matter. J Plast Reconstr Aesthet Surg. 2023;83:282–8. doi:10.1016/j.bjps.2023.05.012.

86. Dolin SJ, Little HJ. Effects of "nitrendipine" on nitrous oxide anesthesia, tolerance, and physical dependence. Anesthesiology. 1989;70:91–7. PMC1917760.

87. Koblin DD, Dong DE, Eiger EI 2nd. Tolerance of mice to nitrous oxide. J. Pharmacol Exp Ther. 1979;211:317–25. PMID:228023.

88. Rupreht J, Ukponmwan DE, Dworacek B, Admiraal PV, Dzoljic. Enkephalinase inhibition prevented tolerance to nitrous oxide analgesia in rats. Acta Anaesthesiol Scand. 1984:28:617–20. doi:10.1111/j.1399-6576.1984.tb02132.x.

89. Manson HJ, Dyke G, Melling J, Gough M. The effect of naloxone and morphine on convulsions in mice following withdrawal from nitrous oxide. Can Anaesth Soc J.1983;30(1):28–31. doi:10.1007/BF03007713.

90. Shingu K, Osawa M, Fukuda K, Mori K. Acute tolerance to the analgesic action of nitrous oxide does not develop in rats. Anesthesiology. 1985;62:502–4. doi:10.1097/00000542-198504000-00021.

91. Koblin DD, Deady JE, Dong DE, Eiger EI 2nd. Mice tolerant to nitrous oxide are also tolerant to alcohol. J. Pharmacol Exp Ther. 1980;213:309–12. PMID:7365690.9

92. Koblin DD, Deady JE, Nelson NT, Eiger EI 2nd, Bainton CR. Mice tolerant to nitrous oxide are not tolerant to barbiturates. Anesth Analg. 1981;60:138–41. PMID:7193990.

93. Matsushita Y, Ishikawa M, Abe K, Utsunomiya I, Chikuma T, Hojo H, Hoshi K, Quock RM, Taguchi K. Involvement of the protein kinase Cgamma isoform in development of tolerance to nitrous oxide-induced antinociception in mice. Neuroscience 2007;148(2):541-7

94. Kaiyala KJ, Butt S, Ramsay DS. Systems-level adaptations explain chronic tolerance development to nitrous oxide hypothermia in young and mature rats. Psychopharmacology (Berl) 2007b;191:233–242.

95. Dzoljic M, Rupreht J, Erdmann W, Stijnen TH, van Briemen LJ, Dzoljic MR. Behavioral and electrophysiological aspects of nitrous oxide dependence. Brain Res Bull. 1994;33:25–31. doi:10.1016/0361-9230(94)90046-9.

96. Rupreht J, Shimoji K, Fukuda S, Erdmann, Denda S. Tolerance to N2O-induced alterations in somatosensory evoked potentials. J Neurosurg Anesthesiol. 1989;1(2):91–5. doi:10.1097/00008506-198906000-00002.

97. Fischer GJ, Gilman SC, Blank C. Corticosterone response underlying tolerance to stress induced by a gaseous (nitrous oxide) environment. Percept Mot Skills. 1987;64:799–808. doi:10.2466/pms.1987.64.3.799.

98. Harper MH, Winter PM, Johnson BH, Koblin DD, Eiger EI 2nd. Withdrawal convulsions in mice following nitrous oxide. Anesth Analg. 1980;59:19–21. PMID:7188661.

99. Milne B, Cervenko FW, Jhamandas KH. Physical dependence on nitrous oxide in mice: resemblance to alcohol but not to opiate withdrawal. Can Anaesth Soc J. 1981;28(1):46–50. doi:10.1007/BF03007289.

100. Rupreht J, Dworacek B, Ducardus R,Schmitz PI, Dzolijc MR. The involvement of the central cholinergic and endorphinergic systems in the nitrous oxide withdrawal syndrome in mice. Anesthesiology. 1983;58:524–6. doi:10.1097/00000542-198306000-00008.

101. Belknap JK, Laursen SE, Crabbe JE. Ethanol and nitrous oxide produce withdrawal-induced convulsions by similar mechanisms in mice. Life Sci. 1987;41:2033–40. doi:10.1016/0024-3205(87)90477-2.

102. Dzoljic MR, Haffman J, Rupreht J, Adolfs MJ, Dzolijic MM, Cappendijk SL. Decrease of β-endorphin in the brain of rats following nitrous oxide withdrawal. Drug Metab Drug Interact. 1991;9(2):139–48. doi:10.1515/dmdi.1991.9.2.139.

103. Whitwam, JG, Morgan M, Hall GM, Petrie A. Pain during continuous nitrous oxide administration. British Journal Anaesthesiology 1976 ;48(5):425-9

104. Ramsay DS, Leroux BG, Rothen M, Prall CW, Fiset LO, Woods SC. Nitrous oxide analgesia in humans: acute and chronic tolerance. Pain. 2005;114:19–28. doi:10.1016/j.pain.2004.12.011.

105. Rupreht J, Dworacek B, Bonke B, Dzoljic MR, van Eijndhoven JH, de Vlieger M. Tolerance to nitrous oxide in volunteers. Acta Anaesthesiol Scand. 1985 Aug;29(6):635-8. doi: 10.1111/j.1399-6576.1985.tb02271.x. PMID: 4061009.

106. Zacny JP, Cho AM, Coalson DW, Rupani G, Young CK, Klafta JM et al. Differential acute tolerance development to effects of nitrous oxide in humans. Neurosci Lett. 1996;209:73–6. doi:10.1016/0304-3940(96)12626-4.

107. Yajnik S, Zacny JP, Young CJ, Lichtor JL, Ruoani G, Klafta JM et al. Lack of acute tolerance development to the subjective, cognitive, and psychomotor effects of nitrous oxide in healthy volunteers. Pharmacol Biochem Behav. 1996;54(2):501–8. doi:10.1016/0091-3057(95)02278-3.

108. Cohen L, Duroy D, Perozziello A, Sasportes A, Lejoyeux M, Geoffroy PA. A cross-sectional study: nitrous oxide abuse in Parisian medical students. Am J Addict. 2023;32(1):60–5. doi:10.1111/ajad.13363.

109. Guerlais M, Aquizerate A, Lionnet A, Daveluy A, Duval M, Gérardin M et al. Nitrous oxide: a unique official French addictovigilance national survey. Front Public Health. 2023;11:1167746. doi:10.3389/fpubh.2023.1167746.

110. Nugteren-Van Lonkhuyzen JJ, van der Ben L, van den Hengel-Koot IS, de Lange D, van Riel AJHP, Hondebrink L. 2023. High incidence of signs of neuropathy and self-reported substance use disorder for nitrous oxide in patients intoxicated with nitrous oxide. Eur Addict Res. doi:10.1159/000530123.

111. Fidalgo, M., Prud'homme, T., Allio, A., Bronnec, M., Bulteau, S., Jolliet, P., & Victorri-Vigneau, C. (2019). Nitrous oxide: What do we know about its use disorder potential? Results of the French Monitoring Centre for Addiction network survey and literature review. Substance abuse, 40(1), 33–42. https://doi.org/10.1080/08897077.2019.1573210

112. Standardised MedDRA Queries, Medical Dictionary for Regulatory Acitivities, MedDRA, accessed December 2023, (https://www.meddra.org/standardised-meddra-queries)

113. Caveat document, Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of reported potential side effects of medicinal products, World Health Organisation – Uppsala Monitoring Centre (WHO-UMC), accessed December 2023 (https://who-umc.org/media/yzpnzmdv/umc_caveat.pdf)

114. Ramsay DS, Watson CH, Leroux BG, Prall CW, Kaiyala KJ. Conditioned place aversion and self-administration of nitrous oxide in rats. Pharmacol Biochem Behav. 2003;74(3):623–33. doi:10.1016/s0091-3057(02)01048-1.

115. Wood, R. W., Grubman, J., & Weiss, B. (1977). Nitrous oxide self-administration by the squirrel monkey. The Journal of Pharmacology and Experimental Therapeutics, 202(3), 491–499.

116. Richardson KJ, Shelton KL. Discriminative stimulus effects of nitrous oxide in mice: comparison with volatile hydrocarbons and vapor anesthetics. Behav Pharmacol. 2014;25:2–11. doi:10.1097/FBP.0000000000000017.

117. Tracy ME, Slavova-Hernandez GG, Shelton KL. Assessment of reinforcement enhancing effects of toluene vapor and nitrous oxide in intracranial self-stimulation. Psychopharmacology. 2014;231:1339–50. doi:10.1007/s00213-013-3327-y.

118. Goudie AJ, Dickins DW. Nitrous oxide-induced conditioned taste aversions in rats: the role of duration of drug exposure and its relation to the taste aversion-self-administration "paradox". Pharmacol Biochem Behav. 1978;9(5):587–92. doi:10.1016/0091-3057(78)90207-1.

119. Benturquia B, Le Gruen S, Canestrelli C, Lagente V, Apiou G, Roques BP et al. Specific blockade of morphine- and cocaine-induced reinforcing effects in conditioned place preference by nitrous oxide in mice. Neuroscience. 2007;149(3):477–86. doi:10.1016/j.neuroscience.2007.08.003.

120. Benturquia B, Le Marec T, Scherrmann JM, Noble F. Effects of nitrous oxide on dopamine release in the rat nucleus accumbens and expectation of reward. Neuroscience. 2008;155(2):341–4. doi:10.1016/j.neuroscience.2008.05.015.

121. Lynn EJ, Walter RG, Harris LA, Dendy R, James M. Nitrous oxide: It's a gas. J Psychedelic Drugs. 1972;5:1–7. doi:10.1080/02791072.1972.10471462.

122. Block RI, Ghoneim MM, Kumar V, Pathak D. Psychedelic effects of a subanesthetic concentration of nitrous oxide. Anesth Prog. 1990;37(6):271–6. PMID:2097905.

123. Galinkin JL, Janeszewski D, Young CJ, Klafta JM, Klock PA, Coalson DW et al. Subjective, psychomotor, cognitive, and analgesic effects of subanesthetic concentrations of sevoflurane and nitrous oxide. Anesthesiology. 1997;87:1082–8. doi:10.1097/00000542-199711000-00012.

124. Komboj SK, Zhao H, Troebinger L, Piazza G, Cawley E, Hennessy V et al. Rewarding subjective effects of the NMDAR antagonist nitrous oxide (laughing gas) are moderated by impulsivity and depressive symptoms in healthy volunteers. Int J Neuropsychopharmacol. 2021;24(7):551–61. doi:10.1093/ijnp/pyab009.

125. Lynn EJ, James M, Dendy R, Harris LA, Walter RG. Non-medical use of nitrous oxide: a preliminary report. Mich Med. 1971;70(6):203–4. PMID:5547080.

126. Zacny JP, Lichtor JL, Coalson DW, Apfelbaum JL, Flemming D, Foster V. Time course of effects of brief inhalations of nitrous oxide in normal volunteers. Addiction. 1994;89:831–9. doi:10.1111/j.1360-0443.1994.tb00986.x.

127. Walker DJ, Zacny JP. Within- and between-subject variability in the reinforcing and subjective effects of nitrous oxide in healthy volunteers. Drug Alcohol Depend. 2001;64:85–96. doi:10.1016/s0376-8716(00)00234-9.

128. Cho AM, Coalson DW, Klock PA, Klafta JM, Marks S, Toledano AY et al. The effects of alcohol history on the reinforcing, subjective and psychomotor effects of nitrous oxide in healthy volunteers. Drug Alcohol Depend. 1997;45:63–70. doi:10.1016/s0376-8716(97)01346-x.

129. Walker DJ, Zacny JP. Lack of effects of ethanol pretreatment on the abuse liability of nitrous oxide in light and moderate drinkers. Addiction. 2001;96:1839–45. doi:10.1046/j.1360-0443.2001.9612183913.x.

130. Walker DJ, Zacny JP. Analysis of the reinforcing and subjective effects of different doses of nitrous oxide using a free-choice procedure. Drug Alcohol Depend. 2002;66(1):93–103. doi:10.1016/s0376-8716(01)00188-0.

131. Walker DJ. Zacny JP. Bitonic dose–response functions for reinforcing and self-reported effects of nitrous oxide in humans. Pharmacol Biochem Behav. 2003;74:851–7. doi:10.1016/s0091-3057(03)00015-7.

132. Zacny JP, Jun JM. Lack of sex differences to the subjective effects of nitrous oxide in healthy volunteers. Drug Alcohol Depend. 2010;112:251–4. doi:10.1016/j.drugalcdep.2010.06.008.

133. Zacny, J. P., Walker, D. J., & Derus, L. M. (2008). Choice of nitrous oxide and its subjective effects in light and moderate drinkers. Drug and alcohol dependence, 98(1-2), 163–168. https://doi.org/10.1016/j.drugalcdep.2008.06.001

134. Walsh K, Das RK, Kamboj SK. The subjective response to nitrous oxide is a potential pharmaco-endophenotype for alcohol use disorder: a preliminary study with heavy drinkers. Int J Neuropsychopharmacol. 2017;20(4):346–50. doi:10.1093/ijnp/pyw063.

135. Yajnik S, Thapar P, Lichtor JL, Patterson T, Zacny JP. Effects of marijuana history on the subjective, psychomotor, and reinforcing effects of nitrous oxide in humans. Drug Alcohol Depend. 1994;36:227–36. doi:10.1016/0376-8716(94)90149-x.

136. Atkinson RM, Green JD. Personality, prior drug use, and introspective experience during nitrous oxide intoxication. Int J Addictions. 1983;18(5):712–38. doi:10.3109/10826088309027365.

137. Atkinson RM, Morozumi P, Green JD, Kramer JC. Nitrous oxide intoxication: subjective effects in healthy young men. J Psychedelic Drugs. 1977;9(4):317–28. doi:10.1080/02791072.1977.10472063.

138. Zacny JP, Janiszewski DJ, Sadeghi P, Black ML. Reinforcing, subjective, and psychomotor effects of sevoflurane and nitrous oxide in moderate-drinking healthy volunteers. Addiction. 1999;94(12):1817–28. doi:10.1046/j.1360-0443.1999.941218177.x.

139. Nagele P, Zorumski CF, Conway C. Exploring nitrous oxide as treatment of mood disorders. Basic concepts. J Clin Psychopharmacol. 2018;38:144–8. doi:10.1097/JCP.0000000000000837.

140. Dimic N, Djuric M, Nenadic I, Bojic S, Bobos M, Janicijevic A et al. Nitrous oxide – application in modern anesthesia. Curr Anesthesiol Rep. 2023;13:117–23. doi:10.1007/s40140-023-00554-4.

141. Hendrickx J, Peyton P, Carette R, De Wolf A. Inhaled anaesthetics and nitrous oxide. Complexities overlooked: things may not be what they seem. Eur J Anaesthesiol. 2016;33:611–9. doi:10.1097/EJA.0000000000000467.

142. Poonai N, Creene C, Dobrowlanski A, Geda R, Hartling L, Ali S et al. Inhaled nitrous oxide for painful procedures in children and youth: a systematic review and metaanalysis. Can J Emergency Med. 2023;25:508–28. doi:10.1007/s43678-023-00507-0.

143. Zuarez-Easton S, Erez O, Zafrar N, Carmeli J, Garmi G, Salim R. Pharmacologic and nonpharmacologic options for pain relief during labor: an expert review. Am J Obstet Gynecol. 2023;228(5S):S1246–59. doi:10.1016/j.ajog.2023.03.003.

144. Sahyoun C, Cantais A, Gervaix A, Bressan S, Löllgen R, Krauss B et al. Pediatric procedural sedation and analgesia in the emergency department: surveying the current European practice. Eur J Pediatr. 2021;180:1799–813. doi:10.1007/s00431-021-03930-6.

145. Broughton K, Clark AG, Ray AP. Nitrous oxide for labor analgesia: what we know to date. Ochsner J. 2020;20:419–21. doi:10.31486/toj.19.0102.

146. Liu H, Kerzman J, Demchenko I, Wijeysundera DN, Kennedy SH, Ladha KS et al. Nitrous oxide for the treatment of psychiatric disorders: a systematic review of the clinical trial landscape. Acta Psychiatrica Scandinavica. 2022;146:126–38. doi:10.1111/acps.13432.

147. Nagele P, Duma A, Kopec M, Gebara MA, Parsoei A, Walker M et al. Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. Biol Psychiatry. 2015;78:10–8. doi:10.1016/j.biopsych.2014.11.016.

148. Nagele P, Palanca BJ, Gott B, Brown F, Barnes L, Nguyen T et al. A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression. Sci Transl Med. 2021;13:eabe1376. doi:10.1126/scitranslmed.abe1376.

149. Yan D, Liu B, Wei X, Ou W, Liao M, Ji S et al. Efficacy and safety of nitrous oxide for patients with treatment-resistant depression, a randomized controlled trial. Psychiatry Res. 2022;317:114867. doi:10.1016/j.psychres.2022.114867.

150. Liu J, Zhao X, Wei X, Yan D, Ou W, Liao M et al. mpirical evidence for the neurocognitive effect of nitrous oxide as an adjunctive therapy in patients with treatment resistant depression: a randomized controlled study. Psychiatry Res. 2023;326:115326. doi:10.1016/j.psychres.2023.115326.

151. Shao X, Yan D, Kong W, Sun S, Liao M, Ou W et al. Brain function changes reveal rapid antidepressant effects of nitrous oxide for treatment-resistant depression: evidence from task-state EEG. Psychiatry Res. 32023;22:115072. doi:10.1016/j.psychres.2023.115072.

152. Guimarães MC, Guimarães TM, Hallak JE, Abrão J, Macado-de-Sousa JP. Nitrous oxide as an adjunctive therapy in major depressive disorder: a randomized controlled double-blind pilot trial. Braz J Psychiatry. 2021;43(5):484–93. doi:10.1590/1516-4446-2020-1543.

153. Kim WSH, Dimick MK, Omrin D, Mitchell RHB, Riegert D, Levitt A et al. Proof-of-concept randomized controlled trial of single-session nitrous oxide treatment for refractory bipolar depression: focus on cerebrovascular target engagement. Bipolar Disord. 2023;25(3):221–32. doi:10.1111/bdi.13288.

154. Gillman MA, Lichtigfeld F, Young T. Psychotropic analgesic nitrous oxide for alcoholic withdrawal states. Cochrane Database Syst Rev. 2007;(2): CD005190. doi:10.1002/14651858.CD005190.pub2.

155. Alho H, Methuen T, Paloheimo M, Seppä K, Strid N, Apter-Kaseva N et al. Nitrous oxide has no effect in the treatment of alcohol withdrawal syndrome: a double-blind placebo-controlled randomized trial. J Clin Psychopharmacol. 2003;23(2):211–4. doi:10.1097/00004714-200304000-00019.

156. World Health Organization Model List of Essential Medicines – 23rd List. The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines, 24–28 April 2023. Geneva: World Health Organization; 2023 (https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.01).

157. World Health Organization Model List of Essential Medicines for Children – 9th List. The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines, 24–28 April 2023. Geneva: World Health

Organization; 2023 (https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.01).

158. Nitrous oxide market share, size, trends, industry analysis report. New York (NY): Polaris Market Research; 2023 (https://www.polarismarketresearch.com/industry-analysis/nitrous-oxide-market, accessed 20 August 2023).

159. Adhikari BM, Truong T, Bansai N, Bhandar B. Use of gases in dairy manufacturing: a review. Crit Rev Food Sci Nutr. 2017;58(15):2557–69. doi:10.1080/10408398.2017.1333488.

160. Sikin AM, Walkling Rebeiro M, Rizvi SS. Synergistic processing of skim milk with high pressure nitrous oxide, heat, nisin, and lysozyme to inactivate vegetative and spore-forming bacteria. Food Bioprocessing Technol. 2017;10:2132–45. doi:10.1007/s11947-017-1982-4.

161. De Aguiar Saldanha Pinheiro AC, Urbaniti E, Toppi S, Picone G, Patrignani F, Lanciotti R et al. The impact of gas mixtures of argon and nitrous oxide (N2O) on quality parameters of sardine (*Sardina pilchardus*) fillets during refrigerated storage. Food Res Int. 2019;115:268–75. doi:10.1016/j.foodres.2018.12.030.

162. EU 2012. Commission regulation (EU) No 231/2012 of 9 March 2012 Laying down Specifications for Food Additives Listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. In: Union European (ed.). Brussels (Belgium): Official Journal of the European Union.

163. Lemieux P. Nitrous oxide cooling in hybrid rocket nozzles. Prog Aerospace Sci. 2010;46:106–15. doi:10.1016/j.paerosci.2009.12.001.

164. Crossin R, Crossin, Whelan J, Ball J. Defining and measuring "inhalant" use in population-based surveys. Int J Drug Policy. 2023. doi:10.1016/j.drugpo.2023.103991.

165. The 2007/08 New Zealand Alcohol and Drug Use Survey: online data tables. Wellington: Ministry of Health; 2010 (https://www.health.govt.nz/publication/2007-08-new-zealand-alcohol-and-drug-use-survey-online-data-tables, accessed 13 July 2023).

166. Deaths related to volatile substances where nitrous oxide was mentioned on the death certificate, England and Wales, registered between 2001 and 2021. London: Office for National Statistics; 2022 (https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/15557deathsrelatedtonitrousoxideenglandandwalesregisteredbetween2001and2021/nitrousoxide.xlsx).

167. van Amsterdam J, Nabben T, van den Brink W. Recreational nitrous oxide use: prevalence and risks. Regul Toxicol Pharmacol. 2015;73:790–6. doi:10.1016/j.yrtph.2015.10.017.

168. van Laar M, Cruts AAN, van Miltenburg CJA, Strada L, Ketelaars APM, Croes EA et al. Nationale Drug Monitor Jaarbericht 2019. Utrecht: Trimbos-Instituut; The Hague: Netherlands Institute of Mental Health and Addiction; 2020 (https://www.trimbos.nl/docs/2611d773-620a-45af-a9e5-c27a7e6688e4.pdf, accessed 17 September 2023).

169. van Laar MW, van Beek RJJ, Beenakkers EMT, Cruts AAN, Kuin MC, Meijer RF et al. Nationale Drug Monitor Jaarberich 2021. Utrecht: Trimbos-Instituut; The Hague: Netherlands Institute of Mental Health and Addiction; 2022 (https://www.nationaledrugmonitor.nl/wp-content/uploads/2022/07/Bevriezing-NDM-2021_DEF.pdf, accessed 17 September 2023).

170. Results from the 2014 National Survey on Drug Use and Health: detailed tables. Substance Abuse and Mental Health Services Administration, Rockville (MD): Center for Behavioral Health Statistics and Quality; 2015 (https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.pdf, accessed 23 July 2023).

171. Results from the 2018 National Survey on Drug Use and Health: detailed tables. Rockville (MD): Substance Abuse and Mental Health Services Administration (https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetailedTabs2018.pdf, accessed 17 September 2023).

172. Results from the 2020 National Survey on Drug Use and Health: detailed tables. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2021 (https://www.samhsa.gov/data/, accessed 23 July 2023).

173. Results from the 2021 National Survey on Drug Use and Health: detailed tables. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2022 (https://www.samhsa.gov/data/report/2021-nsduh-detailed-tables, accessed 27 February 2023).

174. Winstock et al. (2022)

175. Benschop A, van Bakkum F, Noijem J. Changing patterns of substance use during the coronavirus pandemic: Self-reported use of tobacco, alcohol, cannabis, and other drugs. Front Psychiatry. 2021;12:633551. doi:10.3389/fpsyt.2021.633551.

176. Rosenberg H, Orkin FK, Springstead J. Abuse of nitrous oxide. Anesth Analg. 1979;58:104–6. PMID:571232.

177. Inquimbert C, Maitre Y, Moulise E, Gremillet V, Tramini P, Valcarcel J et al. Recreational nitrous oxide use and associated factors among health profession students in France. Int J Environ Res Public Health. 2022;19(9):5237. doi:10.3390/ijerph19095237.

178. Perino J, Tournier M, Mathieu C, Letiner L, Peyré A, Perret G, Pereira E et al. Psychoactive substance use among students: a cross-sectional analysis. Fundam Clin Pharmacol. 2022;36(5):908–14. doi:10.1111/fcp.12771.

179. Ehirim EM, Naughton DP, Petroczi A. No laughing matter: presence, consumption trends, drug awareness, and perceptions of "hippy crack" (nitrous oxide) among young adults in England. Front Psychiatry. 2018;8:312. doi:10.3389/fpsyt.2017.00312.

180. van den Toren SJ, van Grieken A, Raat H. Associations of socio-demographic characteristics, well-being, school absenteeism, and substance use with recreational nitrous oxide use among adolescents: a cross-sectional study. PLoS One. 2021;16(2):e0247230. doi:10.1371/journal.pone.0247230.

181. Garland EL, Howard MO, Perron BE. Nitrous oxide inhalation among adolescents: prevalence, correlates, and co-occurrence with volatile solvent inhalation. J Psychoactive Drugs. 2009;41(4):337–47. doi:10.1080/02791072.2009.10399771.

182. Chen YH, Chen MH, Wei HT, Chen LY. Survey of substance use among adolescent drug offenders referred from juvenile courts in Taiwan: clinical epidemiology of single versus multiple illicit substance use. J Formosan Med Assoc. 2022;121:2257–64. doi:10.1016/j.jfma.2022.04.009.

183. Peacock A, Karlsson A, Uporova J, Price O, Chan R, Swanton R et al. Australian drug trends 2020: Key findings from the national Ecstasy and Related Drugs Reporting System (EDRS) interviews. Sydney: National Drug and Alcohol Research Centre, University of New South Wales; 2021 (https://ndarc.med.unsw.edu.au/resource/australian-drug-trends-2020-key-findings-national-ecstasy-and-related-drugs-reporting).

184. Bethmont A, Harper CE, Chan BSH, Dawson AH, McAnulty J. Increasing illicit use of nitrous oxide in presentations to NSW emergency departments. Med J Aust. 2019;211(9):429–429.e1. doi:10.5694/mja2.50377.

185. Marsden P, Sharma AA, Rotella JA. Clinical manifestations and outcomes of chronic nitrous oxide misuse: a systematic review. Emerg Med Australas. 2022;34(4):492–503. doi:10.1111/1742-6723.13997.

186. Chien WH, Huang MC, Chen LY. Psychiatric and other medical manifestations of nitrous oxide abuse: implications from case series. J Clin Psychopharmacol. 2020;40:80–3. doi:10.1097/jcp.0000000000001151.

187. Xu, J., Zhang, Y., Lei, C., Sun, P., Chen, R., & Yuan, T. (2023). Using machine learning to identify factors related to nitrous oxide (laughing gas) relapse among adolescents. General psychiatry, 36(2), e101003. https://doi.org/10.1136/gpsych-2022-101003

188. Drug misuse in England and Wales: year ending June 2022. London: Office for National Statistics; 2022 (https://www.ons.gov.uk/peoplepopulationandcommunity/crimeandjustice/articles/drugmisuseinenglandandwales/latest, accessed 6 July 2023).

189. Darke S, Zahra E, Dufluo J, Peacock A, Farrell M, Lappin J. Characteristics and circumstances of volatile solvent misuse-related death in Australia, 2000–2021. Clin Toxicol. 2023;61(4):260–5. doi:10.1080/15563650.2023.2184243.

190. Byard R, Heath K. How common are suicides using nitrous oxide? Med Sci Law. 2019;59(3):160–3. doi:10.1177/0025802419852184.

3.2.2 Carisoprodol

1. Substance identification

A. International Nonproprietary Name

Carisoprodol

B. Chemical Abstracts Service (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; 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 also known as 2-methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate *(1)*. Furthermore, 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)*. The drug is known by other street names, such as 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).

The name "Soma", used for some carisoprodol products, is not directly linked to the hallucinogenic fungus. When carisoprodol was introduced as a medication, its relaxing and sedative effects were likened to the calming, euphoric properties associated with the ancient soma psychoactive drink.

F. Physical appearance

Carisoprodol is a white or almost white, fine powder *(6)* and 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 critical review of carisoprodol at that time.

2. Chemistry

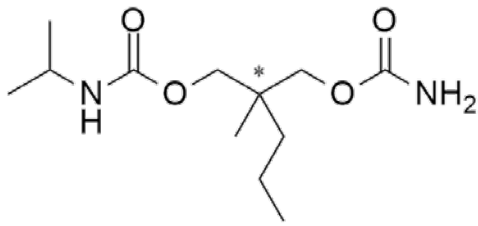
A. Chemical name

IUPAC name: (2RS)-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:

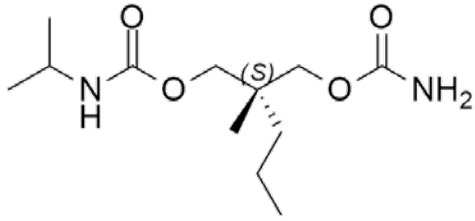


Molecular formula: $C_{12}H_{24}N_2O_4$

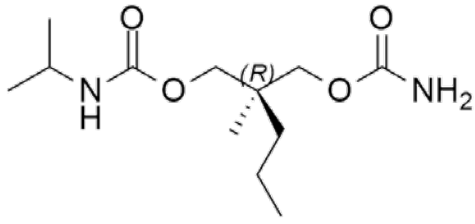
Molecular weight: 260.33 g/mol

C. Stereoisomers

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



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



[(2R)-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 with phosgene. The resulting chloroformate is reacted with isopropylamine to form 2-(hydroxymethyl)-2-methylpentyl N-(1-methylethyl)carbamate). The last step consists of reaction of 5 with either urethane, sodium cyanate or trichloroacetyl isocyanate *(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
92 °C (2 Torr) *(11)*

Boiling-point
160-170 °C *(12)*

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:PBS 1:1 mixture (pH 7.2) at 0.5 mg/mL *(13)*. Carisoprodol has a logP of 2.1 *(14)*.

F. Identification and analysis

Carisoprodol as a pure compound was fully characterized by nuclear magnetic resonance, infra-red spectroscopy and mass spectrometry (MS) *(15)*.

Identification and analysis of carisoprodol as pharmaceutical ingredient is reported in the US Pharmacopoeia *(3)* and in the European Pharmacopoeia *(16)*. The latter reports tests for identification and analysis, including determination of the melting-point (92–95 °C),the comparison of the infra-red spectrum with that of a reference standard, thin-layer chromatography for identification of impurities, a chemical colorimetric assay with cobalt nitrate, and quantitative determination by titration *(16)*.

Several spectroscopic and chromatographic methods have been published for determination of carisoprodol in pharmaceutical formulations *(17–20)*. As carisoprodol does not have an ultraviolet chromophore with significant absorbance, the US Pharmacopeia assay for carisoprodol tablets is based on liquid chromatography 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 gas chromatography coupled to 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 as diagnostic for compound identification *(21)*. Derivatization is, however, difficult and time-consuming, and alternative, sensitive methods have been developed *(22, 23)*.

Currently, methods based on liquid chromatography coupled to either tandem MS or high-resolution MS are the choice for the quantitative determination of carisoprodol in biological fluids *(24–28)*. Qualitative and quantitative determination of carisoprodol and its primary metabolite meprobamate in biological fluids have been achieved by LC-MS *(29, 30)*. 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 *(31)*.

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 *(32)*, which is also a prescription drug and a controlled substance in some countries (e.g. schedule IV of the Controlled Substances Act in the USA) *(33)*. Carisoprodol is metabolized to a lesser extent to hydroxy-carisoprodol *(34)*. Meprobamate and hydroxy-carisoprodol are both metabolized to hydroxy-meprobamate, then partially conjugated *(35)*. To date, no analytical method has been published on the detection of either hydroxy-carisoprodol or hydroxy-meprobamate.

Enzyme-linked immunosorbent assay 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 *(35, 36)*.

3. Ease of conversion into controlled substances

No information was available on whether carisoprodol can be converted into a controlled substance.

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.

B. Pharmacokinetics

Carisoprodol was authorized in 1959 before full characterization of its pharmacokinetics and pharmacodynamics *(37, 38)*. 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. *(39)* quantified the relative bioavailability of carisoprodol and meprobamate. They provided single 250-mg and 350-mg tablets to 24 healthy subjects in a randomized, open-label, crossover study. The dose-adjusted AUC0–∞ values for carisoprodol were 5.29–5.75 μg/mL per h, depending on the dose, and the relative bioavailability was 92%. The mean C_{max} values for carisoprodol were 1.24–1.78 μg/mL, depending on the dose, and the apparent terminal phase half-life ($t_{1/2}$) was 1.74–1.96 hours. Calvo et al. *(37)* conducted a double-blind, placebo-controlled, randomized clinical trial to define the pharmacokinetics of carisoprodol and meprobamate in 13 healthy volunteers in a crossover design. Following a single 350-mg dose, the values for carisoprodol were: C_{max}, 2580 ± 1214 ng/mL, AUC0–∞, 8072 ± 6303 h·ng/mL, and half-life ($t_{1/2}$), 2 ± 0.8 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. 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 *(40)* 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

Carisoprodol undergoes extensive metabolism in the liver, primarily by the liver enzyme CYP2C19, to form its main metabolite, meprobamate. According to Dean et al. *(41)*, 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. *(42)* enrolled 37 healthy White volunteers, of whom 2 were poor metabolizers, 11 intermediate metabolizers and 12 extensive metabolizers; the remaining 12 participants were 6 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 through haemodialysis and peritoneal dialysis. Olsen et al. *(43)* investigated the elimination 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, 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%.

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 *(44, 45)*.

To assess these issues, Kumar et al. *(46)* used whole-cell patch clamp recordings to reveal the capacity of carisolprodol 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 were the most effective in augmenting the GABA response through allosteric modulation. Kumar & Dillon *(47)*, 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. *(48)* 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 modulatory. By analysng 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 the presence of separate binding sites responsible for the distinct effects of carisoprodol in direct gating and allosteric modulation.

In a preclinical investigation, Carbonaro et al. *(49)* investigated the behavioural effects of carisoprodol are direct or whether conversion to meprobamate is required. Rats were conditioned to differentiate the effects of carisoprodol (100 mg/kg) on the temporal pattern and alteration of discriminative effects due to administration of a CYP450 inhibitor (cimetidine) for 4 days. Furthermore, the pharmacokinetics of carisoprodol and meprobamate were evaluated in vivo by microdialysis, with LC-MS-MS of samples of blood and nucleus accumbens. The timeline of the discriminative-stimulus

effects of carisoprodol was closely aligned to its levels in blood and the nucleus accumbans, while those of meprobamate were not, indicating that carisoprodol elicits behavioural effects directly, independently of meprobamate metabolism.

Calvo et al. *(38)* 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 (up to 350 mg/8 h, 14 days). Muscular (electromyogram, muscular strength dynamometry), central (sedation) and tolerability (psychomotor activity test, adverse events) were measured, as were withdrawal symptoms. No explicit indications of direct muscle relaxation were observed; however, certain disparities in sedation were observed during the trial, implying 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

Preclinical data; oral route

Acute toxicity
The LD_{50} was 1.80e+3 mg/kg in mice and 1.32e+3 mg/kg in rats *(50)*.

Subchronic toxicity
At < 100 mg/kg per day in rats, the clinical issues observed were lethargy, diarrhoea, rough hair coat, prostration, urine stain in the vaginal area ataxia and body weight changes *(51)*.

Clinical data
Usually, ingestion of one to three 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 *(52, 53)*. According to TOXBASE® *(54)*, 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 9 g by one person resulted in coma. Agitation, hypertonia and myoclonic encephalopathy can be seen with 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 multiple sedatives to control agitation considered to be due to withdrawal from carisoprodol *(55)*.

A 4-year-old child died after ingesting 3.5 g, and a 2-year-old had severe central nervous system and respiratory depression with hypoxia after ingesting 700 mg *(53)*.

Serotonin syndrome has been reported after ingestion of carisoprodol *(56)*. Because of its limited redistribution, maximum concentrations of carisoprodol appear in cardiac tissue, which, after an may induce direct cardiac toxicity *(57)*. Due to substantial metabolism of carisoprodol 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) *(53)*. An overdose of carisoprodol is not directly reversible with flumazenil, a $GABA_A$ receptor antagonist *(44)*. Nevertheless, meprobamate, like benzodiazepines, acts on the $GABA_A$ receptor *(42)*. Consequently, as the overdose progresses and meprobamate accumulates, flumazenil might counteract the effects *(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.

Several drugs, including carisoprodol

Carisoprodol is aften misused in combination with opiates and opioids *(52)*. Elarabi et al. *(60)* analysed data from a 16-week randomized controlled trial of 141 adult outpatients with opioid use disorder in the United Arab Emirates. Use of several substances, mainly pregabalin, was reported by 117 participants (82.9%). Self-reported independent use of carisoprodol predicted a nonfatal overdose (adjusted odds ratio, 4.52; 95% confidence interval [CI]: 1.81, 11.22). Li et al. (61) compared the risk of overdose associated with concomitant use of opioids and muscle relaxants with that of opioid use alone. This risk appeared to increase for misuse of carisoprodol in combination (1.84; 95% CI: 1.34, 2.54). Concurrent use of hydrocodone, alprazolam and carisoprodol ("Houston cocktail" or "Holy Trinity") 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)*.

Lee et al. *(4)* investigated 80 cases involving drivers who had tested positive for hydrocodone, alprazolam and 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 a pharmaco-epidemiological investigation, Wang et al. *(62)* compared the attributes 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.

The mortality risk associated with carisoprodol may increase when it is taken in combination with other drugs *(63)*. Lee et al. *(64)* investigated fatalities involving drugs reported to the Florida Medical Examiners Commission in the USA between 2001 and 2013. Benzodiazepines, carisoprodol, opioids and zolpidem were more often associated with unintentional fatalities and/or suicide. Khan et al. *(65)* 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 relative to carisoprodol was 1.64 (95% CI: 0.81, 3.34).

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 (3–5%) *(53)*. Cardiovascular (including tachycardia, postural hypotension and facial flushing), gastrointestinal (including nausea, vomiting, hiccup and epigastric distress) and haematological effects may occur. In post-marketing reporting and in 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.

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. 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 the development of tolerance. Withdrawal symptoms were elicited by bemegride and flumazenil. Because of the tolerance and of the withdrawal issues observed, the authors suggested that the potential for addiction to carisoprodol is similar to that of other long-acting benzodiazepine and barbiturate compounds *(66)*.

B. Studies in humans

The active metabolite of carisoprodol, meprobamate, was a frequently misused drug in the 1950s and 1960s, with reported overdoses *(67, 68)*.

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 *(69–72)*, such as anxiety, insomnia, tremors, muscle twitching and, in severe cases, hallucinations and seizures. The withdrawal syndrome can be treated with benzodiazepines *(72)*, a combination of carisoprodol and phenobarbital *(55)* or oral baclofen *(73)*. Like benzodiazepines, potential cravings may persist.

VigiBase is the World Health Organization (WHO) global database of reported adverse events of medicinal products. It is the largest database of its kind in the world, with Individual Case Safety Reports (ICSRs) submitted since 1968, by Members of the WHO Programme for International Drug Monitoring (PIDM) *(74)*. The WHO PIDM is a global network aiming to ensure safety of medicines and vaccines and it consists of more than 177 Members contributing to the database.

VigiLyze, a signal detection and signal management tool with integration of VigiBase data, was used to conduct this assessment. The data search was conducted on 28 June 2023 on ICSRs associated with carisoprodol (as suspected drug) reporting drug abuse and dependence submitted in VigiBase in 2018–2023 *(75)*. The search retrieved 854 reports. The peak of reporting was in 2021. Most patients (about 44%) were aged 18–64 years, and 49% were female; 97% of the reports were from the USA and 2% from Brazil. 99.4% of reports were classified as serious defined with the following criteria: Death, Life threatening, Caused/prolonged hospitalization, Disabling/incapacitating and Other medically important condition. When reports were classified by reported MedDRA terms *(76)*, drug dependence was identified in 386 (45.2%), toxicity to various agents in 317 (37.1%) and overdose in 272 (31.9%). The opioids which were most frequently reported in combination were oxycodone (55.7%) and hydrocodone (41.9%), while alprazolam (26.8%) was the benzodiazepine most frequently identified in combinations. Most co-reported preferred terms included: completed suicide (112 cases; 13.1%), pain (80 cases; 9.4%), drug withdrawal syndrome (69 cases; 8.1%), depression (64 cases; 7.5%) and emotional distress (62 cases; 7.3%).

Tentative and variable nature of the data in VigiBase should be carefully considered due to uncertainty, variability of source, contingent influences, no prevalence data and time to VigiBase. For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account *(77)*.

8. Abuse potential

A. Studies in experimental animals

Gonzalez et al. *(45)* 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, pentobarbital, chlordiazepoxide and meprobamate, Gonzalez et al. *(45)* found that the GABAergic ligands 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 stem to meprobamate. Gatch et al. *(78)* conditioned Sprague-Dawley rats to differentiate propofol (10 mg/kg intraperitoneally) from substances including vehicle, carisoprodol (100 mg/kg), chlordiazepoxide and dizocilpine. The proportion of responses similar to those of propofol was 59% with carisoprodol and 65% with chlordiazepoxide.

B. Studies in humans

Owens et al. *(79)* 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 USA in 2005. Carisoprodol users 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. *(80)* conducted a study involving 15 healthy participants who received carisoprodol at 0, 350 and 700 mg in order to evaluate its subjective and psychomotor effects. 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.

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 *(54)*. 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 *(81)*.

Extent of use for related therapeutic purposes

In England, the prescription cost analysis system for 2000–2005 *(82)* showed that prescriptions for carisoprodol increased over time, from 4100 prescriptions in 2000 to 5000 prescriptions in 2005. In the USA, approximately 4.2 million carisoprodol prescriptions were dispensed in 2017 *(83)*, with a decrease to 3.2 million in 2018. With "rank" referring to the frequency with which a given medication is prescribed in a calendar year, carisoprodol prescriptions in the USA gradually decreased over time, from 175 in 2013 to 343 in 2019 *(84)*. Despite restrictions, carisoprodol is still widely prescribed, with over 3 million prescriptions (a decrease from 10 million in 2008) written in the USA in 2016 *(85)*.

Li et al. *(86)* evaluated the prevalence and duration of treatment with skeletal muscle relaxants in commercially insured adults in the USA, using 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 disorders. 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.

10. Listing on the WHO Model List of Essential Medicines

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

11. Marketing authorizations (as a medicinal product)

Carisoprodol is a prescription medication, which 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 territories, 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, Hong Kong (SAR China), Indonesia, Mexico, Nicaragua, Paraguay, Taiwan (China), Uruguay and the USA *(89)*. In Texas, USA, 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, and 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 *(64)* to be sold without proper medical supervision, increasing potential abuse and adverse consequences. To mitigate the potential for misuse, health-care providers should evaluate patients before prescribing carisoprodol, including their history of substance abuse, addiction or psychological disorders *(94)*. Monitoring of patients given carisoprodol is recommended to identify signs of misuse or escalating doses *(95)*.

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

Alblooshi et al. *(97)* studied 250 patients in the National Rehabilitation Centre of Abu Dhabi. 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. Hardon et al. *(99)* conducted a study in South Sulawesi, Indonesia, with mixed methods including interviews with 142 young people, with focus group discussions and participant observation. The objective was 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 and in the surrounding countryside. Data were collected from 143 community pharmacists between December 2016 and March 2017 with a structured questionnaire. The study showed notable differences between the two areas, with higher instances of drug misuse among adolescents in the countryside than those in Damascus. Carisoprodol and tramadol were the drugs most frequently requested by misusers. These individuals sought the medications without a valid prescription and used various strategies to obtain the drugs: 81% resorted to emotional appeal and 51% attempted to use irregular prescriptions.

In July 2023, "Google trend" research was conducted. The term "carisoprodol" was searched particularly in Latin America (e.g. Guyana, Honduras, Mexico, Nicaragua, Paraguay and the Plurinational State of Bolivia). Most searches with the brand name Soma®, which is popular in the USA, originated from India and the USA, 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 peaked in 2006.

Reddit (a popular social media platform) included discussions on both the effects of carisoprodol at doses > 500 mg and possible alternatives to carisoprodol *(101)*. Most of the threads appeared to be older than 2 years. Some carisoprodol purchase options were also identified.

Qualitative analysis

Three "psychonaut" websites have been analysed *(102 103)*: 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:

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 mentioned as "the ultimate sedation" were 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 of usage 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 USA *(104)* cited the findings of the National Survey on Drug Use and Health, which suggest that about 2 276 000 US residents aged ≥ 12 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 reported non-medical use of Soma® at some time in their life, representing a notable rise from 3.06 million in 2011 *(105, 106)*.

According to the Laboratory Information System, a database managed by the Drug Enforcement Administration in the USA, federal, state and local forensic laboratories identified 3847 items identified as carisoprodol in 2013 and 1735 in 2017, with a preliminary count of 1305 in 2018 *(83)*.

Between 1996 and 2005, the number of emergency department visits due to carisoprodol in the USA increased from 6569 to 19 513, the drug being listed at that time as one of the 25 most dangerous in the country *(85)*. 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, while 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 *(105)*.

Illicit distribution

Carisoprodol is a drug that can be diverted. In March 2011, the street price for Soma® tablets was US$ 1–5 per tablet. In 2017, the American Association of Poison Control Centers reported a total of 2236 cases related to carisoprodol, including 901 single exposures and 2 deaths *(83)*.

Paulozzi et al. *(107)* in 2013 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 USA. 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

In the USA, 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. *(108)* 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. *(109)* 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 a personal injury within the first week of dispensing of a drug. People who had received a prescription for carisoprodol had a standardized incidence ratio (IRR) of 3.7 (95% CI: 2.9, 4.8), which was comparable to the risk associated with diazepam (IRR 2.8; 95% CI: 2.2, 3.6).

15. Licit production, consumption and international trade

Carisoprodol is available as a medication in many countries.

16. Illicit manufacture and traffic and related information

Law enforcement officers reported that young people living in Arizona and California, USA, often obtained carisoprodol at pharmacies in Mexico *(104)*. 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 *(110)*.

A preliminary informal search carried out in July 2023 indicated that it is possible to purchase carisoprodol online without a prescription on various websites, including OutlookIndia *(111)* and Westshore Women's Health *(112)*.

17. Current international controls and their impact

Høiseth et al. *(63)* reported that the rescheduling and withdrawal of carisoprodol from the Norwegian market reduced the prevalence of carisoprodol in 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. *(113)* conducted a prospective, longitudinal, register-based study covering a population of 4.9 million inhabitants between 1 November 2006 and 31 January 2009, before and after withdrawal of carisoprodol from the Norwegian market in 2008. The 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 11% of people who formerly used carisoprodol initiated use of opioids, 6.5% began to use benzodiazepine, and 12.9% initiated use of nonsteroidal anti-inflammatory drugs.

In response to steps being taken by US health-care systems to address the epidemic of opioid overdoses, Losby et al. *(114)* 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 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 USA, Sun et al. *(115)* compared the volume of calls related to carisoprodol abuse or misuse to a state poison control system 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. *(33)* observed a reduction of 20% in carisoprodol dispensing after its scheduling in the USA. The decrease was particularly large among younger people and among patients with injuries. Caulkins et al. *(116)* 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 influence the outcomes significantly.

18. Current and past national controls

In 2007, the European Medicines Agency Committee for Medicinal Products for Human Use suspended all marketing authorizations for carisoprodol throughout Europe *(117)*. Norwegian medical regulatory authorities conducted a review of carisoprodol in March 2007 and took it off the market in that country in May 2008. Carisoprodol was taken off the market in Sweden in November 2007. 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 n September 2013 due to its diversion, dependence and side-effects. Carisoprodol is no longer a licensed product in Australia but can be accessed via the Special Access Scheme *(86)*. Carisoprodol is not on the United Kingdom Home Office list of most commonly encountered 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 *(72)*. Carisoprodol-containing products are not available in Chile *(118)* or Peru.

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

No other matters were identified.

References

1. Carisoprodol. In: Buckingham R, editor. Martindale, the Extra Pharmacopoeia. 30th edition. London: Pharmaceutical Press; 1989.
2. Carisoprodol. USP32-NF27. In: US Pharmacopeia. Rockville (MD): US Pharmacopeial Convention, Inc.; 2009 (https://pubchem.ncbi.nlm.nih.gov/compound/2576).
3. Horsfall JT, Sprague JE. The pharmacology and toxicology of the "Holy Trinity". Basic Clin Pharmacol Toxicol. 2016;120(2):115–9. doi:10.1111/bcpt.12655.
4. Lee JR, Stout P, Egdorf D. Houston cocktail: Driving under influence of hydrocodone, alprazolam, and carisoprodol. Forensic Sci Int. 2021;323:110819. doi:10.1016/j.forsciint.2021.110819.
5. Gupta M. Case report: Carisoprodol abuse in adolescence. Cureus. 2020;12(11):e11525. doi:10.7759/cureus.11525.
6. European Pharmacopoeia, 10th Edition (10.3-10.4-10.5). Strasbourg: European Directorate for the Quality of Medicines and Health Care; 2023 (https://cymitquimica.com/products/41-PUB200333/european-pharmacopoeia-10th-edition-103-104-105-book-english/).
7. USP 43-NF 38. US Pharmacopoeia and National Formulary. Rockville (MD): US Pharmacopeial Convention, Inc.; 2020 (https://www.usp.org/news/usp-extends-standards-implementation-for-uspnf-fcc-pubs).
8. Carisoprodol. In: O'Neil MJ, editor. The Merck Index – An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station (NJ): Merck and Co., Inc.; 2006
9. Powell LS (1963). Method of manufacturing nu-substituted 2, 2-disubstituted-1, 3-propanediol dicarbamate. Patent number US3092656A.

10. Vardanyan RS, Hruby VJ. Synthesis of Essential Drugs. Amsterdam: Elsevier B.V; 2006 (https://www.sciencedirect.com/book/9780444521668/synthesis-of-essential-drugs).

11. Lide DR. Handbook of Chemistry and Physics. 88th edition. Boca Raton (FL): CRC Press; 2007 (https://pubs.acs.org/doi/10.1021/ja077011d).

12. Iwase U. N-Isopropyl-2-methyl-2-propylpropane-1,3-diol dicarbamate. Patent number JP38017665, 1963 (https://patents.google.com/patent/CN101412705A/en).

13. Carisoprodol (item No. 30778). Ann Arbor (MI): Cayman Chemicals Company; 2020 (https://www.caymanchem.com/product/30778/carisoprodol, accessed 28 June 2023).

14. Carisoprodol (HMDB0014539). Human Metabolome Database; 2022 (https://hmdb.ca/metabolites/HMDB0014539, accessed 3 August 2023).

15. Coutts RT. Mass spectra of nine medicinal carbamates. J Pharmaceutical Sci. 1973;62(5):769–73. doi:10.1002/jps.2600620513.

16. Carisoprodol. In: The European Pharmacopoeia, 10th edition. Strasbourg: Council of Europe, European Directorate for the Quality of Medicines; 2020 (https://www.edqm.eu/en/european-pharmacopoeia).

17. Rabinowitz MP, Reisberg,P, Bodin JI. GLC assay of meprobamate and related carbarnates. J Pharmaceutical Sci. 1972;61(12):1974–6. doi:10.1002/jps.2600611219.

18. Allen L. Quantitative determination of carisoprodol, phenacetin, and caffeine in tablets by near-IR spectrometry and their identification by TLC. J Pharmaceutical Sci. 1974;63(6:912–6. doi:10.1002/jps.2600630621.

19. Honigberg I, Stewart JT, Smith MO. Liquid chromatography in pharmaceutical analysis. IX: Determination of muscle relaxant–analgesic mixtures using normal phase chromatography. J Pharmaceutical Sci. 1978;67(5)675–9. doi…10.1002/jps.2600670528.

20. Murali D, Purna Chandra Rao P. Spectrophotometric methods for the quantification of carisoprodol using ferric chloride, o-phenanthroline, and p-nitroaniline, sodium nitrite as analytical reagents. Asian J Pharmaceutical Clin Res. 2019;384–390. doi:10.22159/ajpcr.2019.v12i2.29902.

21. Kim JY, In MK, Paeng K, Chung BC. Simultaneous determination of carisoprodol and meprobamate in human hair using solid-phase extraction and gas chromatography/mass spectrometry of the trimethylsilyl derivatives. Rapid Commun Mass Spectrom. 2005;19(21):3056—62. doi:10.1002/rcm.2173.

22. Kintz P, Mangin P, Lugnier A, Chaumont A. A rapid and sensitive gas chromatographic analysis of meprobamate or carisoprodol in urine and plasma. J Anal Toxicol. 1988;12(2):73–4. doi:10.1093/jat/12.2.73.

23. Matsumoto T, Sano T, Matsuoka T, Aoki M, Maeno Y, Nagao M. Simultaneous determination of carisoprodol and acetaminophen in an attempted suicide by liquid chromatography–mass spectrometry with positive electrospray ionization. J Anal Toxicol. 2003;27(2):118–22. doi:10.1093/jat/27.2.118.

24. Gergov M, Ojanperä I, Vuori E. Simultaneous screening for 238 drugs in blood by liquid chromatography–ionspray tandem mass spectrometry with multiple-reaction monitoring. J Chromatogr B. 2003;795(1):41–53. doi:10.1016/s1570-0232(03)00498-7.

25. Pelander A, Ojanperä I, Laks S, Rasanen I, Vuori E. Toxicological screening with formula-based metabolite identification by liquid chromatography/time-of-flight mass spectrometry. Anal Chem. 2003;75(21):5710–8. doi:10.1021/ac030162o.

26. Herrin G, McCurdy HH, Wall WH. Investigation of an LC-MS-MS (QTRAP(R)) method for the rapid screening and identification of drugs in postmortem toxicology whole blood samples. J Anal Toxicol. 2005;29(7):599–606. doi:10.1093/jat/29.7.599.

27. Mueller C, Weinmann W, Dresen S, Schreiber A, Gergov M. Development of a multi-target screening analysis for 301 drugs using a QTrap liquid chromatography/tandem mass spectrometry system and automated library searching. Rapid Commun Mass Spectrom. 2005;19(10), 1332–8. doi:10.1002/rcm.1934.

28. Hegstad S, Khiabani HZ, Kristoffersen L, Kunøe N, Lobmaier P, Christophersen AS. Drug screening of hair by lquid chromatography-tandem mass spectrometry. J Anal Toxicol. 2008;32(5):364–372. doi:10.1093/jat/32.5.364.

29. Coulter C, Garnier M, Tuyay J, Orbita J, Moore C. Determination of carisoprodol and meprobamate in oral fluid. J Anal Toxicol. 2012;36(3):217–20. doi:10.1093/jat/bks009.

30. Essler S, Bruns KA, Frontz M, McCutcheon JR. A rapid quantitative method of carisoprodol and meprobamate by liquid chromatography–tandem mass spectrometry. J Chromatogr B. 2012;908:155–60. doi:10.1016/j.jchromb.2012.09.001.

31. Logan BK, Stafford DT. Direct analysis of anticonvulsant drugs in vitreous humour by HPLC using a column switching technique. Forensic Sci Int. 1989;41(1–2):125–34. doi:10.1016/0379-0738(89)90244-2.

32. Tse SA, Atayee RS, Best BM, Pesce AJ. Evaluating the relationship between carisoprodol concentrations and meprobamate formation and inter-subject and intra-subject variability in urinary excretion data of pain patients. J Anal Toxicol. 2012;36(4):221–231. doi:10.1093/jat/bks018.

33. Li Y, Delcher C, Brown JD, Wei Y, Reisfield GM, Winterstein AG. Impact of Schedule IV controlled substance classification on carisoprodol utilization in the United States: An interrupted time series analysis. Drug Alcohol Depend. 2019;202:172–7. doi:10.1016/j.drugalcdep.2019.05.025.

34. Tse SA, Atayee RS, Joseph D, Best BM. Factors affecting carisoprodol metabolism in pain patients using urinary excretion data. J Anal Toxicol. 2014;38(3):122–8. doi:10.1093/jat/bku002.

35. Wang G, Huynh K, Barhate R, Rodrigues W, Moore C, Coulter C et al. Validation of a new homogeneous immunoassay for the detection of carisoprodol in urine. J Anal Toxicol. 2011;35(2):108–12. doi:10.1093/anatox/35.2.108.

36. Lu A, Scott KS, Chan-Hosokawa A, Logan BM. Impact of expanding ELISA screening in DUID investigations to include carisoprodol/meprobamate and zolpidem. J Anal Toxicol. 2016;41(2):134–9. doi:10.1093/jat/bkw106.

37. Calvo A, Alonso S, Prieto EL, Ascaso A, Ortuño J, Fernández N, et al. Single and multiple dose PK–PD characterization for carisoprodol. Part I: Pharmacokinetics, metabolites, and 2C19 phenotype influence. Double-blind, placebo-controlled clinical trial in healthy volunteers. J Clin Med. 2022;11(3):858. doi:10.3390/jcm11030858.

38. Calvo A, González-Hidalgo M, Terleira A, Fernández N, Portolés A. Carisoprodol single and multiple dose PK-PD. Part II: Pharmacodynamics evaluation method for central muscle relaxants. Double-blind placebo-controlled clinical trial in healthy volunteers. J Clin Med. 2022;11(4):1141. doi:10.3390/jcm11041141.

39. Simon S, D'Andrea C, Wheeler WJ, Sacks H. Bioavailability of oral carisoprodol 250 and 350 mg and metabolism to meprobamate: a single-dose crossover study. Curr Therapeutic Res. 2010;1(1):50–9. doi:10.1016/j.curtheres.2010.02.003.

40. Lewandowski T. Pharmacokinetic modeling of carisoprodol and meprobamate disposition in adults. Hum Exp Toxicol. 2016;36(8):846–53. doi:10.1177/0960327116672912.

41. Dean L. Carisoprodol therapy and CYP2C19 genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, editors. Medical genetics summaries. Bethesda (MD): National Center for Biotechnology Information; 2017 (https://www.ncbi.nlm.nih.gov/books/NBK425390/).

42. Bramness JG, Skurtveit S, Gulliksen M, Breilid H, Steen VM, Mørland J. The CYP2C19 genotype and the use of oral contraceptives influence the pharmacokinetics of carisoprodol in healthy human subjects. Eur J Clin Pharmacol. 2005;61(7):499–506. doi:10.1007/s00228-005-0970.

43. Olsen H, Koppang E, Alván G, Mørland J. Carisoprodol elimination in humans. Ther Drug Monit. 1994;16(4):337–40. doi:10.1097/00007691-199408000-00001.

44. Gonzalez LA, Gatch MB, Taylor C, Bell-Horner CL, Forster MJ, Dillon GH. Carisoprodol-mediated modulation of GABAA receptors: in vitro and in vivo studies. J Pharmacol Exp Ther. 2009;329(2):827–37. doi:10.1124/jpet.109.151142.

45. Gonzalez LA, Gatch MB, Forster MJ, Dillon GH. Abuse potential of Soma®: the GABA(A) receptor as a target. Mol Cell Pharmacol. 2009;1(4):180–6. PMID:20419052.

46. Kumar M, Gonzalez LA, Dillon GH. Assessment of subunit-dependent direct gating and allosteric modulatory effects of carisoprodol at GABAA receptors. Neuropharmacology. 2015;97:414–25. doi:10.1016/j.neuropharm.2015.04.007.

47. Kumar M, Dillon GH. Assessment of direct gating and allosteric modulatory effects of meprobamate in recombinant GABAA receptors. Eur J Pharmacol. 2016;775:149–158. doi:10.1016/j.ejphar.2016.02.031.

48. Kumar M, Kumar M, Freund JM, Dillon GH. A single amino acid residue at transmembrane domain 4 of the α subunit influences carisoprodol direct gating efficacy at GABAA receptors. J Pharmacol Exp Ther. 2017;362(3):395–404. doi:10.1124/jpet.117.242156.

49. Carbonaro TM, Nguyen V, Forster MJ, Gatch MB, Prokai L. Carisoprodol pharmacokinetics and distribution in the nucleus accumbens correlates with behavioral effects in rats independent from its metabolism to meprobamate. Neuropharmacology. 2020;174:108152 doi:10.1016/j.neuropharm.2020.108152.

50. Carisoprodol. PubChem. 78-44-4. Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine; 2023 (https://chem.nlm.nih.gov/chemidplus/rn/78-44-4, accessed 15 July 2023).

51. Hazard evaluation support system integrated platform. Tokyo: Safety Assessment Division, Chemical Management System, National Institute of Technology and Evaluation; 2023 (https://www.nite.go.jp/en/chem/qsar/hess-e.html, accessed 25 July 2023).

52. Nebhinani N, Aggarwal M, Mattoo SK, Basu D. Carisoprodol: an underrecognized drug of abuse in north India. Gen Hosp Psychiatry. 2013;35(1):89–92. doi:10.1016/j.genhosppsych.2012.07.011.

53. Merative Micromedex. Ann Arbor (MI), 2023 (https://www.merative.com/clinical-decision-support).

54. TOXBASE® (www.toxbase.org, accessed 10 July 2023).

55. Vo KT, Horng H, Smollin CG, Benowitz NL. Severe carisoprodol withdrawal after a 14-year addiction and acute overdose. J Emergency Med. 2017;52(5):680–3 doi:10.1016/j.jemermed.2016.11.015.

56. Bramness JG, Mørland J, Sørlid HK, Rudberg N, Jacobsen D. Carisoprodol intoxications and serotonergic features. Clin Toxicol. 2005;43(1):39–45. doi:10.1081/clt-45020.

57. Eeckhout E, Huyghens L, Loef BG, Maes V, Sennesael J. Meprobamate poisoning, hypotension and the swan-ganz catheter. Intensive Care Med. 1988;14(4):437–8. doi:10.1007/bf00262904.

58. Roberge RJ, Lin E, Krenzelok EP. Flumazenil reversal of carisoprodol (Soma®) intoxication. J Emergency Med. 2000;18(1):61–4. doi:10.1016/s0736-4679(99)00177-8.

59. Chegondi M, Badheka A, Chacham S, Kahana M. Intravenous lipid emulsion rescue therapy in a child with carisoprodol overdose. Cureus. 2019;11(11):e6250. doi:10.7759/cureus.6250.

60. Elarabi HF, Radwan DN, Adem A, Marsden J, Lee A. Polysubstance use in adults with opioid use disorder receiving buprenorphine maintenance. J Addict Med. 2022;17(1):74–8 doi:10.1097/adm.0000000000001039.

61. Li Y, Delcher C, Wei Y, Reisfield GM, Brown JD, Tighe PJ et al. Risk of opioid overdose associated with concomitant use of opioids and skeletal muscle relaxants: a population-based cohort study. Clin Pharmacol Ther. 2020;108(1):81–9. doi:10.1002/cpt.1807.

62. Wang Y, Delcher C, Li Y, Goldberger BA, Reisfield GM. Overlapping prescriptions of opioids, benzodiazepines, and carisoprodol: "Holy Trinity" prescribing in the state of Florida. Drug Alcohol Dependence. 2019;205:107693. doi.:10.1016/j.drugalcdep.2019.107693.

63. Høiseth G, Karinen R, Sørlid HK, Bramness JG. The effect of scheduling and withdrawal of carisoprodol on prevalence of intoxications with the drug. Basic Clin Pharmacol Toxicol. 2009;105(5):345–9. doi:10.1111/j.1742-7843.2009.00459.x.

64. Lee D, Delcher C, Maldonado-Molina MM, Thogmartin JR, Goldberger BA. Manners of death in drug-related fatalities in Florida. J Forensic Sci. 2016;61(3):735–42. doi:10.1111/1556-4029.12999.

65. Khan NF, Bykov K, Barnett ML, Glynn RJ, Vine S, Gagne JJ. Comparative risk of opioid overdose with concomitant use of prescription opioids and skeletal muscle relaxants. Neurology. 2022;99(13):e1432–42. doi:10.1212/wnl.0000000000200904.

66. Gatch MB, Nguyen JD, Carbonaro TM, Forster MJ. Carisoprodol tolerance and precipitated withdrawal. Drug Alcohol Dependence. 2012;123ª1–3):29–34. doi:10.1016/j.drugalcdep.2011.10.010.

67. Kamin I, Shaskan DA. Death due to massive overdose of meprobamate. Am J Psychiatry. 1959:115(12):1123–4. doi:10.1176/ajp.115.12.1123-a.

68. Ferguson MJ, Germanos S, Grace WJ. Meprobamate overdosage. Arch Intern Med. 1960:106(2):237. doi:10.1001/archinte.1960.03820020077011.

69. Reeves RR, Beddingfield JJ, Mack JE. Carisoprodol withdrawal syndrome. Pharmacotherapy. 2004;24(12):1804–6. doi:10.1592/phco.24.17.1804.52333.

70. Eleid MF, Krahn LE, Agrwal N, Goodman BP. Carisoprodol withdrawal after internet purchase. Neurologist. 2010;16(4):262–4. doi:10.1097/nrl.0b013e3181aa917e.

71. Reeves RR, Burke RS, Kose S. Carisoprodol. South Med J. 2012;105(11):619–23. doi:10.1097/smj.0b013e31826f5310.

72. Carisopprodol and meprobamate: risks outweigh benefits. London: Medicines and Healthcare products Regulatory Agency; 2014 (https://www.gov.uk/drug-safety-update/carisoprodol-and-meprobamate-risks-outweigh-benefits).

73. Paul G, Parshotam G, Garg R. Carisoprodol withdrawal syndrome resembling neuroleptic malignant syndrome: diagnostic dilemma. J Anaesthesiol Clin Pharmacol. 2016;32(3):387. doi:10.4103/0970-9185.173346.

74. The WHO Programme for International Drug Monitoring, World Health Organisation, accessed December 2023 (https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/networks/pidm)

75. VigiLyze, 2018–2023 (https://who-umc.org/pv-products/vigilyze/, accessed 10 July 2023).

76. Standardised MedDRA Queries, Medical Dictionary for Regulatory Acitivities, MedDRA, accessed December 2023, (https://www.meddra.org/standardised-meddra-queries)

77. Caveat document, Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of reported potential side effects of medicinal products, World Health Organisation – Uppsala Monitoring Centre (WHO-UMC), accessed December 2023 (https://who-umc.org/media/yzpnzmdv/umc_caveat.pdf)

78. Gatch MB, Forster MJ. Behavioral and toxicological effects of propofol. Behav Pharmacol. 2011;22(7):718–22. doi:10.1097/fbp.0b013e32834aff84.

79. Owens C, Pugmire B, Salness T, Culbertson VL, Force RW, Cady PS et al. Abuse potential of carisoprodol: a retrospective review of Idaho Medicaid pharmacy and medical claims data. Clin Ther. 2007;29(10):2222–5. doi:10.1016/j.clinthera.2007.10.003.

80. Zacny JP, Paice JA, Coalson DW. Characterizing the subjective and psychomotor effects of carisoprodol in healthy volunteers. Pharmacol Biochem Behav. 2011;100(1):138–43. doi:10.1016/j.pbb.2011.08.011.

81. Carisoprodol. DrugBank. Edmonton: Wishart Research Group; 2023 (https://www.drugbank.ca/drugs/DB00395, accessed 7 July 2023).

82. Carisoprodol. Volume 454: debated on Thurdsday 7 December 2006. Hansard, Parliament; 2006 (https://hansard.parliament.uk/Commons/2006-12-07/debates/0612088000010/Carisoprodol, accessed 15 August 2023).

83. Carisoprodol (Trade Name: Soma®). Springfield (VA): Drug Enforcement Administration, Diversion Control Division, Drug & Chemical Evaluation Section; 2019 (https://www.deadiversion.usdoj.gov/drug_chem_info/carisoprodol/carisoprodol.pdf).

84. Carisoprodol. Drug Usage Statistics, United States, 2013–2020. Arlington Heights (VA): ClinCalc LLC; 2020 (https://clincalc.com/DrugStats/Drugs/Carisoprodol, accessed 25 July 2023).

85. Carisoprodol. Inglewood (CA): The Drug Classroom; 2016 (https://thedrugclassroom.com/video/carisoprodol/).

86. Li Y, Delcher C, Reisfield GM, Wei Y, Brown JD, Winterstein AG. Utilization patterns of skeletal muscle relaxants among commercially insured adults in the United States from 2006 to 2018. Pain Med. 2021;22(10):2153–61. doi:10.1093/pm/pnab088.

87. WHO Model List of Essential Medicines, 23rd List. Geneva: World Health Organization; 2023 (https://www.who.int/publications-detail-redirect/WHO-MHP-HPS-EML-2023.02).

88. Olivera ME, Uema SN, Romañuk CB, Caffaratti M, De Carvalho Mastroianni P, Varallo FR et al. Regulatory issues on pharmacovigilance in Latin American countries. Pharmaceuticals Policy Law. 2014;16(3–4):289–312. doi:10.3233/ppl-140390.

89. Carisoprodol (International). Auckland: Drugs.com; 2023 (https://www.drugs.com/international/carisoprodol.html#, accessed 31 August 2023).

90. Carisoprodol. Austin: Texas State Board of Pharmacy; 2023 (https://www.pharmacy.texas.gov/files_pdf/TSBP%20Rules_MASTER%20FILE.pdf, accessed 31 August 2023).

91. Medicines Amendment Regulations 2009. Wellington: New Zealand Legislation; 2009 (https://www.legislation.govt.nz/regulation/public/2009/0212/latest/whole.html; accessed 15 August 2023).

92. The Drug and Health Product Register. Ottawa: Government of Canada; 2023 (https://hpr-rps.hres.ca/pdl.php; accessed 31 August 2023).

93. Carisoprodol. Ottawa: National Association of Pharmacy Regulatory Authorities; 2013 (https://www.napra.ca/nds/carisoprodol/, accessed 15 August 2023).

94. Conermann T, Christian D. Carisoprodol. Treasure Island (FL): StatPearls Publishing; 2022. PMID: 31971718.

95. Preuss CV, Kalava A, King KC. Prescription of controlled substances: benefits and risks. Treasure Island (FL): StatPearls Publishing; 2023. PMID: 30726003.

96. Siddiqui MZ, Piserchio JP, Patel M, Park J, Foster M, Desrosiers CE et al. Examination of multiple drug arrests reported to the Maine Diversion Alert Program. Forensic Sci Med Pathol. 2022;18:133–40. doi:10.1007/s12024-021-00454-1.

97. Alblooshi H, Hulse GK, Kashef AE, Hashmi HA, Shawky M, Ghaferi HA et al. The pattern of substance use disorder in the United Arab Emirates in 2015: results of a National Rehabilitation Centre cohort study. Subst Abuse Treat Prev Policy. 2016;11(1):19. doi:10.1186/s13011-016-0062-5.

98. Hardon A, Ihsan A. Somadril and edgework in South Sulawesi. Int J Drug Policy. 2014;25(4):755–61. doi:10.1016/j.drugpo.2014.05.012.

99. Hardon A, Idrus NI, Hymans TD. Chemical sexualities: the use of pharmaceutical and cosmetic products by youth in South Sulawesi, Indonesia. Reprod Health Matters. 2013;21(41):214–24. doi:10.1016/s0968-8080(13)41709-3.

100. Alaryan T, Hasan TA, Eshelli M, Alzeer S. The misuse of prescribed drugs during the Syrian crisis: a cross-sectional study. Int J Ment Health Addiction. 2019;19(3):714–23. doi.org/10.1007/s11469-019-00180-4.

101. Carisoprodol. San Francisco (CA): Reddit, 2023 (https://www.reddit.com/r/researchchemicals/comments, accessed 15 July 2023).

102. Orsolini L, Papanti GD, Francesconi G, Schifano F. Mind navigators of chemicals' experimenters? A web-based description of e-psychonauts. Cyberpsychol Behav Soc Networking. 2015;18(5):296–300. doi:10.1089/cyber.2014.0486

103. Schifano F, Chiappini S, Corkery J, Scherbaum N, Guirguis A. The e-psychonaut drugs' psychopharmacology. Curr Opinion Pharmacol. 2021;57:165–74 doi:10.1016/j.coph.2021.02.008.

104. Soma. Fast Facts. Johnstown (PA):National Drug Intelligence Center; 2006 (https://www.justice.gov/archive/ndic/pubs10/10913/index.htm; accessed 16 August 2023).

105. Estimating mental illness among adults in the United States: Revisions to 2008 estimation procedures. 2012 National Survey on Drug Use and Health. Rockville (MD): Substance Abuse and Mental Health Services Administration, 2015 (https://www.ncbi.nlm.nih.gov/books/NBK519744/).

106. ED visits involving the muscle relaxant carisoprodol. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2011 (https://www.datafiles.samhsa.gov/study-publication/ed-visits-involving-musclerelaxant-carisoprodol-nid13834).

107. Paulozzi LJ, Strickler GK, Kreiner P, Koris CM. Controlled substance prescribing patterns — prescription behavior surveillance system, eight states, 2013. Morbid Mortal Wkly Rep. 2015;64(SS-9):1–14. doi:10.15585/mmwr.ss6409a1.

108. Rudisill TM, Zhu M, Kelley GA, Pilkerton C, Rudisill BR. Medication use and the risk of motor vehicle collisions among licensed drivers: a systematic review. Accident Anal Prev. 2016;96:255–70. doi:10.1016/j.aap.2016.08.001.

109. Bramness JG, Skurtveit S, Mørland J, Engeland A. The risk of traffic accidents after prescriptions of carisoprodol. Accident Anal Prev. 2007;39(5):1050–5. doi:10.1016/j.aap.2007.02.002.

110. Dipa A. BNN seizes millions of "PCC" in raid on illicit Bandung pill factory. The Jakarta Post, 26 February 2020 (https://www.thejakartapost.com/news/2020/02/26/bnn-seizes-millions-of-pcc-in-raid-on-illicit-bandung-pill-factory.html).

111. Carisoprodol, Soma trial pack, buy carisoprodol 350mg & 500mg online in USA, United Kingdom. OutlookIndia, 9 September 2023. India, 2023 (https://www.outlookindia.com/business-spotlight/carisoprodol-soma-trial-pack-buy-carisoprodol-350mg-500mg-online-in-usa-uk-news-246259, accessed 25 July 2023).

112. Soma online. Westlake (OH): Westshore Women's Health, 2023 (https://www.westshorewomenshealth.com/about-us/soma-online, accessed 25 July 2023).

113. Bramness JG, Furu K, Skurtveit S, Engeland A. Effect of the market withdrawal of carisoprodol on use of other prescribed drugs with abuse potential. Clin Pharmacol Ther. 2012;91(3):438–41. doi:10.1038/clpt.2011.250.

114. Losby JL, Hyatt JD, Kanter MH, Baldwin G, Matsuoka D. Safer and more appropriate opioid prescribing: a large healthcare system's comprehensive approach. J Eval Clinical Pract. 2017;23(6):1173–9. doi:10.1111/jep.12756.

115. Sun C, Hollenbach K, Cantrell FL. Trends in carisoprodol abuse and misuse after regulatory scheduling: a retrospective review of California poison control calls from 2008 to 2015. Clin Toxicol. 2017;56(7):653–5. doi:10.1080/15563650.2017.1414950.

116. Caulkins JP, Goyeneche LA, Guo L, Lenart K, Rath M. Outcomes associated with scheduling or up-scheduling controlled substances. Int J Drug Policy. 2021;91:103110. doi:10.1016/j.drugpo.2021.103110.

117. Overall summary of the scientific evaluation of medicinal products containing carisoprodol. In: Annex II. Scientific conclusions and grounds for suspension of the marketing authorisations presented by the EMEA. Amsterdam: European Medicines Agency; Committee for Medicinal Products for Human Use; 2007 (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/carisoprodol_107/WC500012425.pdf).

118. Registro Sanitario de Productos Farmacéuticos [Health Registry of Pharamaceutical Products]. Santiago: Institute of Public Health, 2023 (https://www.ispch.gob.cl/anamed/medicamentos/registro-sanitario-de-productos-farmaceuticos).

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

Bromazolam

Of the 70 countries that agreed to provide data, 29 reported that they had information on use of bromazolam in their country for medical, scientific, industrial or other professional purposes, for non-medical consumption, for recreational purposes or for any other purpose (Table A1).

Table A1. Numbers of countries that provided information on bromazolam

Region	No. of countries with no information	No. of countries with information
African	9	2
Americas	7	2
South-East Asian	3	1
European	13	19
Eastern Mediterranean	7	0
Western Pacific	2	5
Total	41	29

Approved medical, scientific or industrial use

No country reported approved therapeutic indications for bromazolam, and none reported that bromazolam 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-one countries (14 in the European, four in the Western Pacific, two in the Americas and one in the South-East Asian regions) reported evidence of use of bromazolam for nonmedical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived mainly from data on seizures for law enforcement (n=17), customs (suggesting detection at international border points; (n=10), toxicology reports after deaths (n=3), toxicology reports from emergency departments (n=3), drug checking (n=3) and poisons information calls (n=2). Other sources included reports submitted to or published by treatment providers, doctors and drug treatment centres and reports related to recreational use.

Routes of administration and formulations

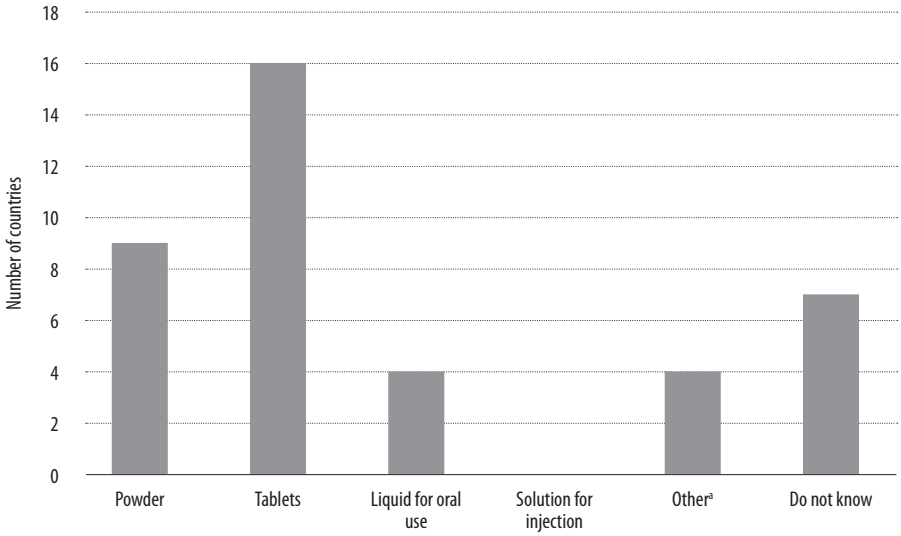
The most common reported route of administration was oral (Table A2).

Table A2. Reported routes of bromazolam administration

Route of administration	No. of countries
Smoking	0
Oral	17
Inhalation	2[a]
Sniffing	1
Injection	2
Other	0
Do not know	3

[a] "Inhalation route if consumed in combination with fentanyl", further described in the "Other" section.

The most common formulation of bromazolam reported was tablets (Fig. A1).



[a] Other formulations included herbs or herbal products, blotting paper, chocolates, "residue", rock-like solid, crystalline substance, liquid, food, capsules.

Fig. A1. Formulations of bromazolam

Perceived negative health impact

Twelve countries (six in the European, two in the Americas, two in the Western Pacific, one in the African and one in the South-East Asia regions) reported that the negative health effect of non-medical consumption of bromazolam was "especially serious" or "substantial" (Fig. A2).

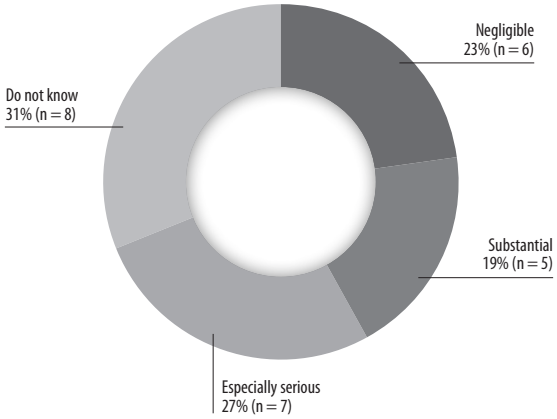


Fig. A2. Negative health impacts of non-medical consumption of bromazolam

Emergency department visits

Seven countries (five in the European, one in the Western Pacific and one in the Americas regions) were aware of emergency department visits related to bromazolam. Five countries described emergency department presentations by people who had consumed bromazolam with other substances. Four reported the year in which the presentations occurred: 20 presentations in 2023 (16 in the Americas and 4 in the European regions), seven presentations in 2022 (four in the European and three in the Americas regions) and one presentation in 2021 (in the European Region).

The adverse effects (e.g. non-fatal intoxications) seen in patients who presented to emergency departments after use of bromazolam included dizziness, confusion, tachycardia, hallucinations, psychosis, depression, vomiting, unconsciousness, respiratory depression, memory loss, seizure, coma, delusional idea of persecution, addiction and psychiatric and psychotic disorders.

Deaths

Five countries (four in the European and one in the Americas regions) reported bromazolam-related deaths between 2021 and 2023. In the four countries that reported the number of bromazolam-related deaths in 2021–2023 the number ranged from 1 to 53. One country in the European Region reported deaths in which bromazolam was the only drug involved and also those in which another substance was involved, three countries (two in the European and one in the Americas regions) reported deaths in which another substance was involved, and one country did not know whether other drugs had been involved.

Drug dependence

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

Current national controls

Twelve countries (nine in the European, two in the Western Pacific and one in the Africa regions) reported that the availability of bromazolam was controlled under substance-specific legislation, and five countries (two in the European, two in the Americas and one in the Western Pacific regions) reported that the availability of bromazolam was controlled under legislation on analogue or generic drugs.

Illicit manufacture and trafficking

Table A3 shows the main reported illicit activities involving bromazolam.

Table A3. Reported activities involving bromazolam for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	9
Smuggling (from other countries)	6
Internet sales (other or location of sellers and website unknown)	6
Internet sales (from abroad to buyers in the respondent's country)	5
Internet sales (seller or website located in respondent's country)	4
Manufacture of the substance by chemical synthesis	1
Direct sales	1
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	11
Other	0

Detection in falsified medicines

Six countries (three European, two Americas, one Western Pacific) indicated that bromazolam was falsely sold as Xanax or alprazolam.

Seizures

Ten countries (six in the European, two in the Western Pacific, one in the Americas and one in the South-East Asia regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 144, and the amounts seized ranged from 8 to 2306 g and 8 to 1518 tablets (Table A4).

Seizures were reported in 2022 by 17 countries (14 in the European, 2 in the Western Pacific and 1 in the South-East Asia regions). The number of seizures per country ranged from 1 to 5168, and the amounts seized ranged from < 1 to 2119 g.

Nine countries (eight in the European and one in the Western Pacific regions) reported seizures in 2021. The number of seizures per country ranged from 1 to 1164, and the amounts seized were 3 to 2733 g.

Table A4. Reported seizures of bromazolam

Year	No. of countries that reported seizures	No. of seizures
2023	10	238
2022	14	5662
2021	9	1328

Laboratory capacity

Twenty-three of the 28 countries that provided information (16 in the European, four in the Western Pacific, two Americas and one in the South-East Asia regions) reported that they had the laboratory capacity to analyse bromazolam.

Flubromazepam

Of the 70 countries that agreed to provide data, 26 had information on use of flubromazepam in their country for medical, scientific, industrial or other professional purposes or for non-medical consumption, recreational or any other purpose (Table A5).

Table A5. Numbers of countries that provided information on flubromazepam

Region	No. of countries with no information	No. of countries with information
African	7	1
Americas	7	2
South-East Asia	3	1
European	12	18
Eastern Mediterranean	5	0
Western Pacific	2	4
Total	36	26

Approved medical, scientific or industrial use

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

Epidemiology of non-medical use

Eighteen countries (12 in the European, three in the Western Pacific, two Americas and one in the South-East Asia regions) reported use of flubromazepam for non-medical purposes (i.e. outside the medical, industrial or scientific context). The evidence was derived from data on seizures by law enforcement (n=11) , seizures from customs (suggesting detection at international border points; n=9), toxicology reports of deaths (n=5), toxicology reports from emergency departments (n=3), poisons information calls (n=2), drug checking (n=2), hospitalization (n=1), presence of dark web cryptomarket listings that deliver to a country (n=1) and published reports of recreational use (n=1).

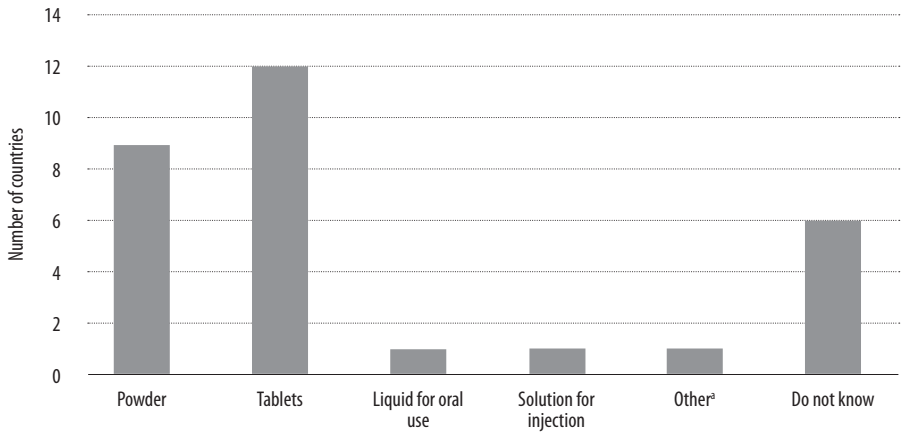
Routes of administration and formulations

The most commonly reported route of administration of flubromazepam was oral (Table A6).

Table A6. Reported routes of flubromazepam administration

Route of administration	No. of countries
Oral	13
Injection	2
Inhalation	1
Sniffing	0
Smoking	0
Do not know	6

The most common reported formulations of flubromazepam were tablets and a powder (Fig. A3).



[a] Other formulation descriptions included "rock-like solid, liquid, crystalline substance, syringe, capsule".

Fig. A3. Formulations of flubromazepam

Perceived negative health impact

Eight countries (six in the European, one in the Western Pacific and one in the South-East Asia regions) reported that the negative health impact of non-medical consumption of flubromazepam was "especially serious" or "substantial" (Fig. A4).

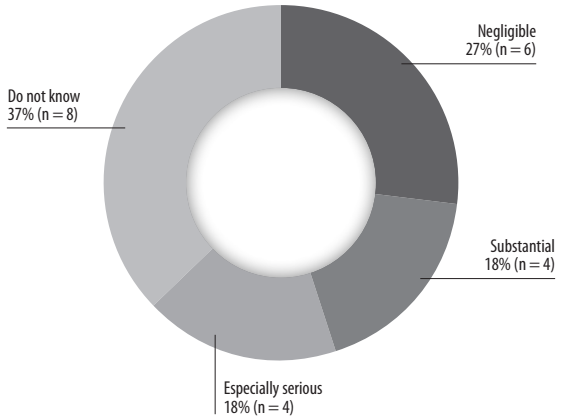


Fig. A4. Negative health impacts of non-medical consumption of flubromazepam

Emergency department visits

Five countries (four in the European and one in the Americas regions) were aware of emergency department visits related to flubromazepam. Three countries described emergency department presentations by people who had consumed flubromazepam with other substances and also reported the year in which the presentations occurred, with one in 2023 (in the Americas Region), one in 2022 (in the European Region) and one in 2021 (in the European Region). One country in the European Region reported 38 flubromazepam-related emergency department presentations in the years before 2021.

Adverse effects (e.g. non-fatal intoxications) in patients who presented to emergency departments after use of flubromazepam were reported by three countries in the European Region. They included hypotension, tachycardia, hallucinations, chest pain, drug dependence, persecution delusion, psychotic and psychiatric disorders, coma with a Glasgow Coma Scale score of 8 to 3, mydriasis, cramp, rhabdomyolysis, impaired renal function, unrousable or difficult to wake, tired and lethargic, somnolent, lethargic, slowed heart rhythm, slurred speech and fluctuating or reduced consciousness.

Deaths

Three countries (two European and one in the Americas regions) reported nine flubromazepam-related deaths in which other substances were also involved between 2021 and 2023. Two countries (one in the European and one in the Americas regions) reported three flubromazepam-related deaths in 2023 in which other substances were also involved. Three countries (two European and one in the Americas regions) reported five flubromazepam-related deaths in 2022 in which other substances were also involved. One country in the Americas Region reported one flubromazepam-related death in 2021 in which other substances were also involved. One country in the European Region reported 24 flubromazepam-related deaths that occurred before 2021, in which flubromazepam was the only substance involved and 23 in which other substances were involved.

Drug dependence

One country in the European Region reported that people presented for treatment for drug dependence due to use of flubromazepam.

Current national controls

Twelve countries (nine in the European and three in the Western Pacific regions) reported that flubromazepam was controlled under substance-specific legislation, and 2 countries (one in the European and one in the Americas regions) reported that the availability of flubromazepam was controlled under analogue or generic legislation.

Illicit manufacture and trafficking-related information

Table A7 lists the main reported illicit activities involving flubromazepam.

Table A7. Reported activities involving flubromazepam for purposes other than medical, scientific or industrial use

Activity	No. of countries
Smuggling (from other countries)	2
Trafficking	4
Internet sales (from abroad to buyers in the respondent's country)	8
Internet sales (other or location of sellers and website unknown)	4
Internet sales (seller or website located in respondent's country)	3
Direct sales	1
Manufacture of the substance by chemical synthesis	0

Table A7. *continued*

Activity	No. of countries
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion	0
Do not know	9

Detection in falsified medicines

Three countries (two European and one in the Americas regions) were aware that flubromazepam had been detected in falsified medicines or other products. These countries indicated that flubromazepam was falsely sold as Xanax, alprazolam and hydromorphone.

Seizures

Seven countries (four in the European, one in the Western Pacific, one in the Americas and one in the South-East Asia regions) reported seizures in 2023. The number of seizures per country in 2023 ranged from 1 to 144, and the amounts seized ranged from 1 to 1074 g (Table A8).

Eleven countries (nine in the European, one in the Americas and one in the Western Pacific regions) reported seizures in 2022. The number of seizures per country in 2022 ranged from 1 to 1798, and the amounts seized ranged from < 1 to 1707 g and from 10 to 415 tablets.

Six countries (five in the European and one in the Americas regions) reported seizures in 2021. The number of seizures per country ranged from 1 to 235, and the amounts seized ranged from 1 to 2733 g.

Table A8. Reported seizures of flubromazepam

Year	No. of countries that reported seizures	No. of seizures
2023	7	160
2022	11	2205
2021	6	384

Laboratory capacity

Twenty of the 24 countries (15 in the European, two Western Pacific, two Americas and one in the South-East Asia regions) reported that they had the laboratory capacity to analyse for flubromazepam.

Butonitazene

Of the 70 countries that agreed to provide data, 15 provided information on butonitazene (Table A9).

Table A9. Numbers of countries that provided information on butonitazene

Region	No. of countries with no information	No. of countries with information
African	7	0
Americas	7	2
South-East Asia	4	0
European	19	11
Eastern Mediterranean	4	0
Western Pacific	4	2
Total	45	15

Approved medical, scientific or industrial use

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

Epidemiology of non-medical use

Six countries (three in the European, two Americas and one in the Western Pacific regions) reported evidence of the use of butonitazene for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived primarily from data on seizures by law enforcement (n=5) and customs (n=2) agencies. Toxicology reports on deaths (n=2) and from emergency departments (n=1), a published report on emergency department presentations (n=1) and lists of dark web cryptomarkets that deliver to the country (n=1) were available.

Routes of administration and formulations

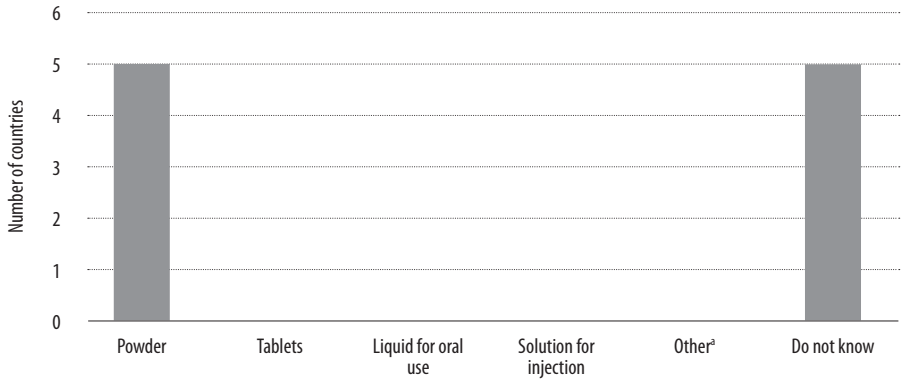
The most common reported route of administration was injection, followed by smoking, oral, sniffing and nasal spray (Table A10).

Table A10. Reported routes of butonitazene administration

Route of administration	No. of countries
Smoking	1
Oral	1
Inhalation	0
Sniffing	1
Injection	2
Other[a]	1
Do not know	7

[a] Nasal spray (n=1)

The most common formulation of butonitazene reported was as a powder (Fig. A5).



[a] Other formulations were not specified.

Fig. A5. Formulations of butonitazene

Perceived negative health impact

Four countries (three in the European and one in the Americas regions) reported that the negative health impact of non-medical consumption of butonitazene was "especially serious" or "substantial" (Fig. A6).

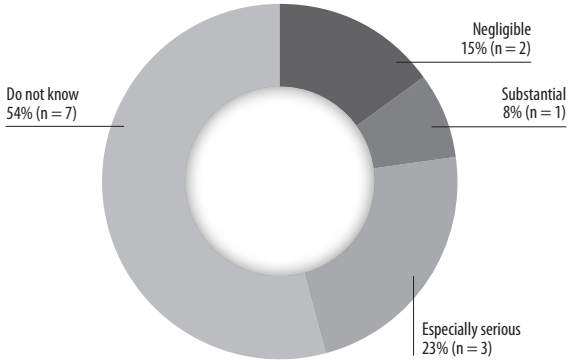


Fig. A6. Negative health impacts of non-medical consumption of butonitazene

Emergency department visits

Two countries (one in the European and one in the Western Pacific regions) were aware of emergency department visits related to butonitazene. The country in the Western Pacific Region cited published reports on use of butonitazene by patients presenting to hospital emergency departments.

Deaths

One country (in the Americas Region) reported one death in 2021 in which butonitazene was identified post mortem; it was not known whether other substances were involved.

Drug dependence

No countries reported presentations for treatment of drug dependence due to use of butonitazene.

Current national controls

Seven countries (six in the European and one in the Americas regions) responded that butonitazene was currently regulated under substance-specific legislation, and seven countries (three in the European, three in the Western Pacific and one in the Americas regions) reported that the availability of butonitazene was controlled under analogue or generic legislation.

Illicit manufacture and trafficking-related information

Table A11 shows the main reported illicit activities involving butonitazene.

Table A11. Reported activities involving butonitazene for purposes other than medical, scientific or industrial use

Activity	No. of countries
Smuggling (from other countries)	1
Trafficking	2
Internet sales (from abroad to buyers in respondent's country)	2
Internet sales (other or location of sellers and website unknown)	1
Internet sales (seller or website located in respondent's country)	0
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	0
Do not know	7
Other	0

Detection in falsified medicines

One country in the Western Pacific Region reported that butonitazene was detected in falsified medicines.

Seizures

Two countries (one in the Americas and one in the European regions) reported seizures in 2023. The amounts seized in 2023 ranged from 0 to 58 g (Table A12). Two countries (one in the Americas and one in the European regions) reported seizures in 2022. The amounts seized ranged from 0 to 944 g (Table A4). Four countries (three in the European and one in the Americas regions) reported seizures in 2021. The number of seizures per country ranged from 1 to 12 and the amounts seized from 0.1 to 8 g. One country (in the Western Pacific region) reported seizures (number and year were not specified).

Table A12. Reported seizures of butonitazene[a]

Year	No. of countries that reported seizures	No. of seizures
2023	2	4
2022	2	49
2021	4	14

[a] Other formulations were not specified.

Laboratory capacity

Thirteen countries (nine in the European, two Americas and two Western Pacific regions) reported that they had the laboratory capacity to analyse butonitazene.

3-CMC

Of the 62 countries that agreed to provide data, 27 had information on 3-CMC (Table A13).

Table A13. Numbers of countries that provided information on 3-CMC

Region	No. of countries with no information	No. of countries with information
African	8	0
Americas	7	2
European	7	22
Eastern Mediterranean	4	0
South-East Asia	4	0
Western Pacific	3	3
Total	33	27

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for 3-CMC, and none reported that 3-CMC was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). None reported use for industrial purposes.

Epidemiology of non-medical use

Nineteen countries (15 in the European, two Americas and one in the Western Pacific regions) reported evidence of the use of 3-CMC for non-medical purposes (outside the medical, industrial or scientific context). The evidence was derived primarily from data on seizures by law enforcement (n = 13) and customs agencies (n = 9), post-mortem reports (n=4), toxicology reports from emergency departments (n= 2) and poison information calls (n = 2). Other sources included drug checking (n = 2), driving under the influence of drugs, declarations to drug monitoring centres and listing of the drug on the dark web. One country in the European Region reported that 3-CMC had been detected as a replacement for 3-MMC.

Routes of administration and formulations

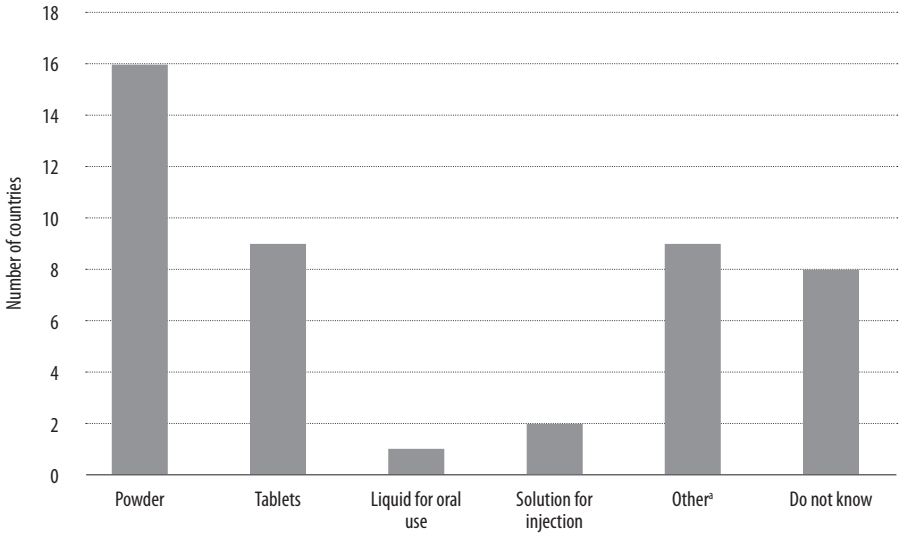
The most common reported route of administration was oral, followed by sniffing and smoking or injection (Table A14).

Table A14. Reported routes of 3-CMC administration

Route of administration	No. of countries
Oral	8
Sniffing	5
Injection	3
Smoking	3
Inhalation	2
Other[a]	1
Do not know	15

[a] Rectal use (with syringe without needle).

The most common known formulations of 3-CMC reported were powders and crystals or a crystalline substance (Fig. A7).



[a] Other formulations referred to most commonly were crystals or crystalline substance (n=8), capsule (n = 1), rocks (n=1) and whitish substance (n = 1).

Fig. A7. Formulations of 3-CMC

Perceived negative health impact

Eight countries in the European Region reported that the negative health impact of non-medical consumption of 3-CMC was "especially serious" or "substantial" (Fig. A8).

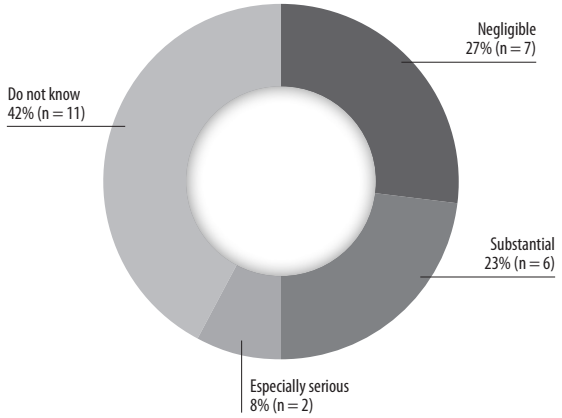


Fig. A8. Negative health impacts of non-medical consumption of 3-CMC

Emergency department visits

Five countries in the European Region were aware of emergency department visits related to 3-CMC. One country described 3-CMC as the only substance involved in five presentations in 2023, 12 presentations in 2022, one presentation in 2021 and two presentations in 2019. Two countries reported presentations for 3-CMC and other substances involved, comprising 12 presentations in 2023, 31 presentations in 2022, four presentations in 2021, one presentation in 2020 and 1 in 2019. One country reported the number of presentations in which it was not known whether 3-CMC was involved: 53 presentations in 2023, 53 presentations in 2022, 16 presentations in 2021 and 37 presentations between 2015 and 2018.

A wide range of adverse effects was described in non-fatal intoxications for which patients presented to an emergency department after use of 3-CMC. They included headache, dizziness, confusion, both hypertension and hypotension, agitation, tachycardia, hallucinations, psychosis, anxiety, vomiting, unconsciousness, nausea and chest pain. Other adverse effects were palpitations, hyperthermia, mydriasis, cramp, restlessness, cold sweats, itching, discomfort in breathing, feeling strange, redness, swelling, numbness in arm, anaphylactic reaction, difficulty in waking up, hyperventilation, slurred speech, elevated transaminases, haematuria, shaking, tired, restless leg syndrome, eye tics, hypokalaemia, burning in the throat, tongue and lips, intoxication, weight loss, dyskinesia, mydriasis and coma. The presentations included intentional poisonings and those in which 3-CMC dependence was involved.

Deaths

One country in the European Region reported three 3-CMC-related deaths in which it was the only substance involved. Two countries reported 2 deaths in which 3-CMC and other substances were involved in 2023. Two countries reported 13 deaths between 2023 and 2021 in which it was not known whether other substances were involved and 2 further deaths for which the year was not specified.

Drug dependence

Two countries in the European Region reported that people presented for treatment of drug dependence associated with use of 3-CMC. One country reported that increased numbers had been reported in their local news media.

Extent and magnitude of public health problems or social harm

One country in the European Region reported public health problems or social harm due to use of 3-CMC, as reported in news media, increased numbers of seizures and calls to poison information centres, cases of driving under the influence of drugs, two deaths, minor drug offences and detection at drug treatment clinics.

One country reported that 3-CMC was used in the context of sexual activity (chemsex, mainly via injection), sometimes with very high consumption over several days and with other stimulating substances. The administration routes reported include nasal, oral and injection and also the rectal route with a pump. Risk was associated with intravenous injection, repeated consumption over short periods and combining use with other stimulants. An increase in the occurrence of serious cases was reported since 2019 in one country in the European Region, where increased presentations related to addiction or dependence were noted.

Current national controls

Sixteen countries (15 in the European and one in the Western Pacific regions) responded that 3-CMC was currently regulated under substance-specific legislation. Seven countries (four in the European, two in the Western Pacific and one in the Americas regions) responded that the availability of 3-CMC was currently regulated under analogue or generic legislation. Four countries (three in the European and one in the Americas regions) responded that 3-CMC was not controlled under any legislation.

Illicit manufacture and trafficking-related information

Table A15 shows the main reported illicit activities involving 3-CMC.

Table A15. Reported activities involving 3-CMC for purposes other than medical, scientific or industrial use

Activity	No. of countries
Smuggling (from other countries)	7
Internet sales (from abroad to buyers in respondent's country)	7
Internet sales (other or location of sellers and website unknown)	7
Trafficking	6
Internet sales (seller or website located in respondent's country)	3
Direct sale	3
Manufacture of the substance by chemical synthesis	1
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion	0
Do not know	9
Other[a]	1

[a] Includes street dealing and dealing via social media

Detection in falsified medicines

No countries reported that 3-CMC had been detected in falsified medicines.

Seizures

Six countries in the European Region reported seizures in 2023 involving 3-CMC. The number of seizures ranged from 3 to 689, and the amounts seized ranged from 2.16 to 150 kg (Table A16).

Fourteen countries (12 in the European and two in the Western Pacific regions) reported seizures in 2022 involving 3-CMC. The number of seizures ranged from 1 to 1017, and the amounts seized ranged from 0.1 g to 192 kg. One country reported that several tonnes of 3-CMC were seized in 2022.

Seven countries (in the European region) reported seizures in 2021 involving 3-CMC. The number of seizures ranged from 1 to 479 and the amounts seized from 28.8 g to 115 kg. One country specified that several tonnes of 3-CMC were seized in 2021.

Table A16. Reported seizures of 3-CMC

Year	No. of countries that reported seizures	No. of seizures
2023	6	1088
2022	14	1362
2021	7	514

Laboratory capacity

Twenty-six countries (22 in the European, two in the the Americas and two in the Western Pacific regions) reported that they had the laboratory capacity to analyse 3-CMC.

Dipentylone

Of the 58 countries that agreed to provide data, 28 had information on dipentylone (Table A17).

Table A17. Numbers of countries that provided information on dipentylone

Region	No. of countries with no information	No. of countries with information
African	5	1
Americas	6	3
South-East Asia	2	1
European	10	19
Eastern Mediterranean	4	0
Western Pacific	2	4
Total	29	28

Approved medical, scientific or industrial use

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

Epidemiology of non-medical use

Nineteen countries (11 in the European, four in the Western Pacific, three in the Americas and one in the South-East Asia regions) reported evidence of use of dipentylone for non-medical purposes (outside the medical, industrial or scientific context). The evidence was derived from data on seizures for law enforcement (n=14), customs (n=7), drug checking or harm reduction services (n=5), post-mortem reports (n=3), toxicology reports from emergency departments (n=1), poisons information calls (n=1), drug treatment centres (n=1) and reports from police or service users (n=1).

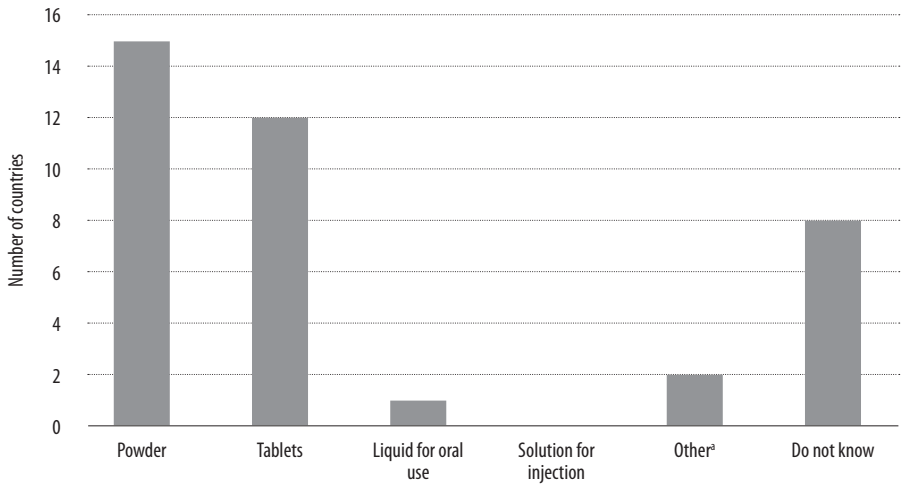
Routes of administration and formulations

The most common reported route of administration was oral, followed by sniffing and smoking (Table A18).

Table A18. Reported routes of dipentylone administration

Route of administration	No. of countries
Oral	9
Sniffing	3
Smoking	2
Inhalation	0
Injection	0
Other	0
Do not know	15

The most common formulations of dipentylone reported were as a powder and as tablets (Fig. A9).



[a] Other formulations referred to were crystals or pieces.

Fig. A9. Formulations of dipentylone

Perceived negative health impact

Five countries (two in the Americas and one each in the European, South-East Asia and Western Pacific regions) reported that the negative health impact of non-medical consumption of dipentylone was "especially serious" or "substantial" (Fig. A10).

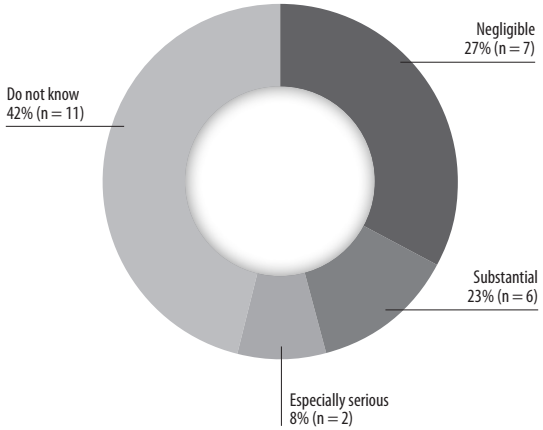


Fig. A10. Negative health impacts of non-medical consumption of dipentylone

Emergency department visits

Two countries in the European Region were aware of emergency department visits related to dipentylone. One country described an emergency visit in 2023 in which other substances were involved. Another country described one emergency visit in which other substances were involved, but the year was not given.

The reported adverse effects (e.g. non-fatal intoxications) in patients who presented to emergency departments after use of dipentylone include agitation, tachycardia and falls.

Deaths

Two countries (one in the Americas and one in the Western Pacific regions) reported a total of 11 deaths involving dipentylone between 2023 and 2022. One country in the Americas region reported one dipentylone-related death in 2023 in which no other substance was involved; 8 deaths in which dipentylone and other substances were involved were reported in 2023. One country in the Western Pacific Region reported 2 deaths involving dipentylone in 2022 in which other substances were involved.

Drug dependence

No country reported that people had presented for treatment of drug dependence in their country due to use of dipentylone.

Extent and magnitude of public health problems or social harm

Five countries (three in the European, one in the South-East Asia and one in the Western Pacific regions) reported on public health problems associated with dipentylone. Four countries (two in the European, one in the South-East Asia and one in the Western Pacific regions) reported that dipentylone had been detected in seizures identified in laboratories or at drug checking sites. One country reported that dipentylone was not a drug of choice and sometimes occurred as an adulterant in other stimulants in 2022.

Current national controls

Nine countries (five in the European, three in the Western Pacific and one in the Americas regions) reported that dipentylone was controlled under analogue or generic legislation. Nine countries (seven in the European, one the Americas and one the South-East Asia regions) reported that dipentylone was controlled under substance-specific legislation. Nine countries (six in the European, two in the Western Pacific and one in the Americas regions) reported that dipentylone was not controlled under any legislation.

Illicit manufacture and trafficking-related information

Table A19 shows the main reported illicit activities involving dipentylone.

Table A19. Reported activities involving dipentylone for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	5
Internet sales (other or location of sellers and website unknown)	6
Internet sales (from abroad to buyers in respondent's country)	3
Smuggling (from other countries)	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	0
Do not know	13
Other	0

Detection in falsified medicines

No country reported that dipentylone had been detected in falsified medicines. One country (in the Americas) reported that dipentylone had been sold as "tusi" and in the form of ecstasy-type tablets.

Seizures

Nine countries (five in the European, two in the Western Pacific, one in the Americas and one in the South-East Asia regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 2591, and the amounts seized ranged from 0.12 g to 33 kg (Table A20). In addition, one country (South-East Asia) reported that 3200 tablets were seized in 2023. Eleven countries (seven in the European, two in the Western Pacific, one in the South-East Asia and one in the Americas regions) reported seizures in 2022. The number of seizures per country ranged from 1 to 5381 and the amounts seized from 2.9 g to 73 kg. In addition, one country (South-East Asia) reported that 393 tablets containing dipentylone were seized in 2022. Two countries (one in the Americas and one in the Western Pacific regions) reported seizures in 2021. The number of seizures ranged from 2 to 396, and the total amount seized was 3347 g.

Table A20. Reported seizures of dipentylone

Year	No. of countries that reported seizures	No. of seizures
2023	8	2687
2022	11	5461
2021	2	398

Laboratory capacity

Twenty-five countries (16 in the European, five in the Western Pacific, three in the Americas one in the South-East Asia regions) reported that they had the laboratory capacity to analyse dipentylone.

2-Fluorodeschloroketamine

Of the 70 countries that agreed to provide data, 28 provided information on 2-fluorodeschloroketamine (Table A21).

Table A21. Numbers of countries that provided information on 2-fluorodeschloroketamine

Region	No. of countries with no information	No. of countries with information
African	6	1
Americas	6	3
South-East Asia	2	1
European	11	18
Eastern Mediterranean	4	0
Western Pacific	1	5
Total	30	28

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for 2-fluorodeschloroketamine, and none reported that 2-fluorodeschloroketamine was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). None reported use for industrial purposes.

Epidemiology of non-medical use

Twenty countries (13 in the European, four in the Western Pacific, two in the Americas and one in the South-East Asian regions) reported evidence of the use of 2-fluorodeschloroketamine for non-medical purposes (outside the medical, industrial or scientific context). The evidence was derived from data on seizures for law enforcement (n=14) and customs (n=10). Toxicology reports from post-mortem examinations (n=8) and from emergency departments (n=3), poisons information calls (n=1), drug checking (n=4), driving under the influence of drugs (n=1), drug monitoring centres (n=1), drug testing programmes (n=1), an online survey of new psychoactive substances (n=1) and lists of dark web cryptomarkets that deliver to the country (n=1).

Routes of administration and formulations

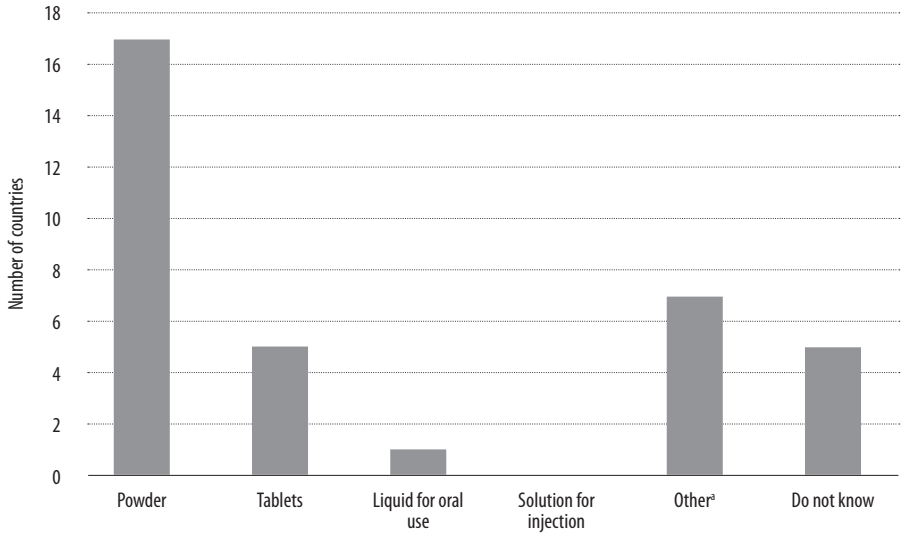
The most common reported route of administration was oral, followed by sniffing and injection (Table A22).

Table A22. Reported routes of 2-fluorodeschloroketamine administration

Route of administration	No. of countries
Smoking	0
Oral	10
Inhalation	0
Sniffing	7
Injection	2
Other[a]	1
Do not know	13

[a] Rectal

The most common known formulations of 2-fluorodeschloroketamine reported were a powder, tablets and a crystalline substance (Fig. A11).



[a] Other formulations most commonly referred to were crystalline substance (n=5), chocolate (n=1) and spray (n=1).

Fig. A11. Formulations of 2-fluorodeschloroketamine

Perceived negative health impact

Eight countries (four in the European, two in the Western Pacific, one in the Americas and one in the South-East Asia regions) reported that the negative health impact of non-medical consumption of 2-fluorodeschloroketamine was "especially serious" or "substantial" (Fig. A12).

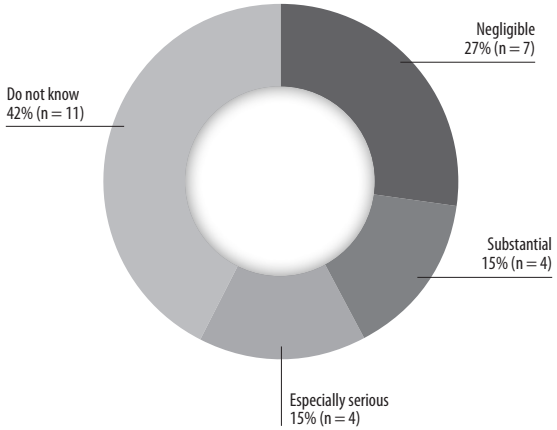


Fig. A12. Negative health impacts of non-medical consumption of 2-fluorodeschloroketamine

Emergency department visits

Four countries (three in the European and one in the Americas regions) were aware of emergency department visits related to 2-fluorodeschloroketamine. One country in the European Region reported the occurrence of dizziness, confusion, agitation, anxiety and memory loss.

Three emergency presentations involved 2-fluorodeschloroketamine alone between 2021 and 2022, and 15 emergency presentations involved people who had consumed 2-fluorodeschloroketamine with other substances between 2021 and 2023. One country in the European Region reported that it was not known whether other substances were involved.

One country in the Americas described effects such as unconsciousness after 2-fluorodeschloroketamine was taken with other substances.

Deaths

At least 6 deaths have been related to 2-fluorodeschloroketamine. Two countries (one in the Americas and one in the European regions) reported three 2-fluorodeschloroketamine-related deaths between 2021 and 2022 in which other substances were involved. One country in the European Region reported deaths in which other substances were involved but did not specify the number of deaths. Three countries in the European Region also reported three deaths related to 2-fluorodeschloroketamine before 2021 in which other substances were involved.

Drug dependence

Two countries (one in the European and one in the Western Pacific regions) reported that people presented for treatment of drug dependence in their country due to use of 2-fluorodeschloroketamine.

Current national controls

Eight countries (six in the European, one in the South-East Asia and one in the Western Pacific regions) responded that the availability of 2-fluorodeschloroketamine was currently regulated under substance-specific legislation, and nine countries (four in the European, four in the Western Pacific and one in the Americas regions) reported that 2 -fluorodeschloroketamine was controlled under analogue or generic legislation.

Illicit manufacture and trafficking-related information

Table A23 shows the main reported illicit activities involving 2-fluorodeschloroketamine.

Table A23. Reported activities involving 2-fluorodeschloroketamine for purposes other than medical, scientific or industrial use

Activity	No. of countries
Smuggling (from other countries)	3
Trafficking	8
Internet sales (from abroad to buyers in respondent's country)	6
Internet sales (other or location of sellers and website unknown)	9
Internet sales (seller or website located in respondent's country)	2
Manufacture of the substance by chemical synthesis	1
Direct sales	2
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion	0
Do not know	8
Other	0

Detection in falsified medicines

Two countries (one in the European and one in the Western Pacific region) reported that 2-fluorodeschloroketamine was detected in falsified medicines. No further information was provided about the detections.

Seizures

Six countries (five in the European and one in the Western Pacific regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 8 and the amounts seized from 2 to 441 g (Table A24). Fourteen countries (11 in the European, two in the Western Pacific and one in the Americas regions) reported seizures in 2022. The number of seizures per country ranged from 1 to 26 and the amounts seized from 0.01 to 1354.55 g. Ten countries (seven in the European, two in the Western Pacific and one in the Americas regions) reported seizures in 2021. The number of seizures per country ranged from 1 to 54 and the amounts seized from 0.08 to 1503 g. One country (in the Western Pacific Region) reported seizures (number of seizures and year not specified). One country (in the European Region) reported 99 seizures pre 2021.

Table A24. Reported seizures of 2-fluorodeschloroketamine[a]

Year	No. of countries that reported seizures	No. of seizures
2023	6	29
2022	14	92
2021	10	126

[a] Data up to August 2023

Laboratory capacity

Twenty-five countries (16 in the European, five in the Western Pacific, three in the Americas and one in the South-East Asia regions) reported that they had the laboratory capacity to analyse 2-fluorodeschloroketamine.

Nitrous oxide

Of the 70 countries that agreed to provide data, 38 provided information on nitrous oxide (Table A25).

Table A25. Numbers of countries that provided information on nitrous oxide

Region	No. of countries with no information	No. of countries with information
African	5	2
Americas	5	4
South-East Asia	2	1
European	5	23
Eastern Mediterranean	1	3
Western Pacific	1	5
Total	18	38

Approved medical, scientific or industrial use

Thirty countries reported approved therapeutic indications for nitrous oxide. Ten countries reported that nitrous oxide was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). Twenty countries reported use for industrial purposes.

Epidemiology of non-medical use

Twenty-six countries (18 in the European, three in the Western Pacific, two in the Americas, one in the African, one in the Eastern Mediterranean and one in the South-East Asian regions) reported evidence of use of nitrous oxide for non-medical purposes (outside the medical, industrial or scientific context). The evidence was derived primarily from data on seizures for law enforcement (n=13) and customs (suggesting detection at international border points; n=3), toxicology reports after deaths (n=1), toxicology reports from emergency departments (n=6) and poisons information calls (n=8). Additional sources of evidence included surveys (n=3), a variety of reports (n=4), drug treatment service data (n=1), media (n=1), drug monitoring centres (n=1), sales data (n=1) and reports of discarded portable cylinders (n=1).

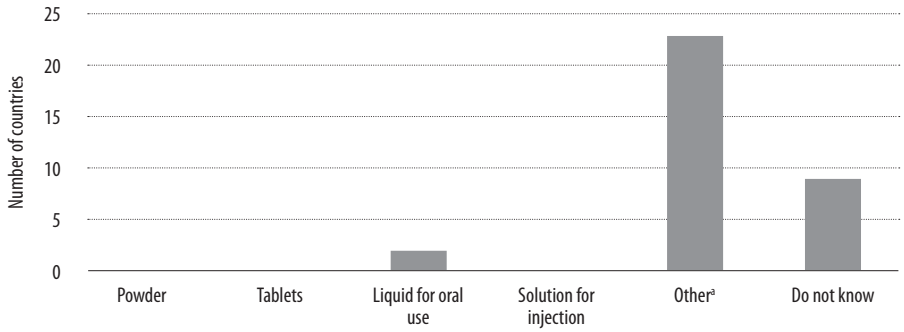
Routes of administration and formulations

The most common reported route of administration was inhalation, followed by sniffing (Table A26).

Table A26. Reported routes of nitrous oxide administration

Route of administration	No. of countries
Smoking	0
Oral	0
Inhalation	26
Sniffing	3
Injection	0
Other	0
Do not know	8

The most common known formulations of nitrous oxide reported were a gas and as part of a liquid or solution for oral administration (Fig. A13).



[a] The other formulation most commonly referred to was gas.

Fig. A13. Formulations of nitrous oxide

Perceived negative health impact

Fifteen countries (10 in the European, two in the Western Pacific, one in the African, one in the Americas and one in the Eastern Mediterranean regions) reported that the negative health impact of non-medical consumption of nitrous oxide was "especially serious" or "substantial" (Fig. A14).

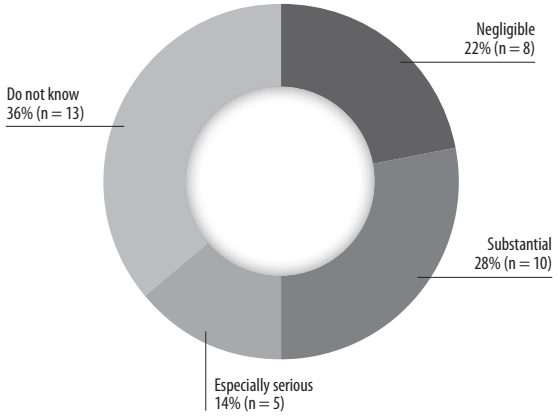


Fig. A14. Negative health impacts of non-medical consumption of nitrous oxide

Emergency department visits

Fourteen countries (eight in the European, three in the Western Pacific, two in the Americas and one in the African regions) were aware of emergency department visits related to nitrous oxide. Four countries (three in the European and one in the Americas) reported emergency presentations by people who had consumed nitrous oxide with other substances.

Six countries (five in the European and one in the Western Pacific regions) reported the occurrence of headache, and seven (five in the European, one in the Americas and one in the Western Pacific regions) described effects such as dizziness and confusion. Unconsciousness was reported by 10 countries (6 in the European, 2 in the Western Pacific, 1 in the African and 1 in the Americas regions). Various cardiovascular effects were reported, including hypertension (one in the Americas and one in the European regions), hypotension (one in the European Region), tachycardia (two in the European and one in the Western Pacific regions), bradycardia (one in the European Region) and chest pain (two in the European and one in the Western Pacific regions). Gastrointestinal effects included nausea (three in the European and one in the Western Pacific regions) and vomiting (two in the European Region). Other effects included agitation (three in the European and one in the Americas regions), hallucinations (four in the European and one in the Western Pacific regions), psychosis (four in the European, one in the Americas and one in the Western Pacific regions), anxiety (three in the European Region), depression (one in the European Region), sweating (one in the European Region) and memory loss (two in the European and one in the Western Pacific regions) in emergency department patients.

Deaths

One country in the European Region reported 9 deaths related only to nitrous oxide between 2021 and 2022. Two countries in the European Region reported three deaths in 2021 and seven deaths in 2022 in which another substance was also involved. One country in the European Region reported one nitrous oxide-related death in which another substance was involved in 2023. Two countries in the European Region also reported three deaths related to nitrous oxide before 2021 in which other substances were involved.

Drug dependence

Six countries (four in the European, one in the Eastern Mediterranean and one in the Western Pacific regions) reported that people presented for treatment of drug dependence due to use of nitrous oxide.

Current national controls

Thirteen countries (eight in the European, four in the Western Pacific and one in the Eastern Mediterranean regions) responded that the availability of nitrous oxide was currently regulated under substance-specific legislation, and five countries (two in the European, one in the Eastern Mediterranean, one in the South-East Asian and one in the African regions) reported that nitrous oxide was controlled under analogue or generic legislation.

Illicit manufacture and trafficking-related information

Table A27 shows the main reported illicit activities involving nitrous oxide.

Table A27. Reported activities involving nitrous oxide for purposes other than medical, scientific or industrial use

Activity	No. of countries
Smuggling (from other countries)	1
Trafficking	7
Internet sales (from abroad to buyers in respondent's country)	6
Internet sales (other or location of sellers and website unknown)	6
Internet sales (seller or website located in respondent's country)	8
Manufacture of the substance by chemical synthesis	0
Direct sales	9
Production of consumer products containing the substance	3
Manufacture of the substance by extraction from other products	0
Diversion	4

Table A27. *continued*

Activity	No. of countries
Do not know	16
Other[a]	1

[a] Includes Internet sales

Detection in falsified medicines

No country reported that nitrous oxide was detected in falsified medicines.

Seizures

Four countries (two in the European, one in the Americas and one in the Western Pacific regions) reported seizures in 2023. The number of seizures per country ranged from 2 to 17. Although the amounts seized were reported in various units, they included large quantities, such as 1900 kg in one country (in the European Region) and 23 315 ampoules and balloons in another (in the European Region) (Table A28). Seven countries (five in the European, one in the Americas and one in the Western Pacific regions) reported seizures in 2022. The number of seizures per country ranged from 1 to 1155. The amounts seized were reported in various units. One country reported seizure of 8640 cylinders, another country reported 7 kg, and a third country reported 11 252 L (in the European Region). Six countries (four in the European, one in the Americas and one in the Western Pacific regions) reported seizures in 2021. The number of seizures ranged from 1 to 1005, and the amounts seized were 300 and 400 capsules and bottles and 9791 L in another country.

Table A28. Reported seizures of nitrous oxide

Year	No. of countries that reported seizures	No. of seizures
2023	4	28
2022	7	1214
2021	6	1141

Laboratory capacity

Twenty-two countries (17 in the European, three in the Western Pacific, one in the South-East Asia and one in the Eastern Mediterranean regions) reported that they had the laboratory capacity to analyse samples for nitrous oxide.

Carisoprodol

Of the 58 countries that agreed to provide data, 22 provided information on carisoprodol (Table A29).

Table A29. Numbers of countries that provided information on carisoprodol

Region	No. of countries with no information	No. of countries with information
African	5	2
Americas	4	4
South-East Asia	1	2
European	21	7
Eastern Mediterranean	3	2
Western Pacific	1	5
Total	35	22

Approved medical, scientific or industrial use

Seven countries (three in the Americas, two in the Eastern Mediterranean, one in the African and one in the Western Pacific regions) reported approved human therapeutic indications for carisoprodol. One country in the Americas reported approved veterinary therapeutic indications for the drug.

Six countries (three in the Americas, two in the Eastern Mediterranean and one in the African regions) reported that carisoprodol is used as an analgesic or muscle relaxant. Two countries (one in the Americas and one in the South-East Asia regions) reported that carisoprodol had been used as a registered medicine but that it was no longer approved.

Epidemiology of non-medical use

Eight countries (two in the Americas, two in the European, two in the Eastern Mediterranean, one in the South-East Asia and one in the Western Pacific regions) reported use of carisoprodol for non-medical purposes (outside the medical, industrial or scientific context). The evidence was derived primarily from data on seizures by law enforcement (n=6) and customs authorities (n=3), post-mortem reports (n=3), emergency departments (n=2), poisons information calls (n=2), clinical and medical data (n=2) and dark web cryptomarkets for sale (n=1).

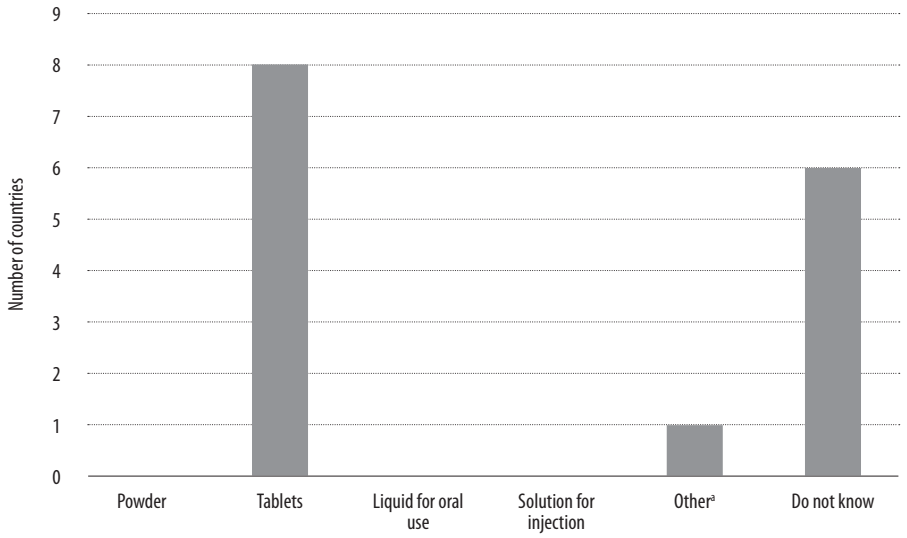
Routes of administration and formulations

The most common reported route of administration was oral (Table A30).

Table A30. Reported routes of carisoprodol administration

Route of administration	No. of countries
Oral	9
Smoking	0
Inhalation	0
Sniffing	0
Injection	0
Other	0
Do not know	5

The most common known formulation of carisoprodol reported was a tablet (Fig. A15).



[a] Another formulation referred to was a "whitish substance".

Fig. A15. Formulations of carisoprodol

Perceived negative health impact

Five countries (one in the African, one in the European, one in the Eastern Mediterranean, one in the South-East Asia and one in the Western Pacific regions) reported that the negative health impact of non-medical consumption of carisoprodol was "especially serious" or "substantial" (Fig. A16).

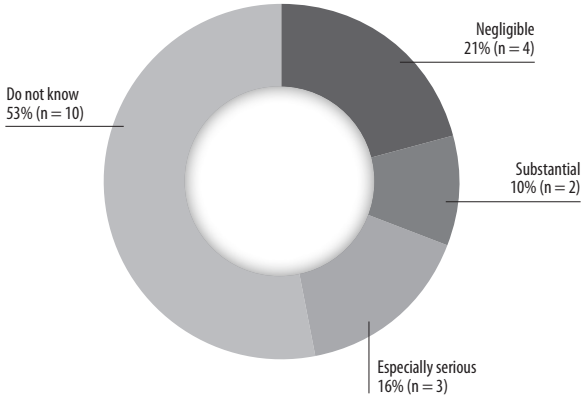


Fig. A16. Negative health impacts of non-medical consumption of carisoprodol

Emergency department visits

Three countries (one in the Americas, one in the European and one in the South-East Asia regions) were aware of emergency department visits related to carisoprodol. One country in the South-East Asia Region reported 14 emergency presentations in 2022 in which carisoprodol was the only substance involved. The country also reported five emergency presentations in 2023 in which carisoprodol and other substances were detected.

One country in the European Region reported 1 emergency presentation in 2023, 6 emergency presentations in 2022 and 2 emergency presentations in 2021 involving carisoprodol. It was not known whether other substances were involved.

One country in the Americas reported a single emergency presentation but did not specify the year.

The adverse effects (such as non-fatal intoxications) of patients who presented to emergency departments after use of carisoprodol included headache, dizziness, confusion, hypotension, tachycardia, unconsciousness, nausea, seizures, limb paralysis, clonic movements, stupor, coma and respiratory depression.

Deaths

One country in the European Region reported two carisoprodol-related deaths in which other substances were involved in 2023. Two other countries (in the African and South-East Asia regions) noted that deaths had been reported but did not specify the numbers. One of the deaths occurred in 2017; the date of the other death was not specified.

Drug dependence

Three countries (one in the Americas, one in the South-East Asia and one in the Eastern Mediterranean regions) reported that people presented for treatment of drug dependence in their country due to use of carisoprodol. One country in the South-East Asia Region reported that specific treatment for carisoprodol was required after an assessment, which included a community intervention and outpatient and inpatient care.

Extent and magnitude of public health problems or social harm

Three countries reported public health problems linked to carisoprodol use. One country in the European Region reported two deaths linked to carisoprodol use. One country in the South-East Asia Region reported that carisoprodol was misused, usually for analgesia or relaxation. One country in the Eastern Mediterranean Region reported addiction to carisoprodol.

Current national controls

Fourteen countries (5 in the Western Pacific, four in the European, two in the South-East Asia, two in the Eastern Mediterranean and one in the Americas regions) reported that carisoprodol was currently controlled under substance-specific legislation. One country in the African Region responded that carisoprodol was currently controlled under analogue or generic legislation. Five countries (three in the European and two in the Americas regions) reported that carisoprodol was not controlled under any legislation.

Illicit manufacture and trafficking-related information

Table A31 shows the main reported illicit activities involving carisoprodol.

Table A31. Reported activities involving carisoprodol for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	4
Smuggling (from other countries)	3
Internet sales (other or location of sellers and website unknown)	3
Internet sales (from abroad to buyers in respondent's country)	1
Diversion	1
Internet sales (seller or website located in respondent's country)	0
Manufacture of the substance by chemical synthesis	0
Production of consumer products containing the substance	0

Table A31. *continued*

Activity	No. of countries
Manufacture of the substance by extraction from other products	0
Direct sales	1
Do not know	9
Other	0

Detection in falsified medicines

Three countries (two in the Western Pacific and one in the Americas regions) reported that carisoprodol had been detected in falsified medicines. One country in the Western Pacific Region reported that illegal tablets that were seized were labelled "carisoprodol tablets", and carisoprodol was also detected in unlabelled tablets and cough syrups. The country in the Americas Region reported that carisoprodol had been falsely sold as alprazolam tablets.

Seizures

Four countries (one in the Americas, one in the South-East Asia, one in the European and one in the Western Pacific regions) reported seizures in 2023. The number of seizures per country ranged from 1 to 92, and the amounts seized were 1.9 kg, 5000 units, 8015 tablets and 12 617 tablets (Table A32). Five countries (two in the Western Pacific, one in the Eastern Mediterranean, one in the Americas and one in the European regions) reported seizures in 2022. The number of seizures per country ranged from 1 to 404, and the amounts seized ranged from 20 to 28 323 tablets, with one total seizure of 58 kg. Four countries (two in the Western Pacific, one in the Americas and one in the European regions) reported seizures in 2021. The number of seizures per country ranged from 1 to 608 and the amounts seized from 3.5 to 46 kg and 1333 to 9176 tablets.

Table A32. Reported seizures of carisoprodol

Year	No. of countries that reported seizures	No. of seizures
2023	4	95
2022	5	405
2021	4	610

Laboratory capacity

Fifteen countries (six in the European, three in the Americas, three in the Western Pacific, two in the South-East Asia and one in the Eastern Mediterranean regions) reported that they had the laboratory capacity to analyse carisoprodol.

Annex 2. List of participants

Expert Committee members

Patrick M. Beardsley, Department of Pharmacology and Toxicology and Centre for Biomarker Research and Personalized Medicine, Virginia Commonwealth University (VA), USA

Wim Best, Freudenthal Instituut, Utrecht University, Netherlands (Kingdom of the)

Sandra Comer, Department of Psychiatry, Columbia University (NY), USA

Ifeoma Toyin Ekwere, Department of Anaesthesiology, University of Benin, Nigeria

Simon Elliott, Elliott Forensic Consulting, England, United Kingdom

Raka Jain, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, India

Pamela Kaduri, Department of Psychiatry, University of Toronto and adjunct faculty, Muhimbili University of Health and Allied Sciences, United Republic of Tanzania (Rapporteur)

Junichi Kitanaka, Laboratory of Drug Addiction and Experimental Therapeutics, Hyogo College of Medicine, Japan

Antonio Pascale Prieto, Department of Toxicology, Faculty of Medicine, University of Montevideo Uruguay

Afarin Rahimi-Movaghar, Iranian National Centre for Addiction Studies, Tehran University of Medical Sciences, Islamic Republic of Iran (Co-Chair)

Sutisa Nudmamud-Thanoi, Centre of Excellence in Medical Biotechnology, Naresuan University, Thailand

Jason White, School of Pharmacy and Medical Sciences, Division of Health Sciences, University of South Australia, Australia (Chair)

Observers

Ha Fung Ng, secretariat, International Narcotics Control Board, Vienna, Austria

Jagjig Pavadia, Member, International Narcotics Control Board, Vienna, Austria

Conor Crean, Laboratory and Scientific Division, United Nations Office of Drugs and Crime, Vienna, Austria

WHO secretariat (WHO headquarters, Geneva, Switzerland)

Giuseppe Cannazza (Temporary Adviser), University of Modena and Reggio Emilia, Modena, Italy

David Gorelick (Temporary Adviser), University of Maryland School of Medicine, Baltimore, United States of America

Gilles Forte (secretary), Access to Medicines and Health Products, Geneva, Switzerland

Benedikt Huttner, Health Product Policy and Standards, Geneva, Switzerland

Thomas Le Ruez, Consultant, Expert Committee on Drug Dependence, Newcastle, United Kingdom

Eduard Markov, Compliance and Risk Management and Ethics, Geneva, Switzerland

Yukiko Nakatani, Access to Medicines and Health Products, Geneva, Switzerland

Claudia Nannini, International, Constitutional, and Global Health Law, Geneva, Switzerland

Suzanne Nielsen (Temporary Adviser), Monash University, Victoria, Australia

Dilkushi Poovendran, Health Product Policy and Standards, Geneva, Switzerland

Fumihito Takanashi, Regulation and Prequalification, Geneva, Switzerland

Vladimir Poznyak, Alcohol, Drugs & Addictive Behaviours, Geneva, Switzerland

Annette Verster, Testing, Prevention and Populations, Geneva, Switzerland

The Forty-sixth Meeting of the World Health Organisation (WHO)'s Expert Committee on Drug Dependence (ECDD) was convened from 16 to 19 October 2023 and was coordinated from the WHO headquarters in Geneva.

The Forty-sixth WHO ECDD critically reviewed six new psychoactive substances: including two benzodiazepines (bromazolam, flubromazepam), one novel synthetic opioid (butonitazene), two cathinones/stimulants (3-CMC, dipentylone) and one dissociative-type substance (2-fluorodeschloroketamine). 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.

In addition, the Forty-sixth ECDD carried out a pre-review of nitrous oxide and carisoprodol to consider whether current information justified a critical review.

This report summarizes the findings of the forty-sixth ECDD meeting.

9789240092464