

WHO Expert Committee on Drug Dependence

Forty-third report



World Health
Organization

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Abbreviations and acronyms

5F-ADB	methyl 2-({[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl} amino)-3-methylbutanoate; 5F-MBMB-PINACA
5F-AMB-PINACA	methyl 2-({[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl} amino)-3-methylbutanoate
cAMP	cyclic adenosine monophosphate
CAS	Chemical Abstracts Services
CB1	cannabinoid
CND	Commission on Narcotic Drugs
CYP	cytochrome P450
DAMGO	[D-Ala ² , N-mePhe ⁴ , Gly-ol]-enkephalin
DAT	dopamine receptor transporter
DEA	Drug Enforcement Administration (USA)
DOM	(-)-2,5-dimethoxy-4-methylamphetamine
EC ₅₀	half maximal effective concentration
ECDD	Expert Committee on Drug Dependence
ED ₅₀	median effective dose
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
ESI	electrospray ionization
EWA	Early Warning Advisory
fEPSP	field excitatory postsynaptic potential
3-FPM	3-fluorophenmetrazine
GABA	γ-aminobutyric acid
GC	gas chromatography

GC-MS	gas chromatography–mass spectrometry
GCS	Glasgow coma scale
hCB1	human cannabinoid type 1
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
5-HT	5-hydroxytryptamine
IC50	half maximal inhibitory concentration
INCB	International Narcotics Control Board
IUPAC	International Union of Pure and Applied Chemistry
K _i	inhibitory constant
LC-HRMS	liquid chromatography–high-resolution mass spectrometry
LSD	lysergic acid diethylamide
MDMA	±-3,4-methylenedioxyamphetamine
MDMB	methyl 2,3-dimethyl butanoate
MDMB-4en- PINACA	methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate
MDPV	methylenedioxypropylvalerone
MeO	methoxy
5-MeO-DALT	5-methoxy- <i>N,N</i> -diallyltryptamine
3-MeO-PCP	3-methoxyphencyclidine
MOR	μ-opioid receptor
MS	mass spectrometry
MS-MS	tandem mass spectrometry
MXP	methoxydiphenidene

NET	norepinephrine receptor transporter
NMDA	<i>N</i> -methyl-D-aspartate
NMR	nuclear magnetic resonance
NPS	new psychoactive substance
PCP	phencyclidine
PPI	prepulse inhibition
QSAR	quantitative structure–activity relationship
SERT	serotonin receptor transporter
STRIDA	<i>Samverkansprojekt kring toxicitetsutredning och riskbedömning av Internetdroger baserat på laboratorieanalyser</i>
THC	Δ^9 -tetrahydrocannabinol
TOF	time of flight
U-47700	3,4-dichloro- <i>N</i> -[(1 <i>R</i> ,2 <i>R</i>)-2-(dimethylamino) cyclohexyl]- <i>N</i> -methylbenzamide
UHPLC	ultra-high-performance liquid chromatography
UNODC	United Nations Office on Drugs and Crime
UPLC	ultra-performance liquid chromatography
WEDINOS	Welsh Emerging Drugs and Identification of Novel Substances

Introduction

The forty-third meeting of the WHO Expert Committee on Drug Dependence (ECDD) was convened virtually on 12–16 October 2020, coordinated from WHO headquarters in Geneva, Switzerland.

Information session

On 12 October 2020, before the Expert Committee convened, an information session was held so that the Expert Committee could hear presentations and question representatives of interested parties about data that had been provided on the substances under review.

The session was opened by Dr Mariângela Simão, Assistant Director-General, and chaired by Dr Gilles Forte, Coordinator of the Access to Medicines, Vaccines and Pharmaceuticals Division, WHO.

Dr Simão noted that the open session was an opportunity to share views and experiences on the benefits and risks of the substances under review. She described WHO's major challenges in tackling the world drug problem, while preventing and managing the harm of drug use and ensuring access to controlled medicines for those who need them. She described key areas of WHO work in this area, including the ECDD's review of several new psychoactive substances (NPS) and the recommendations made to the Commission on Narcotic Drugs (CND) that they be placed under international control.

Dr Simão discussed WHO's concern about inadequate access to opioid analgesics for pain relief and palliative care, particularly in low-income countries. She welcomed the support of Member States, civil society groups, the private sector and other non-State actors for ECDD evidence-based decision-making and highlighted close collaboration and dialogue with the United Nations Office on Drugs and Crime (UNODC) and the International Narcotics Control Board (INCB).

Dr Dilkushi Poovendran, Access to Medicines, Vaccines and Pharmaceuticals cluster, 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 CND 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 CND.

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.

43rd Expert Committee on Drug Dependence

Welcoming remarks

Dr Simão welcomed all participants on behalf of the WHO Director-General and thanked the ECDD members for the time and effort they had dedicated to 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.

Statement of confidentiality

Dr Claudia Nannini 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 (3) and the guidance on WHO review of psychoactive substances for international control (4). In accordance with that document, the functions of the ECDD are 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. Dr Nannini also reminded participants of the confidentiality of the ECDD's deliberations.

Declarations of interest

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.

The Secretariat of the 43rd meeting of the ECDD considered that the disclosed interests were not in conflict with any of the issues to be discussed at the meeting or with the recommendations to be issued by the Expert Committee. No other interests declared by members of the Expert Committee or temporary advisers were deemed relevant to the work of the group.

Election of chairperson, co-chairperson and rapporteur

The members of the Expert Committee elected Professor Jason White as Chair, Dr Afarin Rahimi-Movaghar as Co-chair and Dr Pamela Kaduri as Rapporteur. The Chair welcomed all participants, and the agenda proposed by the Secretariat was approved.

1. Updates on ECDD meeting recommendations and outcomes

1.1 Recommendations from the 41st ECDD on cannabis and cannabis-related substances

Dr Forte reported on the discussions that were held at the CND in Vienna on WHO recommendations on cannabis and cannabis-related substances made by the ECDD at its 41st meeting.

WHO communicated the recommendations of the 41st ECDD meeting on cannabis and cannabis-related substances to the CND in January 2019 for further dissemination to Member States. At its 62nd regular session in March 2019, the CND decided to postpone voting on the WHO recommendations in order to provide Member States with more time to consider the recommendations (Decision 62/14).

During the fourth and fifth intersessional meetings of the Commission at its 62nd session, which were held on 24 June and 23 September 2019, the Commission considered the WHO recommendations on cannabis and cannabis-related substances and had the opportunity to address questions to representatives of WHO, specifically on scientific and medical matters.

Furthermore, at its 63rd regular session, in March 2020, the Commission decided to continue consideration of the recommendations of WHO on cannabis and cannabis-related substances in order to clarify the implications and consequences of and the reasoning for the recommendations and decided to vote at its reconvened 63rd session, in December 2020 (Decision 63/14). A series of consultations was held in June, August and October for exchanges of views among Member States on the economic, social, legal, administrative and other implications of the recommendations and ways of addressing them if any of the recommendations was adopted.

At the time of the 43rd ECDD meeting, discussions were ongoing at the CND to define and agree on a voting procedure applicable to the scheduling vote at the 63rd CND reconvened session.

1.2 Recommendations from the 42nd ECDD

The 63rd CND voted in March 2020 to endorse the following recommendations made by the 42nd ECDD:

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

- Crotonylfentanyl
- Valeryl fentanyl

To be added to Schedule I of the 1971 Convention on Psychotropic Substances:

- 2,5-Dimethoxy-4-chloroamphetamine (DOC)

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

- *N*-[(1*S*)-1-(Aminocarbonyl)-2-methylpropyl]-1-[(4-fluorophenyl)methyl]-1*H*-indazole-3-carboxamide (AB-FUBINACA)
- Methyl 2-([1-(5-fluoropentyl)-1*H*-indazol-3-yl]carbonyl)amino)-3-methylbutanoate (5F-AMB-PINACA)
- Methyl 2-([1-(5-fluoropentyl)-1*H*-indole-3-carbonyl]amino)-3,3-dimethylbutanoate (5F-MDMB-PICA)
- Methyl 2-([1-(4-fluorobutyl)-1*H*-indazole-3-carbonyl]amino)-3,3-dimethylbutanoate (4F-MDMB-BINACA)
- 4-Chloromethcathinone (4-CMC)
- *N*-Ethylhexedrone
- α -Pyrrolidinohexiophenone (alpha-PHP)

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

- 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (Flualprazolam)
- 4-(2-Chlorophenyl)-2-ethyl-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine (Etizolam)

In addition, the 42nd ECDD made the following recommendations to WHO:

To be kept under surveillance:

- *N*-(1-Adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide (APINACA)

To proceed to a critical review at a future meeting:

- Preparations of acetyldihydrocodeine, codeine, dihydrocodeine ethylmorphine, nicocodine, nicodicodine, norcedeine and pholcodine listed in Schedule III of the 1961 Single Convention on Narcotic Drugs

1.3 Recommendations from the 8th Working Group

The 8th Working Group, convened in April 2020, recommended that the following substances be placed under WHO Surveillance:

- Kratom
- Mitragynine
- 7-OH-Mitragynine
- *para*-Fluoro furanyl fentanyl
- 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one (alpha-PiHP)
- 1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one (Eutylone)
- 2-Methyl-1-butyl-4-cinnamylpiperazine (2-methyl-AP-237)

2. Review of 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 reviews psychoactive substances in two steps. The first step is a pre-review, which is a preliminary review by the Expert Committee to determine whether a fully documented critical review of the substance is required. 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 representatives of other organizations 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 more thorough review at a future meeting of the Committee. After consideration of a pre-review, however, the Committee may decide to conduct a critical review at the same meeting.

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 CND 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.

Hallucinogen

5-Methoxy-*N,N*-diallyltryptamine (5-MeO-DALT)

Recommended to be kept under surveillance

Substance identification

5-Methoxy-*N,N*-diallyltryptamine (abbreviation: 5-MeO-DALT; chemical name: *N*-allyl-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)prop-2-en-1-amine) is a synthetic hallucinogen. It is a solid, crystalline powder described as white, off-white, grey, light brown or tan. It has also been found as yellow, purple or green tablets.

WHO review history

5-MeO-DALT 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

5-MeO-DALT has a chemical structure similar to that of the hallucinogen 3-[2-(dimethylamino)ethyl]indole (DMT), which is listed under Schedule I of the Convention on Psychotropic Substances of 1971. 5-MeO-DALT binds to various receptors, with no clear mechanism of action; the receptors include serotonergic, adrenergic, histamine, kappa opioid receptors and sigma receptors, as well as the dopamine and serotonin transporters (DAT and SERT).

Its pharmacological profile in studies in laboratory animals indicates that the effects of 5-MeO-DALT are consistent with those of hallucinogens such as (–)-2,5-dimethoxy-4-methylamphetamine (DOM) and lysergic acid diethylamide (LSD), although some effects differ from those of other hallucinogens.

Dependence potential

No controlled experimental studies to determine the probable dependence potential of 5-MeO-DALT have been reported, although unvalidated reports on online forums describe the development of tolerance when 5-MeO-DALT was used daily. As it is similar to DOM, 5-MeO-DALT would be expected to have little potential to produce dependence.

Actual abuse and/or evidence of likelihood of abuse

Preclinical studies suggest that 5-MeO-DALT has abuse potential, as it shares discriminative stimulus effects with DOM. No studies to determine the abuse liability of 5-MeO-DALT in humans have been reported.

5-MeO-DALT is sold online, and sales and seizures have been reported in many countries in several regions. A few reports have been made of adverse effects, including agitation and aggression, related to possible use of 5-MeO-DALT. The presence of the substance was not, however, biologically confirmed in the majority of cases.

Therapeutic usefulness

5-MeO-DALT is not known to have any therapeutic use.

Recommendation

5-Methoxy-*N,N*-diallyltryptamine or 5-MeO-DALT (chemical name: *N*-allyl-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)prop-2-en-1-amine)) is a synthetic hallucinogen with some effects similar to those of other hallucinogens such as DOM that are controlled under Schedule I of the 1971 Convention on Psychotropic Substances. Its mode of action is unclear, and there is very limited information on its effects in humans. While its use may constitute a risk to public health, the current evidence is insufficient to recommend international control.

Recommendation: The Committee recommended that 5-methoxy-*N,N*-diallyltryptamine (5-MeO-DALT, chemical name: *N*-allyl-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)prop-2-en-1-amine)) be kept under surveillance by the WHO Secretariat.

Stimulant

3-Fluorophenmetrazine (3-FPM)

Recommended for surveillance

Substance identification

3-Fluorophenmetrazine (chemical name: 2-(3-fluorophenyl)-3-methylmorpholine) is also known as 3F-phenmetrazine, 3-FPM, 3-FPH and PAL-593. 3-Fluorophenmetrazine is a white, solid, crystalline powder and has been found as tablets.

WHO review history

3-Fluorophenmetrazine 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 is of no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

3-Fluorophenmetrazine is a derivative of phenmetrazine, an amphetamine-type substance listed under Schedule II of the Convention on Psychotropic Substances of 1971, with known abuse potential. 3-Fluorophenmetrazine is a potent releaser of dopamine and norepinephrine.

In humans, its effects are similar to those of amphetamine and include euphoria, stimulation, increased energy, talkativeness and insomnia. Adverse effects include tachycardia, agitation, delirium and seizures.

Dependence potential

3-fluorophenmetrazine is a derivative of phenmetrazine, an amphetamine-type substance listed under Schedule II of the Convention on Psychotropic Substances of 1971, with known abuse potential. 3-fluorophenmetrazine is a potent releaser of dopamine and norepinephrine.

In humans, its effects are similar to those of amphetamine and include euphoria, stimulation, increased energy, talkativeness and insomnia. Adverse effects include tachycardia, agitation, delirium and seizures.

Actual abuse and/or evidence of likelihood of abuse

Given the structural similarity between 3-fluorophenmetrazine and phenmetrazine (a stimulant with known abuse liability) and biological effects similar to those of amphetamine-like substances (i.e. through release of dopamine and norepinephrine), 3-fluorophenmetrazine is expected to have similar abuse potential; however, there is no evidence to confirm this assumption.

Case reports have been published of adverse effects including tachycardia, reduced level of consciousness, agitation, anxiety, delirium and, less commonly, kidney damage, hypertension and fatal intoxication. The role of 3-fluorophenmetrazine in the limited number of serious non-fatal and fatal intoxications was, however, inconclusive.

Samples purchased online, as either 3-fluorophenmetrazine or other substances, have been identified as containing 3-fluorophenmetrazine. Seizures have been described in six countries in several regions.

Therapeutic usefulness

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

Recommendation

3-Fluorophenmetrazine (chemical name: 2-(3-fluorophenyl)-3-methylmorpholine) has a mode of action and effects similar to those of phenmetrazine, an amphetamine-type substance listed under Schedule II of the Convention on Psychotropic Substances of 1971. While this suggests that it has a potential for dependence and the likelihood of abuse, there is little supportive evidence. In addition, there is no evidence of the extent of public health and social problems related to use of 3-fluorophenmetrazine and some uncertainty about its toxicity.

Recommendation: The Committee recommended that 3-fluorophenmetrazine (chemical name: 2-(3-fluorophenyl)-3-methylmorpholine) be kept under surveillance by the WHO Secretariat.

Dissociatives

3-Methoxyphencyclidine (3-MeO-PCP)

Recommended for listing under Schedule II of the 1971 Convention

Substance identification
3-Methoxyphencyclidine (3-MeO-PCP) (chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine) is an arylcyclohexylamine and a 3-methoxy derivative of phencyclidine (PCP), which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. It is found as a powder and tablets.
WHO review history
3-methoxyphencyclidine 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
3-methoxyphencyclidine is an N-methyl-D-aspartate (NMDA) receptor antagonist with a mechanism of action and effects similar to those of PCP. The effects include an altered mental state characterized by confusion, disorientation and out-of-body experiences as well as hallucinations and other psychotic symptoms.
Dependence potential
No studies have been reported in animals or humans on the dependence potential of 3-methoxyphencyclidine.
Actual abuse and/or evidence of likelihood of abuse
As 3-methoxyphencyclidine is an NMDA receptor antagonist, it would be expected to have similar effects and similar abuse potential to those of PCP. The adverse effects include cardiovascular effects (such as hypertension and tachycardia) and cognitive effects including psychosis, confusion and agitation. People with a history of or vulnerability to psychotic illness may be at greater risk of psychosis. Cases of severe and fatal intoxication have been reported from several countries and regions. Seizures have been reported in a number of countries in several regions.
Therapeutic usefulness
3-methoxyphencyclidine is not known to have any therapeutic use.

Recommendation

3-Methoxyphencyclidine (chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine) is an analogue of and has similar effects to PCP, which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances. Its mode of action suggests a likelihood of abuse. There is evidence that this substance is used in a number of countries in various regions. 3-Methoxyphencyclidine causes substantial harm, including severe adverse events such as hallucinations, other psychotic symptoms and fatal intoxications. It has no therapeutic use.

Recommendation: The Committee recommended that 3-methoxyphencyclidine (chemical name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Diphenidine

Recommended for listing under Schedule II of the 1971 Convention

Substance identification

Diphenidine (chemical name: 1-(1,2-diphenylethyl)piperidine) is a dissociative and hallucinogenic substance of the 1,2-diarylethylamine class. It is found as a powder and in tablets.

WHO review history

Diphenidine 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

Diphenidine is known to produce hallucinogenic and dissociative effects through its action as an NMDA receptor antagonist. This mechanism of action and its effects are similar to those of PCP, which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances.

Dependence potential

No studies have been reported in animals or humans on the dependence potential of diphenidine.

Actual abuse and/or evidence of likelihood of abuse

As diphenidine is an NMDA receptor antagonist, it would be expected to have abuse potential similar to that of PCP. In addition, diphenidine causes the release of dopamine, in a manner similar to but to a lesser degree than cocaine. This effect may also contribute to its abuse potential.

Cases of intoxication requiring hospitalization have been reported. Adverse effects include cardiovascular effects (such as tachycardia and hypertension) and central nervous system effects, including hallucinations, depersonalization, delusions, paranoia, dissociation, confusion, nystagmus and muscle rigidity. These effects have resulted in acute intoxication requiring emergency admission. A small number of fatal intoxications involving diphenidine have been documented. All the deaths involved multiple drugs; however, the cardiovascular and hallucinogenic symptoms described were consistent with the effects of diphenidine.

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

Therapeutic usefulness

Diphenidine is not known to have any therapeutic use.

Recommendation

The available evidence indicates that the mechanism of action and effects of diphenidine (chemical name: 1-(1,2-diphenylethyl)piperidine) are similar to those of PCP, which is controlled under Schedule II of the 1971 Convention on Psychotropic Substances. Its mode of action suggests the potential for abuse. There is evidence that diphenidine causes significant harm, including psychosis and cardiovascular effects, representing a substantial risk to public health. Diphenidine has no therapeutic use.

Recommendation: The Committee recommended that diphenidine (chemical name: 1-(1,2-diphenylethyl)piperidine) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2-Methoxydiphenidine (2-MeO-DIPHENIDINE)

Recommended to be placed under surveillance

Substance identification

2-Methoxydiphenidine (chemical name: 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine) is also known as 2-MeO-diphenidine, 2-MXP and methoxphenidine. It is a dissociative and hallucinogenic substance of the 1,2-diarylethylamine class. It is found as a powder and tablets.

WHO review history
2-methoxydiphenidine 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
Like PCP, 2-methoxydiphenidine is an NMDA receptor antagonist and has PCP-like effects. Phencyclidine is controlled under Schedule II of the Convention on Psychotropic Substances of 1971.
Dependence potential
No studies have been reported in animals or humans on the dependence potential of 2-methoxydiphenidine.
Actual abuse and/or evidence of likelihood of abuse
<p>As 2-methoxydiphenidine is an NMDA receptor antagonist, its effects and abuse potential would be expected to be similar to those of PCP.</p> <p>A few case reports, often involving multiple substances, describe adverse effects, including acute behavioural effects such as agitation, sedation, depersonalization, hallucinations, delusions and paranoia and physical effects such as tachycardia, syncope and hyperthermia. Online forums present reports from individuals describing its use and effects such as euphoria.</p> <p>While reports of 2-methoxydiphenidine use and its harm are available from a number of countries, these have been less frequent during the past two years, and it is possible that there is no longer significant use of this substance.</p>
Therapeutic usefulness
2-methoxydiphenidine is not known to have any therapeutic use.
Recommendation
<p>2-Methoxydiphenidine (chemical name: 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine) has a mechanism of action similar to that of PCP. Its use has been declining in recent years. There is insufficient evidence of a public health or social problem at this time to warrant placing 2-methoxydiphenidine under international control.</p> <p>Recommendation: The Committee recommended that 2-Methoxydiphenidine (chemical name: 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine) be kept under surveillance by the WHO Secretariat.</p>

Synthetic opioid

Isotonitazene

Recommended for Schedule I of the 1961 Single Convention

Substance identification

Isotonitazene (chemical name: *N,N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine) belongs to the 2-benzylbenzimidazole group of compounds, which include the closely related opioids etonitazene, metonitazene and clonitazene. It is found in yellow, brown or off-white powder forms.

WHO review history

Isotonitazene has not previously 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

Isotonitazene is a chemical analogue of etonitazene and clonitazene, both of which are Schedule I compounds under the Single Convention on Narcotic Drugs, 1961. Isotonitazene is a potent opioid analgesic with a rapid onset of action. Preclinical studies have demonstrated that isotonitazene is more potent than fentanyl and hydromorphone and substantially more potent than morphine. There is limited research on the effects of this compound on the central nervous system, but, given its demonstrated potency at the μ -opioid receptor, it would be expected to produce analgesia, respiratory depression and sedation.

Dependence potential

No controlled animal or human studies have been reported of the dependence potential of isotonitazene. As a potent μ -opioid agonist, it would be expected to produce dependence. An unverified online report described dependent use and withdrawal symptoms, including flu-like symptoms and anxiety.

Actual abuse and/or evidence of likelihood of abuse

No controlled studies have been reported on the abuse potential of isotonitazene, but, as it is a potent μ -opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability.

Because of its relatively recent appearance on the illicit drug market, there is limited information on the prevalence of use of isotonitazene or of its harm. Seizures have been reported in many countries and regions. It is reported to be used through various routes, including sublingually, vaping and intravenously.

The number of deaths involving isotonitazene has increased in a short time. Deaths commonly occur after use in combination with other opioids or benzodiazepines. Deaths due to isotonitazene share features with deaths due to heroin, including evidence of injection and signs consistent with opioid overdose, such as pulmonary and/or cerebral oedema. Deaths due to isotonitazene are likely to be underreported because of its recent, rapid appearance.

Therapeutic usefulness

Isotonitazene is not known to have any therapeutic use.

Recommendation

The mechanism of action of isotonitazene (chemical name: *N,N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine) indicates that it is liable to have similar abuse and similar ill effects as opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects, including death. It has no known therapeutic use and is likely to cause substantial harm.

Recommendation: The Committee recommended that isotonitazene (chemical name: *N,N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-amine) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

Synthetic cannabinoid receptor agonists

MDMB-4en-PINACA

Recommended for Schedule II of the 1971 Convention

Substance identification
MDMB-4en-PINACA (chemical name: methyl-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1 <i>H</i> -indazole-3-carboxamido)butanoate) is a synthetic cannabinoid. It has been identified in seized material formulated for smoking and found as white to yellow–brown powder.
WHO review history
MDMB-4en-PINACA 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
MDMB-4en-PINACA is a synthetic cannabinoid that binds to cannabinoid (CB ₁) receptors as a full and potent agonist. It is structurally similar to 5F-MDMB-PINACA (5F-ADB), which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. A report of an unpublished study in animals indicates that MDMB-4en-PINACA can have the characteristic effects of CB ₁ agonists, such as hypothermia and lethargy. Reports on online user forums describe cannabis-like euphoria at moderate levels of intake, with dissociation described at higher doses. Both sedation and stimulation have been reported, in addition to memory loss, confusion and agitation.
Dependence potential
No studies have been reported in animals or humans on the dependence potential of MDMB-4en-PINACA. As it is a full CB ₁ agonist, it would be expected to produce dependence similarly to other CB ₁ receptor agonists.
Actual abuse and/or evidence of likelihood of abuse
No studies have been reported in animals or humans to indicate the likelihood of abuse of MDMB-4en-PINACA; however, CB ₁ receptor agonists have known abuse potential. A number of countries in various regions have reported use of MDMB-4en-PINACA. Its use has been associated with cases of impaired driving and death.

Therapeutic usefulness

MDMB-4en-PINACA has no known therapeutic use.

Recommendation

MDMB-4en-PINACA (chemical name: methyl-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate) is a potent synthetic cannabinoid receptor agonist with a similar mechanism of action and similar effects to a number of other synthetic cannabinoids that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Use of MDMB-4en-PINACA has been associated with severe adverse effects, including fatal intoxication and cases of impaired driving. MDMB-4en-PINACA has no therapeutic use.

Recommendation: The Committee recommended that MDMB-4en-PINACA (chemical name: methyl (*S*)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

CUMYL-PEGACLONE

Recommended for Schedule II of the 1971 Convention

Substance identification

CUMYL-PEGACLONE (chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1*H*-pyrido[4,3-*b*]indol-1-one) is a synthetic cannabinoid. It has been found in seized material formulated for smoking and vaping.

WHO review history

CUMYL-PEGACLONE 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

CUMYL-PEGACLONE is a synthetic cannabinoid with a mechanism of action similar to that of other synthetic cannabinoids. It is a potent full agonist at CB₁ receptors.

No controlled studies have been reported of its effects, but online user reports describe euphoria, dissociation, red eyes, dry mouth and appetite stimulation. These effects are consistent with the known effects of cannabinoid agonists.

Dependence potential

No controlled studies have been reported in animals or humans on the dependence potential of CUMYL-PEGACLONE. However, CUMYL-PEGACLONE has been shown to be a full, potent agonist at the CB1 receptor and would therefore be expected to produce dependence similarly to other CB1 receptor agonists.

Actual abuse and/or evidence of likelihood of abuse

No controlled animal or human studies have been reported on the abuse potential of CUMYL-PEGACLONE.

A number of countries in several regions have reported that CUMYL-PEGACLONE is being used for its psychoactive properties.

Adverse effects such as seizures and fatalities involving CUMYL-PEGACLONE have been reported. While other drugs were also used, CUMYL-PEGACLONE was deemed to be a causal or contributory factor in a number of these deaths.

Therapeutic usefulness

CUMYL-PEGACLONE is not known to have any therapeutic use.

Recommendation

CUMYL-PEGACLONE (chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1*H*-pyrido[4,3-*b*]indol-1-one) is a synthetic cannabinoid receptor agonist with a mode of action that suggests the likelihood of dependence and abuse and ill effects similar to those of other synthetic cannabinoids. Its use has been associated with severe adverse effects and fatalities. The effects of CUMYL-PEGACLONE are similar to those of other synthetic cannabinoids that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. CUMYL-PEGACLONE has no therapeutic use, and its use constitutes a substantial risk to public health.

Recommendation: The Committee recommended that CUMYL-PEGACLONE (Chemical(chemical name: 5-pentyl-2-(2-phenylpropan-2-yl)-2,5-dihydro-1*H*-pyrido[4,3-*b*]indol-1-one), be added to Schedule II of the Convention on Psychotropic Substances of 1971.

Benzodiazepines

Flubromazolam

Recommended for Schedule IV of the 1971 Convention

identification
Flubromazolam (chemical name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4 <i>H</i> -benzo[<i>f</i>][1,2,4]triazolo[4,3- <i>a</i>][1,4]diazepine) is a 1-4 triazolobenzodiazepine. Flubromazolam is a white powder, often sold as a liquid or as tablets.
WHO review history
Flubromazolam 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
<p>Flubromazolam is a highly potent benzodiazepine with long-lasting depressant effects on the central nervous system. Flubromazolam enhances the effects of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) by binding at the benzodiazepine site of the GABA_A receptor. This mechanism of action, and its effects, are similar to those of the benzodiazepines triazolam and alprazolam, which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.</p> <p>A single pharmacokinetics study showed that a dose of 0.5 mg flubromazolam induced strong sedative effects that lasted more than 10 h and caused partial amnesia for more than 24 h. The effects of flubromazolam have been effectively reversed by the benzodiazepine antagonist flumazenil.</p> <p>Reports on online user forums describe benzodiazepine-like effects, including anxiolytic, euphoric and sedative effects.</p>
Dependence potential
No controlled studies have been reported in animals or humans on the dependence potential of flubromazolam, although many online reports describe severe withdrawal symptoms, such as muscle aches, sleeping disorders, severe anxiety and panic attacks, dissociative symptoms, perceptual distortions, cramping, chills, vomiting and risk of seizures. Loss of control of use and rapid onset of tolerance have also been described. The latter suggest that increased dosing and physical dependence are likely.

Actual abuse and/or evidence of likelihood of abuse

No controlled animal or human studies have assessed the abuse potential of flubromazolam.

Impaired driving has been reported with flubromazolam as the sole intoxicant. Non-fatal intoxications requiring hospital admission and fatal intoxications due to flubromazolam use have been documented, with central nervous system depression and severe sedation as clinical features of presentation. Flubromazolam can increase unintentional opioid overdoses. Its long half-life may increase the risk of accumulation and of interactions when taken with other drugs.

Nonmedical use and seizures due to flubromazolam have been documented in many countries in various regions. It is increasingly sold as falsified pharmaceutical benzodiazepines.

Therapeutic usefulness

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

Recommendation

Flubromazolam (chemical name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine) is a 1-4 triazolobenzodiazepine with actions and effects very similar to those of benzodiazepines listed under Schedule IV in the Convention on Psychotropic Substances of 1971. It can produce a state of dependence and central nervous system depression, like other benzodiazepines. Reports of abuse, impaired driving and fatal and non-fatal intoxications have been increasing. There is sufficient evidence of its abuse to conclude that it constitutes a significant risk to public health; it has no known therapeutic use.

Recommendation: The Committee recommended that flubromazolam (chemical name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

Clonazepam

Recommended for Schedule IV of the 1971 Convention

Substance identification
Clonazepam (chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4 <i>H</i> -benzo[<i>f</i>][1,2,4]triazolo[4,3- <i>a</i>][1,4]diazepine) is a 1-4 triazolobenzodiazepine similar to clonazepam, triazolam and alprazolam. It is sold in powder, blotter, liquid and tablet forms.
WHO review history
Clonazepam 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
Clonazepam enhances the effects of the inhibitory neurotransmitter GABA by binding at the benzodiazepine site of the GABA _A receptor. This mechanism of action and its effects (sedation, muscle relaxation, slurred speech, loss of motor control, amnesia) are similar to those of benzodiazepines such as diazepam, triazolam and alprazolam, which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances. The effects of clonazepam poisoning have been reversed with the benzodiazepine antagonist flumazenil, confirming that its action is mediated via the benzodiazepine receptor in the GABA _A receptor complex.
Dependence potential
No controlled studies have been reported in animals or humans on the dependence potential of clonazepam, although its pharmacological effects and its similarity to other benzodiazepines indicate that it would be expected to produce dependence. Development of tolerance to the effects of clonazepam after repeated use and the onset of withdrawal symptoms after cessation of use have been reported on online forums.
Actual abuse and/or evidence of likelihood of abuse
No studies in humans or animals have examined the abuse liability of clonazepam. Online forums describe its recreational use and consistently report strong anxiolytic effects.

A number of published reports describe the management of cases of intoxication involving clonazepam in emergency departments or intensive care. Use of clonazepam has been confirmed analytically in cases of impaired driving, in combination with other substances. Clonazepam can increase the effects of other drugs, including opioids, and on its own can cause severe central nervous system depression, including somnolence, confusion, sedation and unconsciousness.

Its identification has been reported in many countries in all regions, indicating that its use may be increasing. Clonazepam is increasingly sold as falsified pharmaceutical benzodiazepines.

Therapeutic usefulness

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

Recommendation

Clonazepam (chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine) is a 1-4 triazolobenzodiazepine with actions and effects very similar to those of benzodiazepines listed under Schedule IV in the Convention on Psychotropic Substances of 1971. Like other benzodiazepines, clonazepam can produce a state of dependence and central nervous system depression. There have been a number of reports of abuse, impaired driving and non-fatal intoxications. There is sufficient evidence of its abuse to constitute a public health problem, and it has no known therapeutic use.

Recommendation: The Committee recommend that clonazepam (chemical name: 6-(2-chlorophenyl)-1-methyl-8-nitro-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

Diclazepam

Recommended for Schedule IV of the 1971 Convention

Substance identification

Diclazepam (chemical name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one) is a 2-chloro derivative of the benzodiazepine diazepam. It is found as a white powder, and is commonly sold as tablets, pellets and liquid.

WHO review history

Diclazepam 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

Diclazepam is an agonist at the benzodiazepine site of the GABA_A receptor, acting to increase the effect of the inhibitory neurotransmitter GABA. Diclazepam has effects similar to those of the benzodiazepine diazepam, which is currently controlled under the Convention on Psychotropic Substances of 1971. It is metabolized to the benzodiazepines delorazepam, lorazepam and lormetazepam, which are active and are also pharmaceuticals included in Schedule IV of the Convention on Psychotropic Substances of 1971.

Diclazepam was shown to cause sedation and muscle relaxation in animals. Central nervous system depressant effects have been described in humans.

Dependence potential

No controlled studies have been reported in animals or humans on the dependence potential of diclazepam.

Online user reports describe cross-tolerance with other benzodiazepines and use to self-manage benzodiazepine withdrawal. This evidence and its mechanism of action suggest that diclazepam can produce dependence, like other benzodiazepines.

Actual abuse and/or evidence of likelihood of abuse

No controlled studies in animals or humans have been reported on the abuse liability of diclazepam. On the basis of its mechanism of action and its effects, however, its abuse liability would be expected to be similar to that of other benzodiazepines.

Diclazepam has the potential to increase unintentional opioid overdoses. Its long half-life may increase the risk of accumulation and of interactions when combined with other drugs. Fatal intoxication with diclazepam has been reported.

Seizures have been reported with diclazepam in many countries in various regions. Diclazepam is increasingly being sold as falsified benzodiazepines, commonly as diazepam.

Diclazepam has been implicated in cases of impaired driving, including when it was identified as the main contributor to impairment. It also has been involved in cases of drug-facilitated sexual assault.

Therapeutic usefulness

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

Recommendation

Diclazepam (chemical name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one) is a 2-chloro analogue of the benzodiazepine diazepam, with actions and effects very similar to those of benzodiazepines listed under Schedule IV of the Convention on Psychotropic Substances of 1971. It can produce a state of dependence and central nervous system depression, like other benzodiazepines. There have been reports of abuse, impaired driving and fatal and nonfatal intoxications. There is sufficient evidence of its abuse to conclude that it constitutes a significant risk to public health; it has no known therapeutic use.

Recommendation: The Committee recommended that diclazepam (chemical name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) be added to Schedule IV of the 1971 Convention on Psychotropic Substances.

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Recommendations for the scheduling of psychoactive substances were made by the following Expert Committee Members (in alphabetical order): Patrick Beardsley, Wim Best, Bruna Brands, Ifeoma Ekwere, Simon Elliott, Raka Jain, Pamela Kaduri, Junichi Kitanaka, Antonio Pascale Prieto, Afarin Rahimi-Movaghar, Sutisa Thanoi and Jason White. The 43rd ECDD meeting was chaired by Jason White and co-chaired by Afarin Rahimi-Movaghar. Pamela Kaduri acted as rapporteur.

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43rd ECDD critical review reports and Member State questionnaire

Critical review report: 5-Methoxy-*N,N*-diallyltryptamine (5-MeO-DALT)

Executive summary

The method for synthesizing 5-methoxy-*N,N*-diallyltryptamine (5-MeO-DALT) was first published in 2004 on Erowid, an online drug user forum (1), and it was identified as an NPS in the EMCDDA Early Warning System in 2007 (2). It is a ring-substituted *N,N*-diallyltryptamine that is usually purchased online through the “research chemical” market.

5-MeO-DALT binds to many different types of receptors. It has similar binding affinities (< 10 nM) for all the serotonin (5-hydroxytryptamine; 5-HT) receptor subtypes and similarly high affinities at adrenergic α_{2A} , α_{2B} , α_{2C} , histamine H_1 and H_3 , kappa opioid $\kappa 1$ and $\kappa 2$ receptors, as well as the dopamine and serotonin receptor transporters (DAT and SERT) (3). In rodents, 5-MeO-DALT produced dose-related increases in locomotor activity and fully substituted for the DOM but not the \pm -3,4-methylenedioxymethamphetamine (MDMA) discriminative stimulus (4). Overall, 5-MeO-DALT produced discriminative stimulus effects that were more similar to those of a classical hallucinogen – DOM – than to those of an enactogen like MDMA, which has both stimulant and hallucinogenic effects. However, unlike DOM, 5-MeO-DALT also increased locomotor activity, which was more similar to that of MDMA. Furthermore, 5-MeO-DALT produced an inverted U-shaped dose–response curve in mice for the head-twitch response, which occurs following activation of 5-HT_{2A} receptors (5).

Fatalities have seldom been attributed directly to 5-MeO-DALT, although it has been reported in confiscated drugs and in human body fluids in a few case reports. It appears to be used most often orally, although it is also reportedly used by other routes such as smoking and insufflation. It currently has no legitimate medical or veterinary uses and is available commercially only for research and industrial purposes. Overall, the data currently available on 5-MeO-DALT suggest that it has abuse potential.

1. Substance identification

A. International Nonproprietary Name (INN)

5-MeO-DALT

B. Chemical Abstract Service (CAS) registry number

928822-98-4

1370252-04-2 (HCl)

C. Other chemical names

5-methoxy-*N,N*-diallyltryptamine
 tryptamine, *N,N*-diallyl-5-methoxy
 indole, 3-[2-(diallylamino)ethyl]-5-methoxy
 3-[2-(diallylamino)ethyl]-5-methoxyindole
 5-methoxy-*N,N*-di-2-propen-1-yl-1*H*-indole-3-ethanamine
N,N-diallyl-5-methoxytryptamine
 5-methoxy-*N,N*-diallyl-1*H*-indole-3-ethanamine
N-allyl-*N*-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)prop-2-en-1-amine

D. Trade names

5-methoxy DALT

E. Street names

Foxtrot
 Lucy-N-Nate
 Purple Bomb
 Psychedelic crack
 5-MeO-DALT
 5-methoxy DALT
 DALT
 Meo-dalt-5

Street names for substances that contained 5-MeO-DALT in combination with other substances include: Street Magic (combined with caffeine and ethylphenidate), Black Mamba, Formula X, Project X, Dizzle Dust, Street Magic, B2, B3, Magic, iMerge, Purple Bombs Extreme, Banshee Dust, Blue Snowball, MM1, NRG-2, Bubble, NRG-3, Red Part Mix, Blue Party Mix and N Madcat.

F. Physical appearance

5-MeO-DALT is a solid, crystalline powder. Its colour has been described as white, off-white, grey, light brown or tan. It has also been identified in yellow, purple or green tablets on the illicit drug market.

G. WHO review history

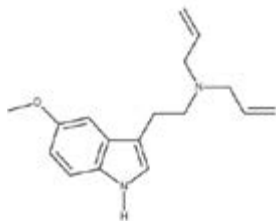
5-MeO-DALT has not previously been reviewed by the WHO ECDD.

2. Chemistry

A. Chemical name

IUPAC name: *N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]-*N*-prop-2-enylprop- 2-en-1-amine

CA Index name: Not found

B. Chemical structure

Molecular formula: $C_{17}H_{22}N_2O$

Molecular weight: 270.37 g/mol

5-MeO-DALT is a ring-substituted *N,N*-diallyltryptamine. The crystalline structure was described recently (6).

C. Stereoisomers

No descriptions of 5-MeO-DALT stereoisomers were found in the scientific literature.

D. Methods and ease of illicit manufacture

The illicit manufacture of 5-MeO-DALT was first described by Shulgin & Shulgin in 2004 and published on Erowid (1). Synthesis of 5-MeO-DALT was subsequently described by Cozzi & Daley (3) as follows: “using the method of Speeter and Anthony, the 5-substituted-glyoxyamides (1b–6b) were obtained by acylation of the 5-substituted-indoles (1a–6a) with oxalyl chloride, followed by reaction with *N,N*-diallylamine to give the 5-substituted-*N,N*-diallylglyoxyamides (1c–6c). The *N,N*-diallylglyoxyamides were rapidly reduced to the *N,N*-diallyltryptamines (1–6) using lithium aluminum hydride in sealed glass tubes under microwave-accelerated conditions as described.”

E. Chemical properties

Boiling-point: $422.8\text{ }^{\circ}\text{C} \pm 45.0\text{ }^{\circ}\text{C}$ at 760 mm Hg (8).

F. Identification and analysis

5-MeO-DALT is a structural analogue of DALT and 5-MeO-DiPT. Various analytical tests have been used to identify 5-MeO-DALT, including a selective reagent ionization–time of flight–mass spectrometry (TOF–MS) method (9). Strano-Rossi et al. (10) used single quadrupole gas chromatography–mass spectrometry (GC–MS), followed by liquid chromatography–high-resolution mass spectrometry (LC–HRMS) in the positive electrospray ionization (ESI) mode at 100 000 full width and half maximum resolution without fragmentation to identify 5-MeO-DALT. Several other techniques, such as nuclear magnetic resonance (NMR) spectroscopy, GC quadrupole and ion trap MS, low and high mass accuracy tandem MS (MS–MS), photodiode array detection and GC solid-state infrared analysis, used to identify *N,N*-diallyltryptamines were described in detail by Brandt et al. (11).

3. Ease of convertibility into controlled substances

No reports of conversion of 5-MeO-DALT into other controlled substances were found.

4. General pharmacology

A. Routes of administration and dosage

Information from drug user forums indicates that 5-MeO-DALT is used orally or smoked (12, 13). Oral doses purportedly range between 4 mg and 35 mg or more; common doses are 12–25 mg, and strong doses are 25–35 mg. Vaporized doses range between 3 mg and 15 mg or more; common doses are 5–10 mg, and a strong dose is 15 mg. 5-MeO-DALT appears to be used most commonly by the oral route.

Intravenous, intranasal and rectal use of 5-MeO-DALT has also been reported, but the amounts used by these routes were not specified (14).

B. Pharmacokinetics

The primary metabolic pathways for 5-MeO-DALT are O-demethylation, hydroxylation and N-deallylation (15, 16). Twenty phase I and eight phase II metabolites were identified in vivo in Wistar rats (16), and an additional eight phase I metabolites were identified in the zygomycete fungus *Cunninghamella elegans* (15).

Information from drug user forums indicates that the duration of action of 5-MeO-DALT is 2–6 h when used orally, with an onset of action of less than 15 min (1, 12, 13). When smoked, the duration of action of 5-MeO-DALT is 15–20 min, with an onset of action within 15–60 s. The following doses and perceived effects, which depended on the route of administration, were reported in drug user forums: 4–5 mg (threshold), 5–35 mg (light), 40–100 mg (strong).

C. Pharmacodynamics

Radioligand binding assays in rat brain membranes demonstrated that 5-MeO-DALT binds to 5-HT receptor subtypes (17). It had the highest affinity at 5-HT_{2B}, 5-HT₆ and 5-HT₇ receptors and the least affinity for 5-HT_{2A} and 5-HT_{2C} receptors (17). Although one study of monoamine uptake and release showed that 5-MeO-DALT had no activity at dopamine, norepinephrine and serotonin receptors in rat brain synaptosomes (18), a study with the [³⁵S]GTPγS binding assay demonstrated that 5-MeO-DALT stimulated G protein binding (19). The half maximal effective concentration (EC₅₀) was 6.6×10^{-7} M, and the percentage of maximum 5-HT activation was 39.6, indicating higher potency and efficacy at 5-HT receptors than the other drugs tested, including several tryptamines (19).

A more recent study of the binding affinities of 5-MeO-DALT for several receptor classes and subtypes (3) demonstrated that 5-MeO-DALT has similar binding affinities (<10 μM) for all the 5-HT receptor subtypes and similarly

high affinities at adrenergic α_{2A} , α_{2B} , α_{2C} , histamine H_1 and H_3 , kappa opioid receptors, κ_1 and κ_2 receptors, as well as DAT and SERT. It did not bind to any appreciable extent to muscarinic M_1 – M_5 , adrenergic α_{1-3} , histaminergic H_4 , central benzodiazepine sites or GABA_A receptors.

Pottie et al. (20) described an assay for measuring 5-HT_{2A} activation via β arr2 recruitment. The maximal efficacy of 5-MeO-DALT was similar to that of LSD, and its rank order of potency in this bioassay was LSD > 5-MeO-DALT > mescaline. However, the authors warned that the high activity exerted by endogenous compounds such as serotonin may “impede” use of this procedure, and these results should be interpreted cautiously.

In mice, 5-MeO-DALT produced dose-related increases in locomotor activity up to a dose of 10 mg/kg intraperitoneally, relative to saline (4). The locomotor stimulating effects occurred within 40 min of administration of 10 mg/kg 5-MeO-DALT and lasted for 3 h. A dose of 25 mg/kg 5-MeO-DALT depressed locomotor activity for the first 1.5 h after administration. In rats trained to discriminate either 1.5 mg/kg MDMA or 0.5 mg/kg DOM (a 5-HT_{2A} agonist) from saline, 5-MeO-DALT fully substituted for DOM (maximum 84% DOM-appropriate responding) but not MDMA (7). Overall, 5-MeO-DALT produced discriminative stimulus effects that were more similar to those of a classical hallucinogen (DOM) than of an enactogen like MDMA. However, unlike the other compounds tested, including DOM, 5-MeO-DALT increased locomotor activity, similarly to MDMA. 5-MeO-DALT also produced an inverted U-shaped dose–response curve in mice for the head-twitch response, which occurs following activation of 5-HT_{2A} receptors and is suppressed by simultaneous administration of 5-HT_{1A} agonists (5).

No controlled studies of 5-MeO-DALT have been reported in the scientific literature, but a drug user website (12) described its effects as follows: “Anecdotal reports characterize the effects of this substance as being primarily physical in nature, lacking the characteristic visual distortions or perceptual depth of most psychedelics. Its headspace has been described as ‘shallow’, albeit suited for sexual contexts due to its potent stimulating and libidinous effects. It is also reported to produce more uncomfortable cardiovascular effects such as increased blood pressure and heart rate relative to other psychedelics”.

5. Toxicology

No formal studies on the toxicology of 5-MeO-DALT have been reported.

6. Adverse reactions in humans

No controlled clinical studies have been reported with 5-MeO-DALT, but various case reports have described adverse reactions that may be associated with its use.

A 2012 report from the United Kingdom described the presence of 5-MeO-DALT “alongside ethanol detection” in a man in his mid-twenties who was involved in a motor vehicle accident after he walked into traffic (14). The man had reportedly snorted 350 mg 5-MeO-DALT, and the cause of death was reported as “injuries sustained after being hit by a lorry while under the influence of 5-MeO-DALT” (14).

A 2014 report from the USA (St Louis, MO) described the case of a 20-year-old college student who was taken to an emergency room after ingesting a capsule purchased at a convenience store under the name “Lucy-N-Nate”, which contained an unknown quantity of 5-MeO-DALT (21). A sample of his urine tested positive for cannabinoids and amphetamines, but the report did not specify whether the presence of 5-MeO-DALT was verified by analytical testing. The man had “complained of feeling ill while at home as though his ‘heart was caving in’, near fainting, consciously falling to the ground and screaming ‘I’m going to die!’, while flailing all four extremities in his parents’ presence. He reported his muscles were ‘going back and forth’ with extraordinary strength; there was no loss of consciousness. In the emergency department of the referring hospital, he was reported to be agitated, combative, warm, flushed and diaphoretic. He had marked tachycardia (180–200 bpm) and tachypnoea. More than eight people attempted to restrain him; he was given several benzodiazepines intramuscularly for sedation (lorazepam and diazepam) as well as a dose of IM haloperidol with little response” (21). He was ultimately given deep sedation and transferred to an intensive care unit, where he was found to have rhabdomyolysis and acute renal failure, which eventually resolved. He was discharged from hospital after several days.

A 2016 report from Denmark described a case of over-intoxication with a combination of oral 5-MeO-DALT and alcohol (22). A 34-year-old man had ingested an unknown amount of 5-MeO-DALT and alcohol, after which he exhibited aggressive behaviour while lying on the floor for several hours (22). After he became unresponsive, he was taken to an emergency department, where he was found to be in an altered state of consciousness and exhibited tachypnoea, tachycardia, mydriasis with no light reflex and elevated temperature. Initial blood work showed rhabdomyolysis and acute renal failure. He was put under deep sedation to depress metabolic demand and control his aggressive behaviour. He was discharged from hospital after 10 days. The report did not specify whether the presence of 5-MeO-DALT was verified by analytical testing.

A 2018 report from France described the presence of various substances in 558 blood and 199 oral fluid samples taken during roadside tests in Belgium obtained from individuals suspected of driving under the influence of drugs (7). Although multiple drugs were most often present in these samples, the one individual who

tested positive for 5-MeO-DALT did not test positive for any other drugs. The observed symptoms included “shiny eyes, mydriasis, pale skin tone, resignation, euphoria, repetition of words, talkative, aggressive and impolite behaviour” (7).

7. Dependence potential

A. Animal studies

No preclinical studies of dependence potential were found in the published scientific literature.

B. Human studies

No clinical studies of dependence potential were found in the published scientific literature. However, as noted on iTrend (Internet tool for research in Europe on new drugs (23)), users reported that tolerance developed when 5-MeO-DALT was used daily at high doses and that tolerance decreased when the drug was used every other day.

8. Abuse potential

A. Animal studies

As noted above, 5-MeO-DALT shared discriminative stimulus effects with DOM, a classical serotonergic hallucinogen, but not with MDMA (4). However, like MDMA, it increased locomotor activity (4) and produced a head-twitch response, which occurs when 5-HT_{2A} receptors are activated (5).

B. Human studies

No controlled clinical studies of abuse potential in humans were found in the published scientific literature.

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

5-MeO-DALT is not approved for therapeutic use in any country.

10. Listing on the WHO Model List of Essential Medicines

5-MeO-DALT is not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

5-MeO-DALT is not approved in any country as a medicinal product.

12. Industrial use

5-MeO-DALT is available for use in research and for industrial purposes.

13. Nonmedical use, abuse and dependence

The extent of misuse and abuse of 5-MeO-DALT is unknown.

The Welsh Emerging Drugs and Identification of Novel Substances project (WEDINOS) reported on 50 samples that were either intended to be purchased as 5-MeO-DALT or other substances and/or positively identified as 5-MeO-DALT (24). Eight samples obtained from two web shops in the United Kingdom in December 2013 and January 2014 contained 5-MeO-DALT almost exclusively (25).

An online drug user forum reported that “5-MeO-DALT is not habit-forming” (12).

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

Only one study confirmed the presence of 5-MeO-DALT alone (7), in an individual who was tested after driving under the influence of drugs. The nature and extent of public health problems related to misuse of 5-MeO-DALT is therefore unclear.

According to iTrend (23) and EMCDDA (26), 5-MeO-DALT was involved in the fatal intoxication of a male drug user in Scotland. Other drugs that were thought to have contributed to the fatality were α -methyltryptamine/5-(2-aminopropyl)indole and ketamine. Drugs that were present but thought not to be involved in the death were lignocaine, propofol, thiopentone and fentanyl.

15. Licit production, consumption and international trade

5-MeO-DALT does not appear to have any licit medicinal or veterinary use in any country.

As described on iTrend (23), 5-MeO-DALT was sold in United Kingdom web shops before a ban went into effect at the following prices: £ 7.99 for 250 mg to £ 675.00 for 100 g.

16. Illicit manufacture and traffic and related information

As described on iTrend (23), 5-MeO-DALT was first reported in Europe by authorities in Finland in 2007 and by the United Kingdom National Focal Point in 2010. As of 2015, it had been notified to the EMCDDA in reports from: Finland (2007), United Kingdom (2010), Belgium (2011), Bulgaria (2011), Germany (2011), Sweden (2011), Hungary (2012), Denmark (2013), France (2013), Croatia (2014), Cyprus (2014), Italy (2014), Norway (2014) and Romania (2014).

5-MeO-DALT appears to be most often sold on the Internet, with prices ranging “from €17–€29 (US\$23–US\$39) for 1 g (sufficient for 40 to 50 doses) up to € 4600–€ 5400 (US\$ 6200–US\$ 7300) for 1 kg” (14).

“According to the European Database on New Drugs (EDND), it was first seen (as two grey tablets) in a customs seizure at Helsinki airport, Finland, in

December 2006, of a postal package with apparent Danish origins. The second report was the present death. Since then, German police seized 687 g of powder in June 2010, Swedish police seized 0.8 g of a dried herbal substance in January, 2011, UK police seized a green mixture containing several substances including 5-MeO-DALT at a ‘headshop’ in March 2011, the Bulgarian authorities seized a capsule in May 2011, and Belgian police seized three minigrip bags at a Brussels Internet shop in August 2011: one contained 20.3 g of beige powder (with traces of methylone) and two contained 18.7 g and 19.0 g respectively of white powder (EDND, 2011)” (14).

As of 2015, 39 seizures had been reported in the United Kingdom in 2013 and 2 in 2014 (iTrend (23)).

One hundred and seventy-seven drug samples seized by police in Finland between 2011 and 2012 and by customs between 2011 and 2013 were analysed by LC-chemiluminescence nitrogen detection (27). 5-MeO-DALT, which was identified in one sample confiscated at the border, had a purity of 102%. Four other seizures of “herbal product samples” by customs agents contained low levels of 5-MeO-DALT (0.15–0.7%) combined with JHW-018 (5.3–8.5%) and/or JHW-073 (3.8–4.7%) (27).

Between 2013 and 2015 in Italy, 162 police seizures of drugs purchased on the Internet were analysed, 5 samples of which contained 5-MeO-DALT (28). Most of the samples contained only one substance, but others included multiple drugs. For example, some of the samples also contained ethylphenidate and caffeine or a combination of 5-MeO-DALT and methylone ethylone, methedrone, 4-fluoroamphetamine and 5-MeO-MiPT (28).

In a study conducted in the Netherlands, 11 samples that purportedly contained 5-MeO-DALT were purchased on the Internet (8 from the United Kingdom and 3 from France (11)). The purity of the samples was nearly 100%, and they contained predominantly what was advertised (i.e. 5-MeO-DALT).

17. Current international controls and their impact

5-MeO-DALT has not been subject to international control under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

18. Current and past national controls

As described on iTrend (23), 5-MeO-DALT is now scheduled in Class A in the United Kingdom under the 2014 revision of the Misuse of Drugs Act 1971 and as a Schedule 1 compound under the Misuse of Drugs regulations 2001.

Corkery et al. (14) report that “The substance is not scheduled in the USA. As an allyl-substituted tryptamine, 5-MeO-DALT does not come within the generic definition of a (Class A) substituted tryptamine under the Misuse of

Drugs Act 1971 in the UK; it would do if it was an alkyl group. However, it is now a controlled substance in Bulgaria, Finland and Romania (EDND, 2011). In Japan, it is now regulated as a ‘designated substance’ in terms of its importation, synthesis, and sale (Kamata et al. 2010).”

A drug user website (12) reported that 5-MeO-DALT is controlled in several countries, including the Austria, China, Germany, Japan, Sweden, Switzerland and the United Kingdom. It may be controlled as an analogue of MeO-DiPT or 5-MeO-DiPT in the USA, and is a Schedule I controlled substance in Florida (12).

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

None.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of 5-MeO-DALT

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, 7 in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. Thirteen countries opted not to participate in the questionnaire (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 30 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on 5-MeO-DALT

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	10	3
Eastern Mediterranean Region	7	4
Europe Region	22	16
South-East Asia Region	5	1
Western Pacific Region	3	5
Total	62	30

Legitimate use

No country reported approved human medical products or veterinary products containing 5-MeO-DALT.

One country (in the Region of the Americas) reported that 5-MeO-DALT was currently used in medical or scientific research (except as an analytical reference standard), specifically in studies in cell lines (binding, functional assays) and animals.

No country reported that 5-MeO-DALT had industrial or other non-medical or non-scientific use.

No country reported approved therapeutic indications for 5-MeO-DALT.

Epidemiology of non-medical and non-scientific use. Use for psychoactive purposes or recreational drug use

Ten countries (one in the Region of the Americas, seven in the European Region and two in the Western Pacific Region) reported that 5-MeO-DALT was being misused or abused for its psychoactive properties or recreational use.

The most common known route of administration reported was oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	8
Injection	0
Inhalation	1
Sniffing	1
Smoking	1
Don't know	16

The most common known formulation of 5-MeO-DALT reported was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	7
Tablets	1
Liquid for oral use	1
Solution for injection	0
Don't know	15

To the above, countries added:

- “capsules”
- “with other synthetic cannabinoids impregnated on plant materials”.

Seven countries reported the negative health impact of non-medical consumption of 5-MeO-DALT as “serious” or “substantial” (Table 4).

Table 4. Level of negative health impact

Serious	Substantial	Negligible	Don't know
3	4	11	11

One country (in the European Region) commented, “... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers etc.”

Three countries (one in the Region of the Americas, two in the European Region) reported emergency room admissions related to non-medical use of 5-MeO-DALT.

Concerning adverse effects, one country (in the Region of the Americas) commented, “Drug-related delirium, agitation, tachycardia, diaphoresis and combativeness leading to physical restraint and sedation”.

One country (in the Western Pacific Region) reported users of 5-MeO-DALT presenting for drug dependence treatment.

No country reported deaths involving 5-MeO-DALT.

Status of national control and potential impact of international control

Sixteen countries responded that the availability of 5-MeO-DALT is currently regulated in national legislation.

Table 5 lists the main reported activities involving 5-MeO-DALT.

Table 5. Reported illicit activities involving 5-MeO-DALT

Activity	Number of countries
Smuggling from other countries	1
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	0
Trafficking	4
Diversion from legal supply chain	0
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	1

Activity	Number of countries
Internet sales – other, or location of sellers and website unknown	3
Direct sales to people who use the substance	1
Don't know	17

To the above, countries added:

- “trafficking through postal service”.

Six countries (one in the Region of the Americas, three in the European Region, two in the Western Pacific Region) reported seizures (Table 6).

Table 6. Reported seizures with 5-MeO-DALT

Year	No. of seizures
2020	1
2019	7
2018	27
Total	35

Twenty-three countries have the forensic laboratory capacity to analyse samples for 5-MeO-DALT.

One country (in the European Region) commented, “Forensic laboratories have the capacity to analyse 5-MeO-DALT if reference material is available”.

Critical review report: 3-Fluorophenmetrazine (3-FPM)

Executive summary

The patent describing the synthesis of 3-fluorophenmetrazine (3-FPM) was filed in 2011 (1), and 3-fluorophenmetrazine was identified as an NPS in the EMCDDA Early Warning System in 2014 (2). It was purportedly identified on the illegal drug market for the first time in 2014 in Hungary, Sweden and the United Kingdom, and in 2015 in Croatia, Czechia, Denmark, France, Germany, Lithuania, Norway, Romania, Slovenia and Spain (3). It is structurally similar to phenmetrazine (trade name, Preludin), a stimulant that was used in Europe in the 1950s as an anorectic agent until it was withdrawn from the market because of its high abuse potential (4).

3-Fluorophenmetrazine is a fully efficacious releaser at monoamine transporters, where it acts as a substrate rather than a blocker. It is potent at releasing dopamine and norepinephrine, with EC_{50} values of 43 and 30 nM, respectively, and less potent at releasing serotonin (5-HT; 2558 nM (1)). These data are consistent with the activity of the parent compound, phenmetrazine (5). The activity of 3-fluorophenmetrazine is therefore more similar to amphetamine-like “releasers” than to cocaine-like “blockers” (6).

Few fatalities have been attributed to 3-fluorophenmetrazine, although several case reports from around the world have identified the substance in human blood and urine samples. It appears to be used most often in combination with other psychoactive substances, the most common being benzodiazepines. It currently has no legitimate medical or veterinary uses and is available commercially only for research and industrial purposes.

1. Substance identification

A. International Nonproprietary Name (INN)

3-fluorophenmetrazine

B. Chemical Abstract Service (CAS) Registry Number

1350768-28-3

1803562-83-5 (HCl salt)

C. Other chemical names

2-(3-fluorophenyl)-3-methylmorpholine

2-(3-fluoro-phenyl)-3-methyl-morpholine

morpholine, 2-(3-fluorophenyl)-3-methyl-

D. Trade names

3-fluorophenmetrazine
 PAL-593 or PAL593
 1350768-28-3
 UNII-BEV6RF569G
 BEV6RF569G
 SCHEMBL2599533
 BCP18587
 NS00017993
 Q20707008
 Z2379802370

E. Street names

3-FPM or 3-Fpm
 3-FPH
 PAL-593 or PAL593

F. Physical appearance

3-Fluorophenmetrazine is a white, solid, crystalline powder. It was also identified in yellow, blue or green pellets (tablets).

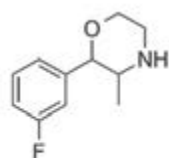
G. WHO review history

3-Fluorophenmetrazine has not been reviewed by the WHO ECDD.

2. Chemistry

A. Chemical name

IUPAC name: 2-(3-fluorophenyl)-3-methylmorpholine; hydrochloride
CA Index name: Not found

B. Chemical structure

3-Fluorophenmetrazine
(3-FPM)

Molecular formula: $C_{11}H_{14}FNO$
 Molecular weight: 195.23 g/mol

C. Stereoisomers

3-Fluorophenmetrazine is a derivative of phenmetrazine. As described by McLaughlin and colleagues (7), “the fluorinated analogs of phenmetrazine

contain two chiral centers which yield the potential for four stereoisomers and two racemic mixtures (i.e., cis- and trans-racemates)". (See Fig. 1 in McLaughlin et al.)

D. Methods and ease of illicit manufacture

As described by McLaughlin and colleagues (7), "The synthesis employed for preparations of 2-, 3- and 4-FPM was adapted from Blough et al (1). The synthesis involved bromination of the fluoropropiophenone starting material (a), yielding α -bromo-fluoropropiophenone (b). This was reacted with ethanolamine to give the intermediate 1-(3-fluorophenyl)-2-((2-hydroxyethyl)amino)propan-1-one (c). Reduction to the alcohol (d) was achieved by reaction with sodium borohydride followed by reaction with concentrated sulfuric acid to aid cyclization and formation of the morpholine ring (e)".

E. Chemical properties

Boiling-point: 280.6 °C \pm 35.0 °C at 760 mm Hg (obtained from an online chemical structure database (8))

F. Identification and analysis

A number of analytical tests have been used to differentiate 3-fluorophenmetrazine from its positional isomers, 2- and 4-FPM, including GC-MS, LC-MS and thin-layer chromatography (7). All the methods successfully differentiated 3-fluorophenmetrazine from its isomers. X-ray crystallography further revealed that the 3-fluorophenmetrazine cation exists in the chair conformation, which is consistent with the conformation of phenmetrazine hydrochloride.

3. Ease of convertibility into controlled substances

No reports of conversion of 3-fluorophenmetrazine into other controlled substances were found.

4. General pharmacology

A. Routes of administration and dosage

Information from drug user forums indicates that 3-fluorophenmetrazine is used orally and by insufflation (9, 10). Oral doses purportedly range between 10 mg and 90 mg or more, common doses being 30–60 mg and strong doses being 60–90 mg. Insufflated doses range between 5 mg and 50 mg or more, common doses being 20–35 mg and strong doses being 35–50 mg. The oral route of administration is reportedly preferred by some users because insufflation of the powder produces a burning sensation (3).

Intravenous use and smoking of 3-fluorophenmetrazine have also been reported, but the amounts used by these routes were not specified (3, 11).

B. Pharmacokinetics

One study described both the *in vivo* metabolism of 3-fluorophenmetrazine in rats and humans and *in vitro* metabolism in wastewater and wastewater-isolated *Pseudomonas putida* (12). In humans, most 3-fluorophenmetrazine was excreted unchanged and in the N-oxide form in urine. In rat urine, aryl hydroxylated metabolites were found, cytochrome (CYP) CYP2A6, CYP2B6 and CYP3A4 being the main CYP isoenzymes involved. The authors concluded that “urinary excretion is assumed to be the main route of excretion for 3-FPM” (12).

Information from drug user forums indicates that the duration of action of 3-fluorophenmetrazine is 4–8 h when used orally, with an onset of action between 20 and 40 min (9, 10). When used via insufflation, the duration of action of 3-fluorophenmetrazine is 3–6 h, with an onset of action within 5 min.

C. Pharmacodynamics

3-Fluorophenmetrazine is potent at releasing dopamine and norepinephrine, with EC₅₀ values of 43 and 30 nM, respectively, and less potent at releasing serotonin (5-HT; 2558 nM (1)). In monoamine release assays with rat brain homogenates, 3-fluorophenmetrazine was 100%, 95%, and 93% effective at dopamine, 5-HT and norepinephrine receptors, respectively, with little activity at 5-HT_{2B} receptors (1).

Radiotracer uptake experiments in human embryonic kidney (HEK293) cells demonstrated that 3-fluorophenmetrazine potently inhibited transporter-mediated uptake of dopamine and norepinephrine, but its potency for inhibiting uptake of serotonin was much lower (13). The ratios of DAT to SERT and norepinephrine transporter (NET) to SERT progressively decreased, whereas the DAT:NET ratio remained relatively constant as the fluorine moved from position 2-, to 3- to 4-.

Rat brain synaptosome assays further revealed that 3-fluorophenmetrazine is a fully efficacious releaser at monoamine transporters, where it acts as a substrate rather than a blocker and, consistent with the data collected in HEK293 cells, is equipotent at DAT and NET and less potent at SERT (13). These data are consistent with the activity of the parent compound, phenmetrazine (14). The activity of 3-fluorophenmetrazine is therefore more similar to that of amphetamine-like “releasers” than to that of cocaine-like “blockers” (6).

5. Toxicology

No formal studies of the toxicology of 3-fluorophenmetrazine have been reported.

6. Adverse reactions in humans

No controlled clinical studies have been reported with 3-fluorophenmetrazine. Adverse reactions to 3-fluorophenmetrazine are expected to be similar to those associated with phenmetrazine as they have similar chemical structures and mechanisms of action. Some case reports of adverse reactions associated with 3-fluorophenmetrazine are available.

A 2016 report from Poland described the presence of 3-fluorophenmetrazine in the blood of a 20-year-old man who was involved in a motor vehicle accident (3). Twenty-four bags of white powder, which he admitted to having used the previous evening, were found in his possession. No other drugs were detected in his blood, and no symptoms were reported on the blood collection form other than a suspicion that he was under the influence of psychotropic drugs. In the introduction to the paper, the authors described short-acting psychoactive effects of 3-fluorophenmetrazine that result in “repetition of doses” over hours or days, with rapid development of tolerance to its effects. Adverse reactions reportedly include anxiety and sweating, as well as jaw clenching and bruxism, while positive effects include “euphoria, stimulation, empathy, increased libido, improvement of concentration and mood, increase of motivation and energy, talkativeness, insomnia and a different perception of music” (3). During the “comedown” period after the drug effects have dissipated, the authors observed a series of unpleasant reactions, including “anxiety, fatigue, depression and irritability” which “appear 9–72 h after the last dose and may persist for up to a week” (3). Benzodiazepines purportedly are taken by users to treat these symptoms. How this information was obtained, however, is not clearly described in the paper.

A 2016 report from Sweden of data from the *Samverkansprojekt kring toxicitetsutredning och riskbedömning av Internetdroger baserat på laboratorieanalyser* (STRIDA) project, described a case-series involving 3-fluorophenmetrazine (11). Between November 2014 and October 2015, eight consultations at the Poison Information Centre were recorded as involving 3-fluorophenmetrazine or “phenmetrazine” intoxication. Of the seven blood and/or urine samples collected from these individuals, six were positive for 3-fluorophenmetrazine and none for phenmetrazine. Thirteen additional cases were identified through the STRIDA project. Blood samples were obtained from all 19 cases, and additional urine samples were obtained from 14 of these cases. 3-Fluorophenmetrazine was identified in 15 of the 19 blood samples and in all 14 urine samples. Other psychoactive substances were present in all the samples, including central nervous system depressants, stimulants and dissociatives, the most commonly co-occurring substances being benzodiazepines. Symptoms commonly associated with acute polysubstance intoxication involving 3-fluorophenmetrazine included tachycardia, reduced level of consciousness,

agitation/anxiety and delirium; less common symptoms included miosis, seizures and hypertension (11). All of the individuals survived the intoxication.

A 2017 report from Poland described one confirmed fatality associated with 3-fluorophenmetrazine (15). Both 3-fluorophenmetrazine (9 ng/mL) and N-ethylhexedrone (37 ng/mL) were measured in the blood of a 27-year-old man who died following a motor vehicle accident, but whether and/or how 3-fluorophenmetrazine contributed to the death is unclear. The article did not specify the country in which the motor vehicle accident occurred or when the blood was collected.

A 2017 paper from the United Kingdom described the clinical course of a 52-year-old man who reportedly injected 3-fluorophenmetrazine intravenously (16). The patient denied recent use of any other non-prescription drugs, but blood or urine drug tests for 3-fluorophenmetrazine or any other substances were not described. The symptoms were characterized as follows: “On the same day, after injecting the drug he started to develop flu-like symptoms feeling feverish with general malaise and tachycardia. Over the next 2 days the symptoms worsened, he started to develop symptoms of shortness of breath, a productive cough of white sputum, central chest pain, fever with rigors and multiple episodes of diarrhea and vomiting. He also complained of cold lower limbs with reduced sensation in both legs”. He developed widespread livedo reticularis and acute kidney injury. All four limbs became ischaemic, and he ultimately required amputation of both legs below the knees.

A 2017 report from the USA described the case of a 34-year-old man who had apparently taken a fatal overdose. He was found dead with hypodermic needles and a plastic bag labelled “5582 mg 3-FPM” nearby (17). Postmortem samples of body fluids, including blood and urine, revealed the presence of 3-fluorophenmetrazine, U-47700, amitriptyline, nortriptyline, diazepam, nordiazepam, temazepam, delorazepam, flubromazolam and amphetamine. The cause and manner of death were characterized as “multiple drug-toxicity; accident” (17).

A 2018 report from Canada described the clinical course of an unresponsive 33-year-old man who presented at an emergency room (18). Family members found him in his bedroom after an hour of “yelling and thrashing”. Empty packages labelled “etizolam 50 mg” and “3-FPM 500 mg” were found on the floor next to him. “A rapid 7-drug urine drug screen was positive for benzodiazepines and indeterminate for amphetamines” (18). During intensive care monitoring on the first day after admission to hospital, abnormal four-limb movements were observed, even after propofol infusion. These abated, however, after administration of lorazepam. Naloxone was ineffective in altering any of these responses. A fever of 38.9 °C was recorded on day 1 after admission and, on

day 5, new but asymptomatic widespread T-wave inversions were noted on the electrocardiogram. All symptoms ultimately resolved before he was discharged on day 7.

7. Dependence potential

A. Animal studies

No preclinical studies of the dependence potential of 3-fluorophenmetrazine in animals were found in the published scientific literature.

B. Human studies

No clinical studies of the dependence potential of 3-fluorophenmetrazine in humans were found in the published scientific literature.

8. Abuse potential

A. Animal studies

No preclinical studies of the abuse potential of 3-fluorophenmetrazine in animals were found in the published scientific literature.

B. Human studies

No studies of the clinical abuse potential of 3-fluorophenmetrazine in humans were found in the published scientific literature.

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

3-Fluorophenmetrazine is not approved for therapeutic use in any country.

10. Listing on the WHO Model List of Essential Medicines

3-Fluorophenmetrazine is not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

3-Fluorophenmetrazine is not approved as a medicinal product in any country.

12. Industrial use

3-Fluorophenmetrazine is available for use in research and for industrial purposes.

13. Nonmedical use, abuse and dependence

Information obtained from drug user forums described 3-fluorophenmetrazine as “habit forming”, “causing psychological dependence” and “tolerance ...

with prolonged and repeated use” (9, 19). but the extent of misuse and abuse of 3-fluorophenmetrazine is unknown. Given the structural similarity between 3-fluorophenmetrazine and phenmetrazine and the pharmacology of 3-fluorophenmetrazine, it is expected to have high potential for nonmedical use.

WEDINOS reported on 30 samples that were either intended to be purchased as 3-fluorophenmetrazine and/or positively identified as 3-fluorophenmetrazine (20).

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

Only one study confirmed the presence of 3-fluorophenmetrazine alone (3) in an individual who was suspected of being under the influence of psychoactive drugs; therefore, the nature and extent of public health problems related to misuse of 3-fluorophenmetrazine is unclear.

15. Licit production, consumption and international trade

3-Fluorophenmetrazine does not appear to have a licit medicinal or veterinary use in any country.

16. Illicit manufacture and traffic and related information

No information was found about illicit manufacture and trafficking of 3-fluorophenmetrazine.

17. Current international controls and their impact

3-Fluorophenmetrazine is not subject to international control under the 1971 United Nations Convention on Psychotropic Substances or the 1961 Single Convention on Narcotic Drugs.

18. Current and past national controls

As described on a drug user website (9), 3-fluorophenmetrazine is controlled in several countries, including the Germany, Isreal, Sweden, Switzerland, United Kingdom.

In the USA, 3-fluorophenmetrazine is not explicitly controlled at national level, though may be controlled as a analogue of phenmetrazine. It was designated as a Schedule 1 controlled substance in Virginia on 16 November 2016, which was to be effective until 10 May 2018. During the 2019 legislative session, the Virginia State legislature was set to vote on a bill that would permanently schedule 3-fluorophenmetrazine as a Schedule 1 substance, but it is unclear whether that occurred.

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

None.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of 3-fluorophenmetrazine (3-FPM)

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, seven in the South-East Asia Region and 10 in the Western Pacific Region). A total of 13 countries opted not to participate in the questionnaire (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 31 countries had information on the substance (Table 1).

Table 1. Number of countries that provided information on 3-fluorophenmetrazine (3-FPM)

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	10	3
Eastern Mediterranean Region	7	4
European Region	21	17
South-East Asia Region	5	1
Western Pacific Region	3	5
Total 92	61	31

Legitimate use

No country confirmed having approved human medical products or veterinary products containing 3-fluorophenmetrazine.

One country (in the Region of the Americas) reported that 3-fluorophenmetrazine was being used in medical or scientific research (excluding use as an analytical reference standard), specifically in cell line studies (binding/functional assays) and animal studies.

One country (in the Region of the Americas) reported that 3-fluorophenmetrazine was used in industrial or other non-medical or non-scientific applications.

No country reported approved therapeutic indications for 3-fluorophenmetrazine.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Thirteen countries reported that 3-fluorophenmetrazine was being misused or abused for its psychoactive properties or recreational use.

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

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	9
Injection	0
Inhalation	0
Sniffing	4
Smoking	4
Don't know	15

The most common known formulation of 3-fluorophenmetrazine reported was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	12
Tablets	4
Liquid for oral use	0
Solution for injection	0
Don't know	14

To the above, countries added:

- “trips, capsule”
- “herbal mixture”.

Eight countries reported the negative health impact of non-medical consumption of 3-fluorophenmetrazine as “serious” or “substantial” (Table 4).

Table 4. Level of negative health-impact

Serious	Substantial	Negligible	Don't know
4	4	10	11

One country (in the European Region) commented, "... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers etc.". Another country (in the Region of the Americas) wrote, "3-FPM was involved in a multiple drug-toxicity fatal overdose (Ellefsen et al., 2017, J Anal Tox 41: 765)".

Three countries (in the European Region) reported admissions to emergency rooms related to non-medical use of 3-fluorophenmetrazine.

With regard to adverse effects, one country (in the European Region) noted "visual, auditory, coloured and moving hallucinations, respiratory distress, strong anxiety, dyspnoea, cyanosis of extremities, scalp pain, absence, paranoia". Another country (in the European Region) noted "hallucinate quite strongly, did not sleep, relatively high heart rate".

No country reported that users of 3-fluorophenmetrazine presented for drug dependence treatment.

Regarding mortality, two countries (in the Region of the Americas and the European Region) reported deaths involving 3-fluorophenmetrazine:

- one fatal case in which other substances were also involved (2017) and
- one fatal case in which it was not reported whether other substances were involved (2019).

Status of national control and potential impact of international control

Nine countries (seven in the European Region, two in the Western Pacific Region) responded that the availability of 3-fluorophenmetrazine is currently regulated under national legislation.

Table 5 shows the main reported activities involving 3-fluorophenmetrazine.

Table 5. Reported illicit activities involving 3-fluorophenmetrazine

Activity	Number of countries
Smuggling from other countries	4
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	0
Trafficking	6
Diversion from legal supply chain	0
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	2
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	0
Don't know	16

To the above, countries added:

- “trafficking through postal services”
- “Internet sales without other information”.

Six countries (one in the Region of the Americas, three in the European Region, two in the Western Pacific Region) reported seizures (Table 6).

Table 6. Reported seizures of 3-fluorophenmetrazine

Year	No. of seizures
2020	21
2019	58
2018	103
Total	182

Twenty-two countries have the forensic laboratory capacity to analyse 3-fluorophenmetrazine.

One country (in the European Region) commented, “Forensic laboratories have the capacity to analyse 3-fluorophenmetrazine if reference material is available”.

Critical review report: 3-Methoxyphencyclidine (3-MeO-PCP)

Executive summary

This critical review is a response to information brought to the attention of WHO that 3-methoxyphencyclidine (3-MeO-PCP) is manufactured by several chemical companies and other producers and case reports demonstrate that ingestion of this new psychoactive compound can lead to severe intoxication and death. User forums give clear warnings, for example, “3-MeO-PCP may be more likely to cause mania, delusions and psychosis than other dissociatives”.

3-methoxyphencyclidine is a controlled substance in at least 12 countries, including Austria, Brazil, Denmark, Germany, Sweden, Switzerland, Turkey and the United Kingdom.

3-methoxyphencyclidine was first synthesized in 1979 and has been available on the grey market since 2010, with wide distribution since 2011. Owing to the short history of human usage (approximately 10 years), only limited information is available on the pharmacological properties, metabolism and toxicity of 3-methoxyphencyclidine.

Chemistry: On the basis of its structure, 3-methoxyphencyclidine is an arylcyclohexylamine and 3-methoxy derivative of PCP, a substance controlled under Schedule II of the 1971 United Nations Convention on Psychotropic Substances. Three positional isomers (2-, 3- and 4-MeO-PCP) have been identified, which can be differentiated by analytical forensic methods. 3-Methoxyphencyclidine can be synthesized by at least one standard procedure within a few days, from standard starting materials, reagents and solvents that can be obtained from chemical companies.

Pharmacology: 3-Methoxyphencyclidine is usually taken orally or nasally, although it may also be smoked and injected. 3-Methoxyphencyclidine is already active in the single milligram range; therefore, accurate dosing may be a problem. Threshold oral doses start at 1 mg and range up to ≥ 30 mg (considered heavy doses). The onset of effects occurs 30–90 min after oral ingestion. The duration is 4–8 h, with a peak effect after 2–3 h. The duration of after-effects, also known as a “hangover” or an “afterglow”, ranges from 4 to 48 h. 3-Methoxyphencyclidine has a much more rapid onset and a shorter duration of effects when vaporized or smoked.

3-Methoxyphencyclidine undergoes extensive metabolism (at least 30 phase-I and -II metabolites can be generated), and its half-life was estimated to be 10–11 h.

Both in vitro and in vivo studies show that 3-methoxyphencyclidine is an NMDA receptor antagonist. 3-Methoxyphencyclidine binds to NMDA receptors more effectively than PCP or ketamine. Like PCP, 3-methoxyphencyclidine also binds to the SERT, and it binds effectively to the σ_1 receptor.

Adverse reactions in humans: Information is available on severe and fatal intoxications from published case reports, from the UNODC Early Warning Advisory (EWA) Tox-Portal and various Internet sources. These reports show that 3-methoxyphencyclidine can cause acute behavioural, emotional, motivational, cognitive and somatosensory and motor changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, acute intoxication can lead to psychotic behaviour, amnesia and emergency department admissions or even death. User forums strongly discourage users from taking this substance at high doses for several days in a row or in combination with other substances that increase the risk of psychosis.

A search of all available information revealed at least 19 cases of severe intoxication that required hospitalization and intensive care. Furthermore, 20 deaths were reported, in at least 7 of which 3-methoxyphencyclidine was determined to be the cause of death. The blood concentrations of 3-methoxyphencyclidine in non-fatal cases ranged from 49 to 350 µg/L and in fatal cases from 50 to 3200 µg/L. This suggests that there is no clear difference between non-fatal and fatal blood concentrations. In most cases of 3-methoxyphencyclidine intoxication, the user had also taken other synthetic or classic drugs.

Dependence and abuse potential: No controlled studies in animals or humans have been reported to assess the dependence or abuse potential of 3-methoxyphencyclidine. According to user reports on online forums, 3-methoxyphencyclidine has greater euphoric properties than other PCP analogues.

Potential therapeutic applications: No information was available.

Extent of public health problems: An estimate of public health problems associated with 3-methoxyphencyclidine is provided by the STRIDA project in Sweden. Over a 21-month period between July 2013 and March 2015, 1243 cases of suspected intoxication with NPS among emergency room or intensive care unit admissions were tested for PCP analogues. In this primarily high-risk population (e.g. psychonauts from the drug scene), 56 (4.5%) patients tested positive for 3-methoxyphencyclidine. Other NPS and/or classical drugs of abuse were detected in most cases (88%), but seven cases were directly related to 3-methoxyphencyclidine as a single substance. The most prominent clinical signs seen in the single-substance 3-methoxyphencyclidine intoxications were hypertension, tachycardia and altered mental state, including confusion, disorientation, dissociation and/or hallucinations. Patients typically required medical care for 1–2 days, and 37% of all cases were graded as severe.

Drug seizures including 3-methoxyphencyclidine have been reported to the EMCDDA by national focal points in Austria, France, Italy, Latvia, Lithuania, Romania, Slovenia and Spain.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available

B. Chemical Abstract Service (CAS) Registry Number

CAS Number: 72242-03-6

C. Other chemical names

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

3-methoxyphencyclidine

3-methoxy PCP

D. Trade names

None

E. Street names

3-methoxyphencyclidine (no other names were used in user forums)

F. Physical appearance

Powder, tablets

G. WHO review history

3-Methoxyphencyclidine has not been pre-reviewed or critically reviewed by the WHO ECDD.

2. Chemistry

A. Chemical name

IUPAC Name: 1-[1-(3-methoxyphenyl)cyclohexyl]piperidine

CA Index name: Not found

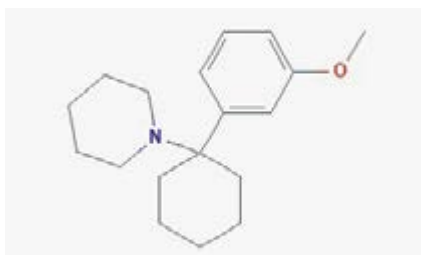
B. Chemical structure

Free base:

Molecular formula: C₁₈H₂₇NO

Molecular weight: 273.412 g/mol

Fig. 1 Structure of 3-methoxyphencyclidine



Source: PubChem

C. Stereoisomers

No stereoisomers of 3-methoxyphencyclidine have been described; however, it has structural (positional) isomers, as shown in Fig. 1.

The structure of 3-methoxyphencyclidine indicates that it is an arylcyclohexylamine and 3-methoxy derivative of PCP, a substance controlled under Schedule II of the 1971 United Nations Convention on Psychotropic Substances. The synthesis of 3-methoxyphencyclidine was first described by Geneste et al. (3). Wallach et al. (2) slightly modified the original synthesis procedure by using the primary amine 3-MeO-PCA as the starting material.

The procedure described by Wallach et al. (2) can easily be adapted by forensic laboratories, but also by chemists who supply the grey market. With this procedure, 3-methoxyphencyclidine can be synthesized within a few days from standard starting materials, reagents and high-performance liquid chromatography (HPLC)-grade solvents that can be obtained from various chemical companies.

D. Chemical properties

Melting-point: 204 °C

Boiling-point: 381 °C

Solubility: Although 3-methoxyphencyclidine is soluble in water, no specific information was available on the absolute amount that is dissolved.

E. Identification and analysis

De Paoli et al. (4) described use of HPLC with MS-MS for the quantification of 3-methoxyphencyclidine in human blood and urine.

Wallach et al. (2) applied a range of analytical methods that enabled discrimination between the positional isomers 3-methoxyphencyclidine and 4-MeO-PCP derived from chemical synthesis.

Michely et al. (5) used LC-high-resolution MS-MS to detect a broad range of 3-methoxyphencyclidine metabolites in urine samples from rats.

To detect 3-methoxyphencyclidine and its metabolites in human urine and blood, Ameline et al. (6) used standard ultra-performance LC-MS (UPLC-MS) and UPLC-MS-MS. They verified their analysis *in vitro* by incubating 3-methoxyphencyclidine with human liver microsomes, which allows production of metabolites, and identified O-demethyl-3-MeO-PCP, piperidine-hydroxy-3-MeO-PCP, O-demethyl-piperidine-di-hydroxy-3-MeO-PCP, piperidine-di-hydroxy-3-MeO-PCP and cyclohexyl-hydroxypiperidine-di-hydroxy-3-MeO-PCP with a retention time of less than 6 min. 3-Methoxyphencyclidine and four of the five metabolites mentioned above were detected in urine and blood samples from two fatal cases (7).

Recently, Nisbet et al. (8) introduced a GC-MS quantification method and analysed more than 20 NPS in whole blood and urine. The detection limit was 0.5 µg/L for 3-methoxyphencyclidine in blood and urine samples. This method

is particularly useful for laboratories that do not have access to LC–MS–MS and for the detection of multiple NPS with different chemical structures in acute fatalities (8).

An old, classical technique for drug identification is the microcrystalline test. In this test, a unique crystalline precipitates when a compound is combined with a specific reagent. Given its high sensitivity and selectivity, microcrystalline testing is a rapid and inexpensive technique for analysing new designer drugs. Quinn et al. (9) described a new microcrystalline test that clearly differentiates and identifies PCP and four of its structural analogues, including 3-methoxyphencyclidine.

3. Ease of convertibility into controlled substances

3-Methoxyphencyclidine is not readily converted into other internationally controlled substances.

4. General pharmacology

A. Routes of administration and dosage

3-Methoxyphencyclidine is usually taken orally or nasally; it may also be smoked or injected. 3-Methoxyphencyclidine is already active in the single milligram range, making accurate dosing difficult. Threshold oral doses start at 1 mg and range up to ≥ 30 mg (considered heavy doses). The onset of effects occurs 30–90 min after oral ingestion. The duration is 4–8 h, with a peak effect after 2 to 3 h. The duration of the after-effects ranges from 4 to 48 h (10). The effects of 3-methoxyphencyclidine have a much more rapid onset and shorter duration when the drug is vaporized or smoked (10). An online forum for people who use psychoactive substances (10) gives a clear warning that “It is strongly discouraged to take this substance in high dosages, for multiple days in a row, or in combination with other substances that increase the risk of psychosis”.

Another online forum (11) provides more detailed information on oral and nasal dosing. The threshold oral doses cited ranged from 1.5 to 3 mg, light doses from 3 to 5 mg, commonly used doses from 5 to 10 mg, strong doses from 10 to 15 mg and a heavy dose is ≥ 15 mg. Threshold nasal doses range from 1 to 2 mg, light doses from 2 to 5 mg, commonly used doses from 5 to 8 mg, strong doses from 8 to 12 mg and a heavy dose is ≥ 12 mg. These narrow dosing ranges indicate that the single-milligram range can make a pronounced difference to the perceived effects and that accurate dosing is problematic.

B. Pharmacokinetics

Michely et al. (5) studied the phase I and II metabolism of 3-methoxyphencyclidine in rats and in human liver microsomes. They also examined the CYP isoenzymes involved. 3-methoxyphencyclidine was administered at a dose of 10 mg/kg body weight for identification of

metabolites and one 1 mg/kg dose corresponding roughly to commonly used doses. 3-Methoxyphencyclidine was extensively metabolized, with 30 phase I metabolites produced via hydroxylation, carboxylation, *O*-demethylation and glucuronidation. Phase II metabolism produced seven glucuronides. The findings of this screening experiment were transferred to a screen in human liver microsomes. *O*-Demethylation and hydroxylation were also observed, and hence five metabolites were detected in both preparations. For 3-methoxyphencyclidine, CYP 2B6 was found to be responsible for aliphatic hydroxylation and CYP 2C19 and CYP 2D6 for *O*-demethylation (5).

Allard et al. (12) applied a molecular networking approach to a large set of MS-MS data. With this *in silico* approach, they were able to identify 12 of the metabolites of 3-MeO-PCP that had been described in the initial biotransformation study by Michely et al. (5). These included seven phase I and five phase II metabolites.

In summary, 3-methoxyphencyclidine undergoes extensive metabolism, and its half-life is estimated to be 11 h. However, the elimination half-life of 3-methoxyphencyclidine was calculated from samples taken from only one case of non-fatal intoxication by repeated sampling over 2 days (13). Nevertheless, this estimated half-life is supported by the findings of Bäckberg et al. (14), who calculated a half-life of about 10 h from two blood samples obtained from one case of intoxication.

C. Pharmacodynamics

Effects *in vitro*

3-Methoxyphencyclidine is an NMDA receptor antagonist. *In vitro* tests have shown that 3-methoxyphencyclidine binds to NMDA receptors more effectively than PCP or ketamine. *In vitro* receptor binding studies by Roth et al. (15) showed that 3-methoxyphencyclidine has a sub-micromolar affinity (inhibitory constant, K_i , 20 nM) for the NMDA receptor, which is greater than that of PCP (250 nM) or ketamine (659 nM). Wallach and Brandt (1) reported a similar K_i of 38 nM for the NMDA receptor.

Mitsuoka et al. (16) developed an immunocytochemical assay based on hippocampal neurons to study NMDA receptor inhibition of PCP analogues and to estimate the inhibitor concentration that reduces activity by half maximal inhibitory concentration (IC_{50}). The inhibitory activity at the NMDA receptor of 3-methoxyphencyclidine ($IC_{50} = 1.51 \mu\text{M}$) was comparable to that of PCP ($IC_{50} = 2.02 \mu\text{M}$).

Roth et al. (15) described K_i determinations, receptor binding profiles and functional assays conducted in a panel of central nervous system receptors and transporters. They found that, like PCP, 3-methoxyphencyclidine also binds to SERT (K_i , 216 nM), whereas a much higher K_i value of 1571 nM for SERT was reported by Wallach and Brandt (1); however, 3-methoxyphencyclidine has no or

low affinity for the DAT or NET. In contrast, both 3-methoxyphencyclidine and PCP inhibit dopamine uptake into synaptosomes, which suggests a functional interaction with the DAT (1). 3-methoxyphencyclidine also binds effectively to the σ_1 receptor, whereas PCP does not.

Importantly, although little discussed in the literature, 3-methoxyphencyclidine shows affinity for σ_1 receptors ($K_i = 42$ nM) (15). Wallach & Brandt (1), however, used the same in vitro experimental conditions and found a higher K_i value of 436 nM on the σ_1 binding site. Although the functional interaction of 3-methoxyphencyclidine with the sigma binding site is not understood, it is noteworthy that the σ_1 receptor is a membrane protein expressed throughout the human body, which acts like an inter-organelle signalling regulator and fine-tunes electrical activity and calcium homeostasis. These regulatory effects may favour cell survival in pathological contexts such as stroke or neurodegenerative diseases. Hence, ligands targeting the σ_1 receptor are undergoing clinical trials for treatment of Alzheimer disease, ischaemic stroke and neuropathic pain (17). It is not known whether the σ_1 receptor activity of 3-methoxyphencyclidine has potential therapeutic implications, and there is so far no experimental or anecdotal evidence to support such a conclusion.

Effects in vivo

NMDA receptor antagonists such as PCP and ketamine interfere with the maximal electroshock seizure test. 3-Methoxyphencyclidine also inhibits tonic hindlimb extension in the maximal electroshock seizure test in mice and rats (1), and the median effective dose (ED₅₀) values are similar to those of PCP and ketamine (18), suggesting that 3-methoxyphencyclidine also acts as an NMDA receptor antagonist in vivo.

5. Toxicology

No published data on the toxicity or the reproductive, carcinogenic or mutagenic potential of 3-methoxyphencyclidine are available.

6. Adverse reactions in humans

Information from published case reports of severe and fatal intoxications, the UNODC EWA Tox-Portal and various Internet sources is summarized below. User experiences between 2011 and 2020 were retrieved from three websites (19–21). 3-Methoxyphencyclidine can cause acute behavioural, emotional, motivational, cognitive and somatosensory and motor changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, acute intoxication can lead to psychotic behaviour and amnesia and require emergency department admission or result in death.

Stevenson & Tuddenham (22) reported a case of severe intoxication with 3-methoxyphencyclidine in Glasgow, Scotland, in a man in his

twenties who had snorted large quantities of 3-methoxyphencyclidine and methylenedioxypropylamphetamine (MDPV). He had also inhaled butane gas. He developed a psychotic state and heard a voice saying “Kill your father”. He immediately attacked his father, who survived the attack only because neighbours heard his screams and called an ambulance. After his arrest, the man experienced visual hallucinations for almost 6 weeks. Despite a previous diagnosis of drug-induced psychosis, he was convicted of attempted murder and sentenced to 4 years in prison (22). MDPV can also induce paranoid psychosis (23); therefore, it cannot be concluded that 3-methoxyphencyclidine was the sole reason for the psychotic state that led to the violent behaviour.

Johansson et al. (13) reported a case of intoxication in a 19-year-old male with a substance use disorder, who required hospitalization. He presented with tachypnoea, tachycardia, hypertension, catatonia and mydriasis. His condition later worsened, with fever and lactic acidosis concomitant with psychomotor agitation and hallucinations. By day 3, all physical parameters were normal and he was discharged from hospital. Four blood samples were taken during his stay, which allowed estimation of the elimination time of 3-methoxyphencyclidine. The concentration was 0.14 µg/g at admission, and the half-life was calculated on an assumption of first-order elimination. From the four samples, the half-life was estimated to be 11 h (13).

The first two cases of intoxication with 3-methoxyphencyclidine in Italy were reported by Bertol et al. in 2017 (24). Two men aged 19 and 21 years were hospitalized in Florence in a comatose state, showing respiratory acidosis, right anisocoria, mydriatic pupils and hypothermia. They recovered within a few hours and reported having consumed a large amount of alcohol and unknown pills. Their blood alcohol concentrations were 2.0 g/L and 1.7 g/L. The presence of 3-methoxyphencyclidine was confirmed and quantified by LC-MS-MS at concentrations in blood and urine of 350 and 6109 ng/mL in one patient and 180 and 3003 ng/mL in the other (24).

3-Methoxyphencyclidine was first detected in Spain in poly-drug poisoning of two patients in Ibiza in 2018. The urinary concentrations of 3-methoxyphencyclidine were 9645 and 560 ng/L, respectively (25).

Thornton et al. (26) described a case in the USA of a 27-year-old man with a medical history of attention deficit hyperactivity disorder, bipolar disorder and hypertension. He was admitted to hospital 8 h after insufflation of an Internet-obtained product. His physical parameters were relatively normal, except for hypertension. He responded to questions in a delayed manner and had complete amnesia about the preceding 8–12 h. Blood samples were taken at 0, 2 and 3 h after arrival at hospital. Quantitative analysis with LC-MS-MS yielded 3-methoxyphencyclidine concentrations of 167 ng/mL, 131 ng/mL and 90 ng/mL, which would imply a more rapid half-life than that reported in references 13 and 14. Methoxetamine was also detected in all three samples (26).

A further case report from the USA described 3-methoxyphencyclidine intoxication in a 27-year-old man who was found unconscious in his car by the police (27). On arrival at hospital, the patient was awake and expressed delusions, including that he “was an alien with green blood”. He had a medical record of schizophrenia and auditory hallucinations secondary to noncompliance with risperidone therapy. His urine was positive for 3-methoxyphencyclidine (27).

Two cases of severe intoxication with 3-methoxyphencyclidine that required hospitalization were reported from Prague, Czechia, by Zidkova et al. (28). Two men had consumed a powdered drug with alcohol at a party. After 15 min, they began experiencing disorientation, hallucinations and spastic leg postures. Following admission to hospital, one patient remained hypertensive and tachycardic and displayed prominent signs of psychosis. After 24 h in intensive care, the patient was discharged but reported complete amnesia regarding the period of intoxication. The other patient, a 40-year-old man, was admitted to intensive care with cramps and a deteriorating state of consciousness. He was discharged after regaining normal clinical status after 8 h. This patient also reported complete amnesia of the episode. 3-Methoxyphencyclidine serum levels 2 h after drug ingestion were 49 ng/mL and 66 ng/mL in the two patients (28).

A case of intoxication in France was reported by Allard et al. (12). A 17-year-old man was admitted to the emergency department with altered consciousness and agitation. He had a history of substance abuse, and a small bag of white powder labelled “3-MeO-PCP” was found in his belongings. The main complication was rhabdomyolysis. The patient was discharged from hospital after 2 days (12, 29). The concentrations of 3-methoxyphencyclidine in blood and urine were 71.1 ng/mL and 706.9 ng/mL, respectively. He returned to the emergency department 7 days later after sniffing 50 mg of 3-methoxyphencyclidine (12).

Another case in France was described by Kintz et al. (30). A 39-year-old woman with a history of drug use (heroin, cannabis, cocaine and γ -hydroxybutyric acid [GHB]) was found dead at home after being killed by her partner, who was under the influence of various drugs. Femoral blood, urine and hair were collected at autopsy. 3-Methoxyphencyclidine or 4-MeO-PCP was identified in the femoral blood. After differentiation of the two structural (positional) isomers with GC-MS, the presence of 3-methoxyphencyclidine was confirmed. The concentrations of 3-methoxyphencyclidine were 63 and 94 ng/mL in femoral blood and urine, respectively. The hair sample also tested positive for 3-methoxyphencyclidine on 3 × 2-cm segments at 731, 893 and 846 pg/mg, indicating long-term use of the drug (30).

In the UNODC EWA Tox-Portal, five cases of intoxication requiring clinical admission were reported from Finland and Italy. Blood concentrations of up to 49 ng/mL of 3-methoxyphencyclidine were measured, and no other drugs were detected. In five postmortem analyses reported from Finland and the USA,

3-methoxyphencyclidine concentrations of up to 299 ng/mL were measured. In three of the five cases, other drugs, such as cocaine and U-47700, were also detected. It is assumed that the intoxication and fatal cases reported in the UNODC EWA Tox-Portal do not overlap with those described in the literature.

A fact sheet on 3-methoxyphencyclidine compiled for the Belgian Early Warning System is available online (31), in which the Belgian National Focal point reported that one death associated with 3-methoxyphencyclidine had occurred in June 2017. Another death was reported by the Portuguese Focal Point on 14 October 2016, in which postmortem femoral blood analysis revealed 0.525 mg/L of 3-methoxyphencyclidine and several other drugs. There were reports of at least three cases of overdose with 3-methoxyphencyclidine in Norway in 2011 that required hospitalization.

In summary, a search of information worldwide showed at least 19 cases of severe intoxication that required hospitalization and intensive care. Furthermore, 21 deaths were reported in at least seven of which 3-methoxyphencyclidine was determined to be the cause of death. Blood concentrations of 3-methoxyphencyclidine in the 16 non-fatal cases ranged from 49 to 350 µg/L, and those in fatal cases ranged from 50 to 3200 µg/L. This suggests that a clear distinction cannot be made between toxic and fatal concentrations. Importantly, most of the non-fatal and fatal intoxications were associated with use of other synthetic drugs or classic drugs. Fourteen fatal cases are described in more detail below.

Bakota et al. (32) reported a fatal case in the USA. A 29-year-old man with a history of illicit drug use was found dead in his bed, with a bag of white powder labelled “fumaric acid 5 G” purchased on the Internet from China next to him. His parents reported that he had been hospitalized on several occasions after using this substance and had a medical history of attention deficit disorder and depression. A concentration of 139 µg/L 3-methoxyphencyclidine was measured in his blood by a quantitative LC-MS-MS method. Diphenhydramine and amphetamine (<0.10 mg/L) were also detected, and the toxicological conclusion was that the cause of death was combined 3-methoxyphencyclidine, diphenhydramine and amphetamine toxicity (32).

Mitchell-Mata et al. (33) reported the first two deaths involving 3-methoxyphencyclidine in Washington State (USA). Case 1 was a 21-year-old male university student who had recently been discharged from a drug treatment centre who was found naked and unresponsive. Case 2 was a 58-year-old man with a history of significant health problems and of previous drug use that included opiates and methamphetamine. GC-MS was used to quantify 3-methoxyphencyclidine concentrations in blood, which were 0.63 and 3.2 mg/L, respectively. Methamphetamine was also detected in the blood of one of the men, while the other tested positive for ethanol, bupropion, delorazepam, paroxetine

and mitragynine. The toxicologists concluded that the cause of death in both cases was acute intoxication due to poly-drug consumption (33).

Johansson et al. (13) reported seven deaths involving 3-methoxyphencyclidine in Sweden. The first death occurred in March 2014 and the seventh in June 2016. The cases involved six men and one woman in their twenties and thirties. All had psychiatric problems and/or ongoing drug use. Intoxication was considered to be the cause of death in six of the cases and asphyxia in one. The femoral blood concentrations of 3-methoxyphencyclidine ranged from 0.05 mg/g to 0.38 mg/g. Six cases involved intoxication with several new synthetic compounds or classical drugs such as buprenorphine, fentanyl and amphetamine. 3-Methoxyphencyclidine was considered to have contributed to death in three of six cases. In one case that involved only 3-methoxyphencyclidine, a 27-year-old man was found dead at home in the bathtub. He had a history of substance use and regularly ordered hallucinogenic drugs online. Autopsy revealed some swelling of the brain, pulmonary oedema and burns on the head, arms, torso and legs due to hot water. The cause of death in this case was certified as intoxication with 3-methoxyphencyclidine (13).

Ameline et al. (6) described two fatal cases in France. Case 1 was a 39-year-old woman with a history of illicit drug use who was found dead due to suspected family violence (see also 30). Case 2 was a 41-year-old man with a history of substance use who was also found dead at home (7). 3-Methoxyphencyclidine and its metabolites were quantified by UPLC-MS-MS in samples of urine and blood. In case 1, 3-methoxyphencyclidine was identified in femoral blood and urine at concentrations of 63 and 94 ng/mL, respectively. In case 2, 3-methoxyphencyclidine was identified in femoral blood and urine at concentrations of 498 and 16 700 ng/mL, respectively (6).

The first fatal case of 3-methoxyphencyclidine intoxication in the Netherlands was reported by de Jong et al. in 2019 (34). A man in his mid-thirties was found dead at a lake. He had a medical history of amphetamine and cannabis addiction and had taken “ant poison” (“Thrive Soluble”), which was sold on the Internet as a product “not for human use”. The urine drug test was positive for tetrahydrocannabinol and cocaine. The blood ethanol concentration was 1.2%. 3-Methoxyphencyclidine was quantified by UPLC-MS-MS, and the serum and blood concentrations were 123 µg/L and 152 µg/L, respectively (34).

7. Dependence potential

A. Animal studies

No information available

B. Human studies

No information available

8. Abuse potential

A. Animal studies

Abiero et al. (35) provided some indirect evidence that the structural isomer 4-MeO-PCP produces rewarding (measured by conditioned place preference) and reinforcing effects (measured by different self-administration schedules) through activation of the mesolimbic dopamine reward pathway and alteration of accumbal CREB, deltaFosB and BDNF levels, three molecules that mediate the reinforcing effects of drugs of abuse. As 4-MeO-PCP is a less active structural isomer of 3-methoxyphencyclidine, it is likely that 3-methoxyphencyclidine produces conditioned place preference, is self-administered in rats and activates the reward pathway.

B. Human studies

According to various drug user forums, 3-methoxyphencyclidine is reported to have greater euphoric properties and be “mentally clearer” than other PCP analogues.

Two case reports (12, 30) point to long-term use of the drug, which was confirmed in one of the cases by positive hair testing (30).

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

No information available

10. Listing on the WHO Model List of Essential Medicines

3-Methoxyphencyclidine is not on the 20th WHO Model List of Essential Medicines or the 6th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

3-Methoxyphencyclidine has never been marketed as a medicinal product.

12. Industrial use

3-Methoxyphencyclidine has no industrial use.

13. Nonmedical use, abuse and dependence

See sections 6 and 7.

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

An estimation of public health problems associated with 3-methoxyphencyclidine is provided by the STRIDA project (a collaborative project between the Swedish Poisons Information Centre and the Karolinska Institute, which

monitors cases of acute intoxication related to NPS from Sweden). Over a 21-month period between July 2013 and March 2015, 1243 samples from cases of suspected NPS intoxication originating from emergency room or intensive care unit admissions were tested for PCP-analogues (14). During this period, 56 (4.5%) patients tested positive for 3-methoxyphencyclidine and 11 (0.9%) for the PCP-analogue 4-MeO-PCP; 8 of these cases involved both substances. The 59 patients were aged 14–55 years (median: 26 years), and 51 (86%) were men. Other NPS and/or classical drugs of abuse were detected in most cases (88%), but seven cases were directly related to 3-methoxyphencyclidine as a single substance. The most prominent clinical signs seen in the cases in which 3-methoxyphencyclidine alone had led to intoxication were hypertension, tachycardia and altered mental status, including confusion, disorientation, dissociation and/or hallucinations. Patients typically required medical care for 1–2 days, and 37% of all cases were graded as severe. In addition to standard supportive therapy, half of the patients were treated with benzodiazepines and/or propofol (14).

In a report from the USA on intoxication with Black Mamba (which is sold as a synthetic cannabinoid), three of eight cases also tested positive for 3-methoxyphencyclidine, with concentrations of up to 114 ng/mL measured in urine samples (36).

Hearne and van Hout (2016) performed systematic Internet searches with the terms “synthetic dissociative” and “3-MeO-PCP”, in combination with “forum”. More than 50 000 hits were obtained. After screening of user trip reports and forums, threads from seven drug forum websites were analysed by content analysis. Consistent information was found on the theme “Advice on administering 3-methoxyphencyclidine in combination with other drugs”. Mixing with other illicit drugs such as heroin, MDMA and cocaine was not advised in most cases. Mixing of 3-methoxyphencyclidine with opiates was considered particularly risky because of potential respiratory depression from the opiates, the anaesthetized state and the feeling of a near-death experience, commonly known as the “k-hole” (37), induced by 3-methoxyphencyclidine. Forum members advised against combinations of different types of NPS with 3-methoxyphencyclidine, particularly because some of these compounds were untested and had unpredictable qualities (38).

15. Licit production, consumption and international trade

Not applicable.

16. Illicit manufacture and traffic and related information

Several reports of drug seizures containing 3-methoxyphencyclidine have been reported to the EMCDDA by national focal points in Austria, France, Italy, Latvia, Lithuania, Romania, Slovenia and Spain (31).

17. Current international controls and their impact

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

18. Current and past national controls

Legal status of 3-methoxyphencyclidine (information from references 10, 39): 3-Methoxyphencyclidine is currently controlled in at least 14 countries, including Austria, Belgium, Brazil, Canada, Denmark, Germany, Italy, Japan, Poland, Singapore, Sweden, Switzerland, Turkey and the United Kingdom.

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

No data.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of 3-methoxyphencyclidine

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, seven in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. A total of 13 countries opted not to participate in the questionnaire (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 31 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on 3-methoxyphencyclidine

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	10	3
Eastern Mediterranean Region	7	4
European Region	21	17
South-East Asia Region	5	1
Western Pacific Region	3	5
Total 92	61	31

Legitimate use

No country reported approved human medical products or veterinary products containing 3-methoxyphencyclidine.

One country (in the Region of the Americas) reported that 3-methoxyphencyclidine was currently used in medical or scientific research (excluding use as an analytical standard), specifically in cell line studies (binding/functional assays) and animal studies.

No country confirmed that 3-methoxyphencyclidine is being used in industrial or other non-medical or non-scientific use.

No country reported approved therapeutic indications for 3-methoxyphencyclidine.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Fifteen countries reported that 3-methoxyphencyclidine is being misused or abused for its psychoactive properties/recreational use.

The most common known route of administration reported was sniffing followed by oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	7
Injection	0
Inhalation	0
Sniffing	9
Smoking	1
Don't know	15

To the above, one country added:

- “plugged (rectally)”.

The most common known formulation of 3-methoxyphencyclidine reported was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	14
Tablets	1
Liquid for oral use	1
Solution for injection	0
Don't know	13
Don't know	15

To the above, countries added:

- blotting paper
- plant matter.

Ten countries reported the negative health impact of non-medical consumption of 3-methoxyphencyclidine as “serious” or “substantial” (Table 4).

Table 4. Level of negative health-impact

Serious	Substantial	Negligible	Don't know
3	7	9	10

One country (in the Western Pacific Region) added, “The social harm caused by 3-MeO-PCP is substantial”. Another country (in the European Region) remarked, “... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centres etc.”

Five countries (in the European Region) reported emergency room admissions related to non-medical use of 3-methoxyphencyclidine.

With regard to adverse effects, one country (in the European Region) noted, “speech disorders, transient gait disturbances, mystical delirium lasting a few hours, behaviour disturbances, delirium, auditory and visual hallucinations, hypertonic crises with eye revulsion, dissociation, mydriasis, tachycardia.”. Another (in the European Region) listed, “High blood pressure, tachycardia, neurological manifestations”. A third country (in the European Region) noted, “plucky, tense, disoriented, fever”.

No country reported that users of 3-methoxyphencyclidine presented for drug dependence treatment.

Regarding mortality, only three countries (one in the Region of the Americas, two in the European Region) reported deaths involving 3-methoxyphencyclidine:

- one fatal case in which other substances were also involved (2020)
- one fatal case in which other substances were also involved (2019)
- three fatal cases in which other substances were also involved (2017).

Status of national control and potential impact of international control

Fifteen countries reported that the availability of 3-methoxyphencyclidine is currently regulated under national legislation.

Table 5 shows the main reported activities involving 3-methoxyphencyclidine.

Table 5. Reported illicit activities involving 3-methoxyphencyclidine

Activity	Number of countries
Smuggling from other countries	5
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	1
Trafficking	5
Diversion from legal supply chain	0
Internet sales – seller or website located in country	2
Internet sales – from abroad to buyers in country	1
Internet sales – other, or location of sellers and website unknown	5
Direct sales to people who use the substance	2
Don't know	14

To the above, countries added:

- trafficking through postal service
- Internet sales (without other information)
- probably drug dealing.

Twelve countries reported seizures (Table 6).

Table 6. Reported seizures of 3-methoxyphencyclidine

Year	No. of seizures
2020	31
2019	84
2018	199
Total	314

Twenty-four countries have the forensic laboratory capacity to analyse 3-methoxyphencyclidine.

One country (in the European Region) commented, “Forensic laboratories have the capacity to analyse 3-MeO-PCP if reference material is available.”

Critical review report: Diphenidine

Executive summary

This critical review was proposed in response to information brought to WHO's attention that the legal status of diphenidine is currently a grey area. This drug is easily obtainable online and is manufactured by several chemical companies. Case reports have shown that ingestion of this new psychoactive compound can lead to severe intoxication and death.

Diphenidine is a dissociative substance of the 1,2-diarylethylamine class. The first report of its synthesis was in 1924, but its recreational use was not reported until 2014. As the history of human use of diphenidine is so short (approximately 7 years), little is known about its pharmacological properties, metabolism or toxicity.

Diphenidine is an NMDA receptor antagonist, with affinity to the binding site similar to that of ketamine. The two enantiomers of diphenidine differ in their ability to block the NMDA receptor: the (S)-enantiomer has a 40 times higher affinity for the receptor than the (R)-enantiomer. Diphenidine is structurally related to 2-methoxydiphenidine.

Diphenidine has dissociative ketamine-like effects at doses starting at around 50–100 mg when administered by the oral or parenteral route. Subjective effects include depersonalization and disconnective effects. It can induce euphoria, but users of diphenidine also describe it as an unpleasant experience. Diphenidine can induce a hallucinogenic state known as “dissociative anaesthesia”, which can lead to a feeling of being detached from the body. The duration of action is reported in online forums and published case reports to be 2–8 h.

Recent case reports have described the detection of diphenidine and noted an association with acute ketamine/PCP-type toxicity and deaths. Published reports of four fatal cases associated with diphenidine mainly involved multiple substances. Most scientific publications on diphenidine date from 2014–2018. The lack of recent publications suggests that there has been less scientific interest (and most likely no recent fatal cases) in the past two years.

Diphenidine has been studied and patented as one of a group of 1,2-diarylethylamines being considered as treatment for neurotoxic injuries. There is no experimental evidence for this potential therapeutic application, although some anecdotal user experience indicates antidepressant effects.

In summary, diphenidine is not approved for any medical or veterinary use. It is used for recreational purposes mainly in Europe, Japan and the USA. It is available on the Internet in powder form for oral administration, smoking,

vaporization or nasal application. Since it first appeared on the drug market in 2013, seizures have been reported around the world, and its use has resulted in several cases of severe intoxication and death, which have led to its scheduling in Canada, Germany and the United Kingdom.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available

B. Chemical Abstract Service (CAS) Registry Number

36794-52-2

C. Other chemical names

diphenidine, DPD, 1-(1,2-diphenylethyl)piperidine, 1,2-DEP

D. Trade names

Not available

E. Street names

Although it has no common street names, diphenidine was sold in Japan in 2014 as a herbal mixture with white powder under the name “Aladdin Spacial Edition”. The seized material had a high content of diphenidine in the presence of 5-fluoro-AB-PINACA (1).

F. Physical appearance

Powder, tablets

G. WHO review history

Diphenidine has not been pre-reviewed or critically reviewed by the WHO ECDD.

2. Chemistry

A. Chemical name

IUPAC name: (\pm)-1-(1,2-diphenylethyl)piperidine

CA Index name: Not available

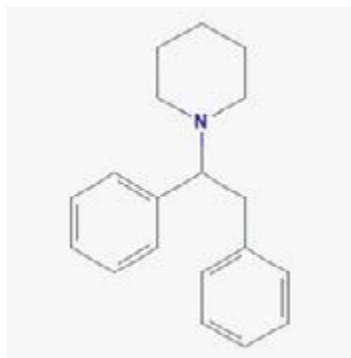
B. Chemical structure

Free base:

Molecular formula: C₁₉H₂₃N

Molecular weight: 265.4 g/mol

Fig. 1. Structure of diphenidine



Source: PubChem.

C. Stereoisomers

Diphenidine is chiral. Two studies reported large differences in NMDA receptor affinity between the two enantiomers of diphenidine: (+)-(S)-diphenidine showed 40 times higher affinity than the (–)-(R)- enantiomer (2, 3). These pronounced differences require chiral separation methods.

D. Methods and ease of illicit manufacturing

Diphenidine was first synthesized in 1924 by Christiaen (4) with a modified Bruylants reaction. Since then, other publications have described the preparation and analytical characterization of diphenidine. For example, Wallach et al. published a detailed description of the synthesis of diphenidine (5). The starting material is 1,2-diphenylethanamine, which is a precursor for the synthesis of (±)-1-(1,2-diphenylethyl)piperidine. The two separated enantiomers of 1,2-diphenylethylamine can also be used as precursors for synthesis of the isomers, (S)- and (R)-1-(1,2-diphenylethyl)piperidine (3), which allows production of high-potency (+)-(S)-diphenidine.

In general, diphenidine can be synthesized within a few days from commercially available 1,2-diphenylethanamine followed by reaction with the corresponding dibromoalkane (5). All reagents and HPLC-grade solvents can be obtained without restriction from chemical companies.

E. Chemical properties

Melting point: 210 °C

Boiling-point: 351.3 ± 11.0 °C at 760 mm Hg

Solubility: Diphenidine is soluble in organic solvents such as ethanol (30 mg/ mL), dimethyl sulfoxide (30 mg/mL) and dimethyl formamide (50 mg/ mL). An organic solvent-free aqueous solution of diphenidine HCl can be prepared by directly dissolving the crystalline solid in aqueous buffers (such as phosphate-buffered saline at pH 7) (7).

F. Identification and analysis

The available methods for the determination of diphenidine in biological materials were summarized by Katselou et al. (6). The first method was described by Kudo et al. (8), who used LC–MS–MS to determine diphenidine in blood and urine samples. They reported a limit of detection of 1 ng/mL. The method was verified in postmortem biological fluids (8). At the same time, diphenidine was detected for the first time in Europe in seized materials that were analysed by GC–MS in a forensic laboratory in Italy between 2013 and 2015 (9). GC–MS can be used both as a general screening method and for quantification of diphenidine and related compounds in seized bulk material (10). A similar method to that described by Kudo et al. (8) was used by Hasegawa et al. (11) to detect and quantify diphenidine in blood, urine and seized bulk material.

Minakata et al. (12) published a description of a matrix-assisted laser desorption/ionization–quadrupole TOF–MS method for the determination of diphenidine and its metabolites in blood and urine. The quantification range was 3–100 ng/mL. This method was verified with postmortem samples of blood and urine (12).

The presence of both diphenidine and the synthetic cannabinoid 5-fluoro-AB-PINACA was identified in a herbal product in Japan by both GC–MS and ESI–MS–MS. The content of diphenidine in the herbal product was as high as 289 ± 23.2 mg/g, which exceeds even very high doses of this drug, especially when it is smoked or vaporized (1). High-resolution ESI–MS can also be used to differentiate the enantiomers of diphenidine (5).

Salomone et al. (13) reported a new ultra-high-pressure-LC–MS–MS method to detect diphenidine in hair samples. They used this method to re-examine 54 hair samples that had tested negative during regular drug screening. Six of the samples tested positive for diphenidine. Diphenidine was also detected in a hair sample by a similar approach 49 days after a single administration of diphenidine (14).

3. Ease of convertibility into controlled substances

Diphenidine is not readily converted into other internationally controlled substances.

4. General pharmacology

A. Routes of administration and dosage

Diphenidine is psychoactive when administered by the oral and parenteral routes (15). According to reports on user forums, active oral doses start at around 50–100 mg; doses of more than 150 mg are described as strong. The duration of action has been reported by users on online forums as 3–6 h and 2–5 h (16, 17).

The onset of effects occurs 15–30 min after oral ingestion. The duration of after-effects, a “hangover” or an “afterglow” ranges from 4 to 24 h.

The effects of diphenidine are reported to have a much more rapid onset and a shorter half-life when it is vaporized or smoked. Vaporization apparently requires as little as 20% of a standard oral dose to produce the same effect (18). Common doses used for smoking are between 20 and 40 mg, whereas strong doses range from 40 to 55 mg and heavy ones are greater than 55 mg. The onset of effects after inhalation occurs within 30–90 s, with a peak effect between 0.5 and 2 h and an after-effect lasting 2–5 h.

B. Pharmacokinetics

Wallach & Brandt (15) summarized the pharmacokinetics of diphenidine. In short, diphenidine is a tertiary amine and a weak base, which explains its high lipophilicity, and high concentrations of diphenidine have been detected in fat tissue of postmortem samples. This is supported by the findings of Hasegawa et al. (11), who reported on a fatal case involving diphenidine and the synthetic cannabinoid receptor agonists 5-F-AMB and AB-CHMINACA. They detected diphenidine in several solid tissues and found the highest concentration in adipose tissue (11).

Wink et al. (19) studied the phase I and II metabolism of diphenidine in rat and human liver microsomes. Diphenidine was administered at a dose of 20 mg/kg body weight to identify the metabolites and one 1-mg/kg dose (by gastric intubation), which corresponds roughly to users' doses. The rats were housed in metabolism cages for 24 h, and urine samples were collected. Diphenidine was found to be extensively metabolized by various pathways. The metabolites identified in rat urine indicated the following metabolic pathways (19): “mono- and bis-hydroxylation followed by methylation of one of the hydroxy groups, N,N-bis-dealkylation, and combinations of them as well as glucuronidation”. A metabolic screen was conducted of human liver microsomes to determine whether the metabolites detected in rat urine are also formed in humans. The mono- and bis-hydroxy as well as the oxo- metabolites were also detected in this preparation (19). The authors also studied the involvement of the CYP isoenzymes. CYP1A2, CYP2B6, CYP2C9 and CYP3A4 were all found to be capable of forming the initial metabolites (19).

Two major metabolites identified in the metabolic screen by Wink et al. (19) were also detected in blood and urine samples from a fatal case involving diphenidine. The metabolites resulted from mono-hydroxylation of the piperidine ring and mono-hydroxylation of the phenyl ring (12). In another fatal case involving diphenidine and the synthetic cannabinoid receptor agonist 5F-ADB, five different mono- and dihydroxy metabolites of diphenidine were detected in blood and urine, and analysis of the metabolic pathway of diphenidine indicated that hydroxylation is possible on any of the ring moieties (20).

C. Pharmacodynamics

Effects in vitro

Diphenidine is an NMDA receptor antagonist. Electrophysiological studies suggest that diphenidine provides receptor antagonism via an uncompetitive channel-blocking effect (21). However, diphenidine induces its specific subjective and mind-altering effects by inhibiting not only NMDA receptors but also monoamine neurotransmitter transporter activity (especially of the DAT); interactions with opioid and sigma receptors and active metabolites may also contribute to the effects of diphenidine (16, 22).

Diphenidine blocks NMDA receptor-mediated field excitatory postsynaptic potentials (fEPSPs) in rat hippocampal slices (21). This is consistent with the effects of a channel blocker such as MK-801, which is the gold standard for uncompetitive NMDA receptor blockade. Several related compounds and known NMDA receptor antagonists were recently studied to determine their effects on NMDA receptor-mediated fEPSPs. The rank order of potency for inhibition was found to be MK-801 > PCP > diphenidine > 3-MXP > 2-MXP > ketamine > memantine (21). This order closely paralleled NMDA receptor affinities (15, 21).

Two studies reported the K_i values at the NMDA receptor for diphenidine as 18 nM (21) and 39 nM (2), respectively.

As the potency of inhibition of monoamine reuptake is up to two orders of magnitude less than that of the NMDA receptor, the contribution of dopamine, serotonin and norepinephrine to the drug effects of diphenidine is suggested to be less relevant. However, a contribution, particularly of the DAT $K_i = 317$ nM (21) and $K_i = 230$ (23) to the potential abuse liability of this drug, especially in cases of high doses or overdoses, cannot be excluded.

Importantly, although little discussed in the literature, diphenidine shows affinity for sigma receptors (σ_1 , $K_i = 290$ nM and σ_2 , $K_i = 193$ nM (21)). Although the functional interaction of diphenidine with the sigma binding sites is not known, it is noteworthy that the σ_1 receptor is a membrane protein expressed throughout the human body, which acts like an inter-organelle-signalling regulator and fine-tunes electrical activity and calcium homeostasis.

Effects in vivo

As with classical NMDA receptor antagonists such as MK-801, a high dose of diphenidine (20 mg/kg) administered subcutaneously significantly disrupted prepulse inhibition (PPI) of the startle reflex in rats (15, 21). PPI of the startle reflex is an established measure of sensorimotor gating. In particular, NMDA receptors in the hippocampus play a critical role in the regulation of PPI. PPI disruption caused by NMDA receptor antagonists may reflect alterations in information processing that contribute to their dissociative effects (25). However, diphenidine was less potent than ketamine in these PPI experiments (26), which was unexpected in view of its higher NMDA receptor affinity (21). This

suggests that pharmacokinetics and/or active metabolites influence the potency of diphenidine in vivo. The reduced potency in PPI is consistent with reports of the drug's relatively low potency in humans; common doses of diphenidine are 50–100 mg.

Other behavioural effects of diphenidine were noted by Wallach & Brandt (15). Stereotypy was induced in rats following administration by three different routes. An ED₅₀ of 220 nmol (versus PCP 50 nmol) was calculated after intracerebroventricular infusions of diphenidine; the ED₅₀ was 2.9 mg/kg after subcutaneous administration and 2.0 mg/kg after intraperitoneal injection (2). The (+)-(S)enantiomer of diphenidine was more potent in eliciting stereotypic behaviour (intracerebroventricular, ED₅₀ = 120 nmol/rat; subcutaneous, ED₅₀ = 0.78 mg/kg; intraperitoneal ED₅₀ = 2.1 mg/kg), which is consistent with a slightly higher NMDA receptor affinity than the racemate (2).

5. Toxicology

No data are available on the toxicity or the reproductive, carcinogenic or mutagenic potential of diphenidine. The only available data are an estimated median lethal dose in mice reported as 325 mg/kg after subcutaneous administration (27).

6. Adverse reactions in humans

Information from published case reports, the UNODC EWA Tox-Portal and various Internet sources (listed in Annex 2) was reviewed. It shows that diphenidine can cause acute behavioural, emotional, motivational, cognitive and somatosensory and motor changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, acute intoxication can lead to emergency department admissions or even death. Experiences described by 14 people who had taken diphenidine between 2014 and 2018 were retrieved from Erowid (28), and an additional 5 reports of user experiences were retrieved from Psychonautwiki (18).

The reports by drug users show that the effect of diphenidine varies greatly from person to person and also with the dose (doses usually range from 50 mg to more than 150 mg). Effects after oral use occur within 15–30 min; however, when diphenidine is smoked, effects occur within seconds. The effect also heavily depends on the set and setting, which is a common drug-use phenomenon. At higher doses (from 150 mg orally), hallucinations and out-of-body experiences can occur. Acute effects of diphenidine often include stimulation and, at high doses, sedation and amnesia. At lower doses, intoxication is sometimes compared to the effects of ethanol. At higher doses, perceptual alterations may occur in all sensory modalities. Hallucinations are particularly common. Cognitive effects include depersonalization, derealization and loss of ego boundaries as well as

altered thought patterns, delusions and paranoia (15, 16). Overall, and especially at higher doses, diphenidine has ketamine-like effects, and this conclusion is supported by their similar pharmacological properties. Several reports from diphenidine users have described it as an unpleasant experience.

Four diphenidine-related deaths (all with multidrug toxicity) and heavy intoxications have been reported in Europe and Japan. Fourteen nonfatal cases of diphenidine-related intoxication were recorded in Sweden in 2014 (29), and toxicological analyses confirmed the presence of diphenidine in blood (2–262 ng/mL) and urine (8–19 000 ng/mL). In 12 of the 14 cases, other NPS and classical drugs of abuse were also detected in blood and urine samples. The following clinical signs were reported: hypertension, tachycardia, anxiety and altered mental status, including confusion, disorientation, dissociation and/or hallucinations. Nystagmus, meiosis and muscle rigidity were also seen (29). The patients recovered within 1–3 days after hospitalization. Three patients had plastic bags containing a white powder labelled “diphenidine”. Analysis of the powder by LC–MS–MS and NMR spectroscopy confirmed the presence of diphenidine, but no other psychoactive substances were detected (29).

Gerace et al. (30) published a case report of a 30-year-old man with a previous history of drug addiction who was found in a confused, agitated state and was unable to communicate. Next to him was a small plastic bag labelled “Diphenidine 1 g”. The content of the bag was analytically confirmed by GS/MS. He had tachycardia, was agitated and disoriented, with miotic non-reactive pupils. He was admitted to the emergency room and sedated with midazolam, diazepam and haloperidol. The patient regained consciousness within 90 min but was still drowsy, with slurred speech. He had no amnesia. The diphenidine concentrations measured in his plasma and urine were 308 and 631 ng/mL, respectively (methylphenidate and diclazepam were also found in plasma) (30)). Diphenidine (4400 pg/mg) was also detected in a hair sample. The patient was discharged from hospital after 5 days.

A fatal intoxication of a 53-year-old man who had taken the synthetic cannabinoid receptor agonist 5F-ADB and diphenidine was reported by Kusano et al. in 2017 (20). Toxicological analysis revealed blood concentrations of 12 ng/mL diphenidine and 0.19 ng/mL 5F-ADB (20).

Hasegawa et al. (11) reported a fatal case in a 30-year-old man who had taken diphenidine. Analysis of various tissues, blood and urine revealed the presence of AB-CHMINACA, 5F-AMB and diphenidine. A particularly high diphenidine concentration of 11 100 ng/g was measured in adipose tissue (11).

A fatal case reported in Japan involved a woman in her thirties who was found dead on a bed. Considerable amounts of “aroma liquid”, “bath salt” products and hypnotic drug tablets were scattered beside the bed. Autopsy showed pulmonary congestion and oedema. Blood samples were positive for

diphenidine (1380 ng/ mL), three synthetic cathinones, ethanol and therapeutic concentrations of benzodiazepines (8).

An autopsy case from Japan involved benzodiazepines and diphenidine. Quantitative toxicological analysis showed concentrations of diphenidine in femoral blood of 0.073 µg/mL. Death was attributed to combined toxicity due to multiple drug interactions. Congestion and oedema were reported (31).

The French Addictovigilance Network retrospectively analysed possible cases of diphenidine use between 2012 and 2016 and identified 11 cases. None of the cases were considered proven, but these possible cases included psychiatric, neurological and cardiovascular problems (32).

7. Dependence potential

A. Animal studies

There are no reports on physical withdrawal reactions or development of tolerance to diphenidine in animals.

B. Human studies

Given the ketamine-like pharmacology of diphenidine, it has been suggested that physical dependence is possible, and that withdrawal symptoms may occur when use is stopped. This assumption is not, however, supported by any systematic study or anecdotal case reports. Prolonged, repeated use of diphenidine may lead to tolerance, and cross-tolerance to other dissociatives may also occur (6). No published or user reports are available to support these assumptions on dependence liability and development of tolerance.

8. Abuse potential

A. Animal studies

Sahai et al. (33) analysed the mechanism of binding and functional relevance between rat DAT (rDAT) and diphenidine and the three structural MXP isomers *in silico* and *in vitro*. Docking simulations and simulations of molecular dynamics in rDAT complexes (rDAT-diphenidine, rDAT-2-MXP, rDAT-3-MXP and rDAT-4-MXP) were conducted in biophysically relevant membrane environments. When diphenidine was bound to DAT, it led to disruption of the extracellular network with the ionic interaction (a feature not seen with the isomers). This suggests a mechanism involving a conformational change of the transporter molecule whereby DAT opens extracellularly. The *in silico* data are in line with the *in vitro* data (33). Thus, diphenidine displaced RTI-121 binding (specific radioligand for the DAT) in a comparable manner to cocaine. Diphenidine also evoked dopamine efflux in the nucleus accumbens as measured by *in vitro* voltammetry; however, this effect was not as pronounced as with cocaine. In conclusion, this set of experiments indicates that diphenidine exhibits pro-dopaminergic stimulant-

type effects. From this neurochemical perspective, there is an indication that this drug has abuse liability.

B. Human studies

No case reports or reports of any systematic study on the abuse liability of diphenidine have been published.

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

Diphenidine is not approved for medical or veterinary use, and it has no industrial or other use (6). It is manufactured by several chemical companies (mainly for research purposes) and is also available from other sources. The medical use of diphenidine has not been explored; however, the class of 1,2-diarylethylamines (which includes diphenidine) may have clinical relevance in a range of therapeutic areas, including management of pain, epilepsy, neurodegenerative disease, alcohol dependence and depression (6, 15).

A European Union patent was approved (EP0346791 (B1)) for the chemical class of 1,2-diarylethylamines, which includes diphenidine, for their potential use in the treatment of neurotoxic injury. In this patent, compounds, compositions and methods of treatment are described to control brain damage associated with anoxia or ischaemia, which typically follows stroke, cardiac arrest or perinatal asphyxia. The administration of a 1,2-diarylethylamine compound such as diphenidine inhibits excitotoxic actions, especially via NMDA receptor blockade.

The therapeutic potential of diphenidine may be due not only to NMDA receptor blockade but also to its interaction with the σ_1 receptor. Ligands targeting the σ_1 receptor are being tested in clinical trials for treatment of Alzheimer disease, ischaemic stroke and neuropathic pain (24). The σ_1 receptor activity of diphenidine may therefore contribute to its therapeutic potential; however, there is no experimental evidence or anecdotal report that would support such an assumption.

10. Listing on the WHO Model List of Essential Medicines

Diphenidine is not on the 20th WHO Model List of Essential Medicines or the 6th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Diphenidine has never been marketed as a medicinal product.

12. Industrial use

Diphenidine has no industrial use.

13. Nonmedical use, abuse and dependence

See section 6. Adverse reactions.

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

As described in section 6, a small number of cases of heavy intoxication with diphenidine that required hospitalization have been reported. In most of those cases, underlying psychiatric disorders and somatic diseases and use of other drugs may have contributed to clinical complications. Impairment of memory function may persist for several days.

An estimate of public health problems associated with diphenidine is provided by the STRIDA project in Sweden. Over a 12-month period in 2014, 750 cases of suspected drug intoxication originating from emergency rooms were studied. Fourteen of the patients were positive for diphenidine (concentration in serum, 2–262 ng/mL), representing 1.9% of the high-risk population (30). The patients who tested positive for diphenidine required hospitalization for 1–3 days. In addition to standard supportive therapy, half of these patients were treated with benzodiazepines and/or propofol. The authors concluded that the adverse effects noted in patients with analytically confirmed intoxication involving diphenidine were similar to those reported for other dissociative substances such as ketamine and methoxetamine. However, the high proportion of polysubstance use might have played a role in the intoxication and clinical features (30).

No relevant publication or case report has appeared in the scientific literature in the past two years, and there are no recent discussions of this drug on online forums. The lack of recent reports of severe intoxication, fatalities or user experiences suggests decreasing interest of the worldwide drug scene in diphenidine.

15. Licit production, consumption and international trade

Not available

See Annex 1. Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

Not available

See Annex 1. Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

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

18. Current and past national controls

Legal status of diphenidine (summarized from references 6 and 18):

- Brazil: Diphenidine was recently included on Brazil's controlled substances lists because of its potential to cause harm to public health.
- Canada: Diphenidine has been a Schedule I controlled substance since March 2016.
- Germany: Diphenidine is a controlled substance, and its production and sale are illegal. Possession is not penalized if intended for self-consumption.
- United Kingdom: It has been illegal to produce, supply or import diphenidine since May 2016.

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

No data.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of diphenidine

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, seven in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. A total of 13 countries opted not to participate (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 32 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on 3-methoxyphencyclidine

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	10	3
Eastern Mediterranean Region	7	4
European Region	21	17
South-East Asia Region	5	1
Western Pacific Region	3	5
Total 92	61	31

Legitimate use

No country reported approved human medical products or veterinary products containing diphenidine.

One country (in the Region of the Americas) reported that diphenidine was currently used in medical or scientific research (excluding use as an analytical reference standard), specifically in cell line studies (binding/functional assays) and animal studies.

No country confirmed that diphenidine was used in industrial or other non-medical or non-scientific use.

No country reported approved therapeutic indications for diphenidine.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Thirteen countries reported that diphenidine was being misused or abused for its psychoactive properties or recreational use. The most commonly reported known route of administration was oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	7
Injection	1
Inhalation	2
Sniffing	1
Smoking	3
Don't know	16

The most commonly reported known formulation of diphenidine was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	12
Tablets	5
Liquid for oral use	1
Solution for injection	0
Don't know	14

To the above, countries added:

- “herbal mixture”
- “in plant materials together with other substances”.

Nine countries reported that the negative health impact of non-medical consumption of diphenidine was “serious” or “substantial” (Table 4).

Table 4. Level of negative health impact

Serious	Substantial	Negligible	Don't know
4	5	10	12

One country (in the European Region) commented, "... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers etc."

Five countries (in the European Region) reported emergency room admissions related to the non-medical use of diphenidine.

With regard to reported adverse effects, one country (in the European Region) noted, "dizziness, coma (Glasgow coma scale [GCS]score, 6), headache, vomiting, visual and auditory hallucinations, paranoia, dissociation, drowsiness, restlessness, extrapyramidal syndrome, nystagmus". Another (in the European Region) noted "pupils, nystagmus, disorientation, anxiety, agitation, decreased consciousness, hallucinations, high heart rate, high blood pressure, muscle rigidity, cramps, elevated body temperature". Another country (in the European Region) noted "In combination with other drugs: agitation, confusion, paranoid ideation, suicidal ideation".

No country reported that users of diphenidine presented for drug dependence treatment.

Regarding mortality, no countries reported deaths involving diphenidine.

Status of national control and potential impact of international control

Fifteen countries responded that the availability of diphenidine is currently regulated under national legislation.

Table 5. Reported illicit activities involving diphenidine

Activity	Number of countries
Smuggling from other countries	3
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	0
Trafficking	4
Diversion from legal supply chain	0
Internet sales – seller or website located in country	2
Internet sales – from abroad to buyers in country	2
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	1
Don't know	17

To the above, countries added:

- “trafficking through postal services”
- “Internet sales (without other information)”
- “probably drug dealing”.

Eight countries (one in the Region of the Americas, six in the European Region, one in the Western Pacific Region) reported seizures (Table 6).

Table 6. Reported seizures of diphenidine

Year	No. of seizures
2020	3
2019	24
2018	34
Total	61

Twenty-four countries have the forensic laboratory capacity to analyse diphenidine.

One country (in the European Region) commented, “Forensic laboratories have the capacity to analyse diphenidine if reference material is available”.

Critical review report: 2-Methoxydiphenidine (2-MXP)

Executive summary

This critical review is proposed on the basis of information brought to the attention of WHO that 2-methoxydiphenidine (2-MeO-diphenidine or 2-MXP) is manufactured by several chemical companies and other producers. Case reports demonstrate that ingestion of this new psychoactive compound can lead to severe intoxication and death. 2-methoxydiphenidine is a controlled substance in Canada, China, Germany, Italy, Sweden and the United Kingdom.

Owing to the very short history of human usage (approximately 7 years), information about the pharmacological properties, metabolism and toxicity of 2-methoxydiphenidine is limited. 2-methoxydiphenidine was first reported in a 1989 patent as a potential treatment for neurotoxic injury. The first reported recreational human use was in 2014, when 2-methoxydiphenidine was sold in powder and tablet form on the online research chemical market.

Chemistry: 2-methoxydiphenidine is a dissociative substance of the 1,2-diarylethylamine class, which can produce ketamine-like effects. Three structural isomers (2-, 3- and 4-MXP) are known, which can be separated by HPLC selected-ion monitoring detection or GC ion trap MS. 2-methoxydiphenidine can be synthesized by at least two procedures within a few days from standard starting materials, reagents and solvents that can be obtained from chemical companies.

Pharmacology: 2-methoxydiphenidine is an NMDA receptor antagonist with an uncompetitive channel-blocking effect. The following rank order of potency for inhibition at the NMDA receptor was found for the three structural MXP isomers: MK-801 > PCP > 3-MXP > 2-MXP > ketamine > 4-MXP > memantine, which closely paralleled NMDA receptor binding affinities. Binding affinities for human monoamine transporters (DAT, SERT and NET) showed the highest affinity for DAT > NET > SERT. 2-Methoxydiphenidine shows affinity for sigma receptors (σ_1 and σ_2); however, the functional interaction of 2-methoxydiphenidine with the sigma binding sites is not known.

No systematic studies of the metabolism of 2-methoxydiphenidine have been published. The main metabolite of 2-methoxydiphenidine detected in blood and urine is hydroxy-2-methoxydiphenidine.

2-methoxydiphenidine is usually taken orally. Threshold doses range between 30 and 50 mg, low doses between 50 and 75 mg, common doses from 75 to 120 mg, and strong doses start at 120 mg. The onset of effects occurs 30 to 60 min after oral ingestion. The duration of effects is 6–8 h, with a peak effect after 2 h. The duration of after-effects, known as a “hangover” or an “afterglow”, ranges from 1 to 3 h. 2-methoxydiphenidine has a much more rapid onset and shorter duration of effects when vaporized or smoked.

No published data are available on the toxicity or the reproductive, carcinogenic or mutagenic potential of 2-methoxydiphenidine.

Adverse reactions in humans: Information from published case reports, the UNODC EWA Tox-Portal and various Internet sources shows that 2-methoxydiphenidine can lead to various adverse reactions. These include acute behavioural, emotional, motivational, cognitive and somatosensory and motor changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, hallucinations and out-of-body experiences can occur. Cognitive alterations at higher doses include depersonalization, derealization, loss of ego boundaries, and, in some cases, delusions and paranoia. Acute intoxication can lead to emergency department admission or even death.

A search of all available information worldwide found that four deaths had been reported and in only two of these cases was 2-methoxydiphenidine determined to be the cause of death. Some descriptions are available of cases of severe intoxication that led to admission to an emergency room and sometimes to admission to a hospital as an inpatient. However, the high proportion of polysubstance use might have played a role in the intoxication and clinical features described in those case reports.

Dependence and abuse potential: One report described symptoms of potential use disorder and withdrawal symptomatology requiring hospitalization. Animal experiments, however, show that 2-methoxydiphenidine does not exhibit pro-dopaminergic stimulant-type effects and, from this neurochemical perspective, there is no indication that this drug has abuse liability. No firm conclusion can be drawn from information retrieved from online forums on the potential for tolerance and cross-tolerance (to other dissociative compounds). In summary, there is limited evidence that 2-methoxydiphenidine has dependence or abuse potential.

Potential therapeutic applications: In 1989, a patent was granted on 1,2-diarylethylamines for controlling brain damage occurring during periods of anoxia or ischaemia, by selectively reducing the hyperexcitatory effects of glutamate, which binds primarily to NMDA receptors. 2-methoxydiphenidine may have a role in controlling brain damage during anoxia or ischaemia and may have clinical relevance in a range of therapeutic areas including pain, neurodegenerative disease, depression and alcohol dependence. On online forums, people who use 2-methoxydiphenidine reported an interest in its therapeutic use as an antidepressant.

Magnitude of public health problems: A few people have required hospitalization for heavy 2-methoxydiphenidine intoxication. In most of these cases, underlying psychiatric disorders and use of other drugs may have contributed to clinical complications. An estimate of public health problems is provided by the STRIDA project from Sweden, which showed that only 0.4% of

the high-risk population (e.g. psychonauts from the drug scene) tested positive for 2-methoxydiphenidine. More importantly, in the past two years, no relevant publication or case report has appeared in the scientific literature, and discussions of its use online have ceased. In conclusion, in recent years, no intoxications, fatalities or user experiences have been reported, which is indicative of decreasing interest of the worldwide drug scene in 2-methoxydiphenidine.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available

B. Chemical Abstract Service (CAS) Registry Number

CAS Number: 127529-46-8

C. Other chemical names

MPX

2-MXP

methoxyphenidine

methoxydiphenidine

1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine

piperidine, 1-(1-(2-methoxyphenyl)-2-phenylethyl)-, (+/-)-

1-(2-methoxyphenyl)-2-phenyl-1-(piperidine-1-yl)ethane

D. Trade names

None

E. Street names

None

F. Physical appearance

Powder, tablets

G. WHO review history

2-methoxydiphenidine has not been pre-reviewed or critically reviewed by the WHO ECDD.

2. Chemistry

A. Chemical name

IUPAC name: 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine

CA Index name: None

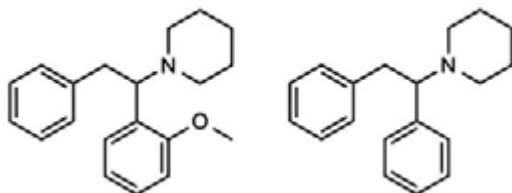
B. Chemical structure

Free base:

Molecular formula: C₂₀H₂₅NO

Molecular weight: 295.426 g/mol

Fig. 1. Structure of (left) and, for comparison, diphenidine (right)



C. Stereoisomers

2-methoxydiphenidine is chiral, which makes the development of chiral separation methods necessary. Weiß et al. (1) tried several methods to separate the enantiomers, but up to now no information about the separation of stereoisomers of 2-methoxydiphenidine has become available. However, three structural isomers (2-, 3- and 4-MXP) are known to exist. These structural isomers can be separated using HPLC selected-ion monitoring detection or GC ion trap MS (2).

D. Methods and ease of illicit manufacture

The three structural MXP isomers (2-, 3- and 4-MXP) can be synthesized by two procedures. Procedure 1 is based on a three-component approach published by Le Gall et al. (3). This one-step procedure can be used to synthesize the desired isomers. Procedure 2 is based on the Grignard reagent, which is added to the Weinreb amide to give the corresponding ketone intermediate (4). Conversion to the primary amine followed by reaction with 1,5-dibromopentane yields the three MXP isomers (see McLaughlin et al. for a full description (2)).

With these two procedures, 2-methoxydiphenidine can be synthesized, within a few days, from standard starting materials, reagents and HPLC-grade solvents that can be obtained from various chemical companies.

E. Chemical properties

Melting-point: 171.5 °C

Boiling-point: Not known

Solubility: ~3 mg/mL in phosphate-buffered saline (pH 7.2), ~30 mg/mL in ethanol and dimethyl sulfoxide, ~50 mg/mL in dimethylformamide (5)

F. Identification and analysis

Standard analyses are conducted with GC and HPLC coupled to various forms of MS (e.g. matrix assisted inlet ionization). NMR spectroscopy, infrared spectroscopy and thin-layer chromatography have also been used (2).

In forensic drug analysis, separation of the three MXP structural isomers is necessary to clarify the identity of the drug that led to intoxication. This can be done with HPLC selected-ion monitoring detection or GC ion trap MS; however, discrimination of structural isomers with these methods is both cost- and

labour-intensive. Therefore, a rapid, highly sensitive isocratic LC–MS friendly method (i.e. retention time within 4 min) was developed. This method is highly suitable for rapid, specific, sensitive detection of structural MXP isomers in bulk forensic samples (6). However, a separation method for the stereoisomers of 2-methoxydiphenidine is still lacking.

3. Ease of conversion into controlled substances

2-methoxydiphenidine is not readily converted into other internationally controlled substances.

4. General pharmacology

A. Routes of administration and dosage

2-methoxydiphenidine is usually taken orally. User forums report that threshold doses range between 30 and 50 mg, lower doses are between 50 and 75 mg, common doses are between 75 and 120 mg and strong doses start at 120 mg (7).

The onset of effects occurs 30–60 min after oral ingestion. The timing depends on several factors, including dose, potential tolerance and cross-tolerance to other dissociatives, and route of administration. The duration of effects is 6–8 h, with a peak effect after 2 h. The after-effects, also known as a “hangover” or an “afterglow”, last from 1 to 3 h (7, 8).

Some users described long-lasting and cumulative psychoactive effects with repeated dosing and they speculated that this might have been due to a long half-life (9).

Almost 30 user experiences with 2-methoxydiphenidine are available on Erowid (10). All of them were reported between 2014 and 2018. This suggests that interest in this drug has declined since 2018. One report describes non-fatal toxicity, which was managed in an emergency department, following consumption of 300 mg of 2-methoxydiphenidine. The toxicity occurred despite the user’s tolerance to ketamine.

2-methoxydiphenidine has a much more rapid onset and shorter duration of effects when vaporized or smoked. Some user reports indicate that the same effect occurs with vaporization at as little as 20% of a standard oral dose (8).

B. Pharmacokinetics

Wallach & Brandt (9) summarized what is known about the pharmacokinetics of 2-methoxydiphenidine. No systematic studies on the metabolism of 2-methoxydiphenidine have been published. The main metabolite detected in blood and urine is hydroxy-2-MXP. Other metabolites are present at much lower concentrations (trace concentrations), including O-demethyl-MXP and hydroxyl-O-demethyl-2-MXP (9).

Hydroxy-MXP, dihydroxy-MXP and hydroxyl-demethyl-MXP metabolites (position of hydroxylation undetermined) were also detected in the urine of a 35-year-old man who was hospitalized as a result of 2-methoxydiphenidine intoxication (11).

Three hydroxylation products O-demethyl-MXP and three glucuronidated hydroxylation products (positions of modifications not specified) were detected in a urine sample collected in a case of acute intoxication (12).

C. Pharmacodynamics

Effects in vitro

2-methoxydiphenidine is an NMDA receptor antagonist (13–16). Electrophysiological studies suggest that 2-methoxydiphenidine provides receptor antagonism via an uncompetitive channel-blocking effect (16). Thus, this substance blocks NMDA receptor-mediated fEPSPs in rat hippocampal slices in a manner consistent with a channel blocker such as MK-801, which is the gold standard for uncompetitive NMDA receptor blockade. For the three structural MXP isomers, the following rank order of potency for inhibition was found: MK-801 > PCP > 3-MXP > 2-MXP > ketamine > 4-MXP > memantine, which closely paralleled NMDA receptor binding affinities (16).

Two studies reported the K_i value at the NMDA receptor for 2-methoxydiphenidine as 36 nM (16) and 170 nM (14), respectively. The discrepancy in binding affinities between these two studies may be explained by the different radioligands and tissue preparations used for NMDA receptor binding. Whereas Wallach et al. (16) used [^3H]MK-801 in rat forebrain, whole rat brain was used in the study in the initial patent description of [^3H]TCP (14).

Binding affinities for human monoamine transporters (DAT, SERT and NET) were also determined. 2-methoxydiphenidine showed the highest affinity for DAT ($K_i = 2915$ nM (16) and $K_i = 4800$ (17)), followed by NET ($K_i = 6900$ nM) and negligible affinity for SERT ($K_i = 20$ μM) (17). The low affinity for SERT relative to NET and DAT was also reflected in very low reuptake inhibition. Thus, the range for the half maximal inhibitory constant (IC_{50}), which more closely reflects the functional strength of the ligand, was between 10 and 741 μM , depending on the study (9). Low affinity/activity for SERT is seen for all structural MXP isomers (9).

Although it has been little discussed in the literature, 2-methoxydiphenidine shows affinity for sigma receptors (σ_1 $K_i = 124$ nM and σ_2 receptor $K_i = 508$ nM (16)). The functional interaction of 2-methoxydiphenidine with the sigma binding sites is not well understood, but it is noteworthy that the σ_1 receptor is a membrane protein expressed throughout the human body. It acts like an inter-organelle signalling regulator and fine-tunes electrical activity and calcium homeostasis.

Effects in vivo

Like classical NMDA receptor antagonists such as MK-801, a high dose of 2-methoxydiphenidine (20 mg/kg, subcutaneously) significantly disrupted PPI of the startle reflex in rats (9). PPI of the startle reflex is an established measure of sensorimotor gating, and NMDA receptors in the hippocampus play a critical role in the regulation of PPI. PPI disruption caused by NMDA receptor antagonists may reflect alterations in information processing that contribute to their dissociative effects (19). However, 2-methoxydiphenidine was less potent in these PPI experiments than ketamine (20), which was unexpected, given its higher NMDA receptor affinity (16).

5. Toxicology

No published data are available on the toxicity or the reproductive, carcinogenic or mutagenic potential of 2-methoxydiphenidine.

6. Adverse reactions in humans

Information from published case reports, the UNODC EWA Tox-Portal and various Internet sources shows that 2-methoxydiphenidine can cause acute behavioural, emotional, motivational, cognitive and somatosensory and motor changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, acute intoxication can lead to emergency department admissions or even to death. Experiences reported by almost 30 users between 2014 and 2018 were retrieved from Erowid (10), and the information obtained by Van Hout & Hearne (21) from the Internet with the keywords “methoxphenidine”, “MXP” and combinations with “experience”, “report”, “forum” and “trip” was consulted.

Drug user experiences show that the effects of 2-methoxydiphenidine vary greatly from person to person and according to the dose taken. The effects occur approximately 30–80 min after oral administration and approximately 10–30 min after nasal administration. The effect also strongly depends on the set and setting, which is a common drug phenomenon. At higher doses (from 70 mg orally), hallucinations and out-of-body experiences can occur. A typical out-of-body experience was described by a user who reported ingesting an extremely high dose of 500 mg of 2-methoxydiphenidine (10). “I could visually see in front of me, but I could no longer feel any of my body. I was no longer in my room, but a collection of static images were ahead of me. The images would shift continually – consisting of a multitude of grainy, static colours. I could hear a very loud audible buzzing coming from all around me. I could still think. And I was stuck in what seemed to be a never ending loop. I was trying to convince myself that I hadn’t died. I’d find a way out of this box I’d found myself in, that my body would start working again if I kept trying to move it. After what genuinely felt as though many years had passed I started to accept my fate. I accepted that this was death,

that my life in the previous world was over and that this was it forever more – slowly, I became content with my surroundings and my presence in whatever world I had found myself in. Suddenly, I was jolted from the static images and I felt as though my body were reconnecting. My vision started to pull upwards – I could see the ceiling in my room again and then I became one with my physical body again” (10).

In addition to out-of-body experiences, depersonalization, delusions, paranoia and amnesia have been described (22, 23). Importantly, polysubstance use might have played a role in most of the intoxication cases and in the clinical features described by users.

Worldwide, four deaths have been reported. In two of these cases, 2-methoxydiphenidine was determined to be the cause of death; in one case, death was due to a fall and in the other to drowning in a bathtub (24–26). These four deaths are described below in more detail, in addition to several severe cases of intoxication.

Fatalities

The first three fatal cases were reported by Elliott et al. (24). Although it is not clear from the publication, the cases presumably occurred in the United Kingdom. The first case report describes a 34-year-old man who was found dead at home. The autopsy revealed an enlarged heart and hypertensive heart disease. 2-Methoxydiphenidine was found to be present at a concentration of 24.0 mg/L in postmortem femoral blood and was also detected in urine. Drug toxicity was probably the cause of death (25). The second case was a 34-year-old man who was found dead at home. He had a medical history of epilepsy, attention deficit hyperactivity disorder and social anxiety. He had been prescribed levetiracetam, dexamphetamine and diazepam. A sachet labelled “methoxphenidine 2 g” was found in his pocket. Autopsy results did not reveal any somatic abnormalities. 2-Methoxydiphenidine was found to be present at a concentration of 2.0 mg/L in postmortem femoral blood and was also detected in urine. Prescription drugs (diazepam and quinine) were found at therapeutic concentrations; no ethanol was detected. The cause of death was most likely 2-methoxydiphenidine toxicity. In the third case, a 38-year-old man with a medical history of schizophrenia was found dead on a road after having jumped or fallen from a road bridge. 2-methoxydiphenidine was found to be present at a concentration of 1.36 mg/L in postmortem femoral blood and was also detected in urine. The prescription antipsychotic drug risperidone was present at a therapeutic concentration; no ethanol was detected. The cause of death was fatal injuries sustained from the fall (24). The fourth death involved a 21-year-old male who drowned in a bathtub. 2-methoxydiphenidine was found to be present at a concentration of 0.19 mg/L in postmortem femoral blood. However, substantial amounts of other drugs were also detected, including lorazepam (5.7 ng/mL), delorazepam (54 ng/mL),

amphetamine (64 ng/mL) and 4-fluoroamphetamine (2.1 ng/mL). His blood alcohol concentration was 0.93% (26). The cause of death was related to multi-intoxication and, finally, drowning.

Intoxication

A 33-year-old man who had taken 2-methoxydiphenidine crashed into a railway-crossing gate (27) and was admitted to hospital. He presented with amnesia, out-of-body experiences and bizarre behaviour. The concentration of 2-methoxydiphenidine in his serum was 57 ng/mL. Amphetamine and MDMA were also present, at concentrations of 111 and 28 ng/mL, respectively.

Another case of intoxication involved a 53-year-old man who was found on the street in a somnolent, confusional state, with transient echolalia and inability to communicate (12). On arrival at the emergency room, he lost consciousness and developed opisthotonus and nystagmus. He also had hypertension and tachycardia. Intravenous lorazepam was administered to treat his hypertension and tachycardia, resulting in a decrease in his blood pressure and heart rate within 30 min. Concomitantly, nystagmus and miosis resolved. He then regained consciousness but was confused and disoriented. He received further lorazepam treatment and by the next morning was asymptomatic except for amnesia regarding the event. 2-Methoxydiphenidine was identified qualitatively in plasma and urine, with trace amounts of benzoylecgonine, amlodipine, buprenorphine, norfentanyl, hydrochlorothiazide, metformin and lidocaine. The man had a history of diabetes mellitus and multiple substance abuse, which contributed to his heavy intoxication.

In a similar case, a 35-year-old man with a history of hypothyroidism, Wolff-Parkinson-White syndrome, adjustment disorder and alcohol dependence was found somnolent in the street (11). He exhibited retrograde amnesia, hypertension and slurred speech. Severe rhabdomyolysis and acute kidney injury were also noted. 2-methoxydiphenidine was identified qualitatively in urine. A methylphenidate metabolite, tramadol and lorazepam were also detected.

In another case, the clinical features present after ingestion of 2-methoxydiphenidine mimicked ischaemic neurological symptomatology (28). A 25-year-old man presented at an emergency room after an episode of syncope with secondary head trauma. He was treated with midazolam and propofol and discharged from hospital two days later. 2-methoxydiphenidine and flubromazepam concentrations in his blood were 247 ng/mL and 411 ng/mL, respectively. Thus, intoxication with 2-methoxydiphenidine may result in atypical neurological symptoms, such as severe focal neurological signs.

A person with a history of polysubstance use developed a serotonin syndrome after using 2-methoxydiphenidine (29). A 33-year-old man with autism, who used methadone, loxapine and lorazepam, was admitted to an emergency room after being found in a state of agitation. The patient presented with profuse

sedation, hyperthermia, tachycardia and mydriasis. Hyperthermia worsened within minutes, and his body temperature rose to 42 °C. Supportive care included mechanical ventilation with sedation, endovascular targeted temperature management, large hydration, haemodialysis and blood transfusion. The patient was discharged after 16 days, having made a good recovery. Qualitative blood analysis revealed 2-methoxydiphenidine and the tryptamine-based hallucinogen α -methyltryptamine (29). Given that α -methyltryptamine blocks serotonin reuptake, it is likely that it also contributed to the observed serotonin syndrome.

7. Dependence potential

A. Animal studies

No information on animal studies was available.

B. Human studies

In 2017, Champeau et al. (30) reported the first case in which 2-methoxydiphenidine was linked with a potential use disorder and with withdrawal symptomatology requiring hospitalization. A 21-year-old man with bipolar disorder was admitted to an emergency room with agitation and aggression. The patient reported chronic consumption of 2-methoxydiphenidine for one month, with doses up to 150 mg. Cessation of 2-methoxydiphenidine led to pronounced craving with anxiety. He also developed physical withdrawal symptoms including abdominal pain, vomiting and low-grade fever (38 °C), which lasted for several days.

8. Abuse potential

A. Animal studies

Sahai et al. (31) analysed the mechanism of binding and functional relevance between rat DAT and structural MXP isomers *in silico* and *in vitro*. In addition to docking simulations, molecular dynamics simulations in rat DAT complexes (rDAT-2-MXP, rDAT-3-MXP and rDAT-4-MXP) were conducted in biophysically relevant membrane environments. When 2-methoxydiphenidine was bound to DAT, it led to an inward-facing conformation of DAT. Although this is a conformation seen with the classical dopamine releaser amphetamine, 2-methoxydiphenidine does not appear to be a DAT inhibitor, nor does it demonstrate reverse transport. These *in silico* data are coherent with the *in vitro* data. Thus, 2-methoxydiphenidine had no significant effect on either binding of RTI-121 (specific radioligand for the DAT) or evoked dopamine efflux in the nucleus accumbens measured by *in vitro* voltammetry. When these experiments are considered together, they do not indicate that 2-methoxydiphenidine has pro-dopaminergic stimulant-type effects and, from this neurochemical perspective, there is no indication that this drug has abuse liability.

B. Human studies

Champeau et al. (30) described a case evaluated on a drug dependence severity scale developed by the Addictovigilance Centre in Nantes, France, which contains mainly items from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. The patient had a high score, endorsing all six domains that could be assessed. These included tolerance, withdrawal and dose escalation as well as behavioural aspects of dependence. This suggested that dependence on 2-methoxydiphenidine can develop.

No firm conclusion can be drawn about tolerance or cross-tolerance (to other dissociative compounds) from the information available.

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

In 1989, a patent was granted for 1,2-diarylethylamines in controlling brain damage during periods of anoxia or ischaemia by selective reduction of the hyperexcitatory effects of glutamate (which binds primarily to NMDA receptors) (32). This patent includes procedures for preparing 2-methoxydiphenidine. Since then, 2-methoxydiphenidine has not been developed for use as a pharmaceutical, but it reappeared in 2013 as an NPS.

2-methoxydiphenidine may have a role in controlling brain damage during periods of anoxia or ischaemia and may have clinical relevance in therapeutic areas such as treatment of pain, neurodegenerative disease, depression and alcohol dependence (9). Some users of 2-methoxydiphenidine reported its therapeutic use as an antidepressant (21). Non-competitive NMDA receptor antagonists such as memantine may have use in preventing relapse in people with alcohol dependence (33). This suggests that 2-methoxydiphenidine may also interfere with chronic alcohol effects.

The therapeutic potential of 2-methoxydiphenidine may be due to NMDA receptor blockade and its interaction with the σ_1 receptor. Ligands targeting the σ_1 receptor are being studied in clinical trials for the treatment of Alzheimer disease, ischaemic stroke and neuropathic pain (18). Although the σ_1 receptor activity of 2-methoxydiphenidine has not been tested experimentally, it may contribute to its therapeutic potential.

10. Listing on the WHO Model List of Essential Medicines

2-methoxydiphenidine is not on the 20th WHO Model List of Essential Medicines or the 6th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

2-methoxydiphenidine has never been marketed as a medicinal product.

12. Industrial Use

2-methoxydiphenidine has no industrial use.

13. Nonmedical use, abuse and dependence

No information was available.

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

As described in section 6, a few people with 2-methoxydiphenidine intoxication have required hospitalization. In most cases, underlying psychiatric disorders and use of other drugs may have contributed to the clinical picture. 2-methoxydiphenidine might have short- to long-term effects on memory function. For example, one user reported that he experienced serious cognitive impairment after using the substance for several days (10).

An indication of the scale of the public health problem related to 2-methoxydiphenidine is provided by the STRIDA project in Sweden. The study covered a 12-month period in 2014 during which 750 cases of suspected drug intoxication from emergency rooms were enrolled. Only three of the patients enrolled tested positive for 2-methoxydiphenidine (with concentrations ranging from 187 to 409 ng/mL in serum) (33).

In the UNODC EWA Tox-Portal, one case of intoxication requiring hospital admission was reported from Germany. The concentration of 2-methoxydiphenidine in the urine was 440 ng/mL. The sample also contained methylone (120 ng/mL) and a very high concentration of desoxypipradrol.

In the past two years, no studies or case reports of 2-methoxydiphenidine use have been published in the scientific literature. Similarly, there have been no recent discussions on online forums. The absence of reports of intoxication, fatalities or user experiences suggest decreasing interest of the worldwide drug scene in 2-methoxydiphenidine.

15. Licit production, consumption and international trade

Not applicable.

16. Illicit manufacture and traffic and related information

Not applicable.

17. Current international controls and their impact

2-Methoxydiphenidine is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

Legal status of 2-methoxydiphenidine (retrieved from references 7, 8, 10):

Brazil: 2-methoxydiphenidine has recently included in Brazil's controlled substances lists due to its potential to cause harm to public health.

Canada: 2-methoxydiphenidine has been a Schedule I controlled substance since March 2016.

China: As of October 2015, 2-methoxydiphenidine has been a controlled substance in China.

Germany: 2-methoxydiphenidine is a controlled substance. Production and sale are illegal. Possession is not penalized if intended for self-consumption.

Italy: 2-methoxydiphenidine is a prohibited substance in Italy.

Sweden: 2-methoxydiphenidine is a prohibited substance in Sweden.

United Kingdom: Since May 2016, it has been illegal to produce, supply or import 2-methoxydiphenidine.

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

No data.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of 2-methoxydiphenidine

Data were obtained from 105 Member States (19 African Region, 16 in the Region of the Americas, 13 in the in the Eastern Mediterranean Region, 40 in the European Region, seven in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. A total of 13 countries opted not to participate (three in the African Region, two in the Eastern Mediterranean Region, two in the European Region, three in the Region of the Americas, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 32 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on 2-methoxydiphenidine

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	10	3
Eastern Mediterranean Region	7	4
European Region	21	17
South-East Asia Region	4	2
Western Pacific Region	3	5
Total 92	60	32

Legitimate use

No country reported approved human medical products or veterinary products containing 2-methoxydiphenidine.

One country (in the Region of the Americas) reported 2-methoxydiphenidine was currently used in medical or scientific research (excluding use as an analytical reference standard), specifically in cell line studies (binding/functional assays) and animal studies.

No country reported use of 2-methoxydiphenidine in industrial or other non-medical or non-scientific applications.

No country reported approved therapeutic indications for 2-methoxydiphenidine.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Eleven countries reported that 2-methoxydiphenidine was being misused or abused for its psychoactive properties or recreational use.

The most commonly reported route of administration was oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	6
Injection	1
Inhalation	0
Sniffing	2
Smoking	0
Don't know	19

The most common known formulation of 2-methoxydiphenidine reported was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	9
Tablets	5
Liquid for oral use	0
Solution for injection	0
Don't know	15

To the above, countries added:

- “liquid (route of administration unknown)”
- “capsule”
- “in plant materials together with other substances”.

Nine countries reported that the health impact of non-medical consumption of 2-methoxydiphenidine was “serious” or “substantial” (Table 4).

Table 4. Level of negative health impact

Serious	Substantial	Negligible	Don't know
4	5	10	12

One country (in the European Region) commented, "... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers etc."

Three countries (in the European Region) reported emergency room admissions related to non-medical use of 2-methoxydiphenidine.

With regard to adverse effects, one country (in the European Region) commented, "High heart rate, pluckiness, warmed up, confused".

No country reported that users of 2-methoxydiphenidine presented for drug dependence treatment.

Regarding mortality, only two countries (in the Region of the Americas and the European Region) reported deaths involving 2-methoxydiphenidine:

- three fatal cases in which other substances were also involved (2015)
- one fatal case in which other substances were also involved (2018).

Status of national control and potential impact of international control

Fifteen countries responded that the availability of 2-methoxydiphenidine is currently regulated under national legislation.

Table 5 shows the main reported activities involving 2-methoxydiphenidine.

Table 5. Reported illicit activities involving 2-methoxydiphenidine

Activity	Number of countries
Smuggling from other countries	4
Manufacture of substance by chemical synthesis	0
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	0
Trafficking	2
Diversion from legal supply chain	0
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	1
Internet sales – other, or location of sellers and website unknown	3
Direct sales to people who use the substance	1
Don't know	17

To the above, countries added:

- “trafficking through postal services”
- “probably drug dealing”.

Seven countries (one in the Region of the Americas, four in the European Region, one in the South-East Asia Region, one in the Western Pacific Region) reported seizures.

Table 6. Reported seizures of 2-methoxydiphenidine

Year	No. of seizures
2020	0
2019	2
2018	40
Total	42

Twenty-five countries have the forensic laboratory capacity to analyse 2-methoxydiphenidine.

One country (in the European Region) commented, “Forensic laboratories have the capacity to analyse 2-methoxydiphenidine if reference material is available”. Another country (in the Western Pacific Region) remarked, “In our opinion 2-methoxydiphenidine is not capable of inducing a psychoactive effect (Regulatory Practice and Analysis, Medsafe, NZ Ministry of Health)”.

Critical review report: Isotonitazene

Executive summary

Isotonitazene is a 5-nitro-2-benzylbenzimidazole belonging to the 2-benzylbenzimidazole group of compounds, which were synthesized more than 60 years ago as potential analgesics. However, these compounds were never clinically approved for marketing. The closely related homologues etonitazene and clonitazene have been scheduled internationally. The synthetic opioid isotonitazene recently appeared on the illicit market. It has been identified in postmortem forensic toxicology reports and in national and international drug seizures since April 2019. Isotonitazene has been identified in Belgium, Canada, Estonia, Germany, Latvia, Sweden, the United Kingdom and the USA.

In vitro radioligand binding and functional experiments indicate that isotonitazene has high affinity for μ -opioid receptors and is more potent than fentanyl in stimulating [35 S]GTP γ S binding. The single in vivo report from the original patent states that isotonitazene is 500 times more potent than morphine. Isotonitazene is also highly lipophilic. When laboratories are identifying and analysing samples suspected of containing isotonitazene, they should consider aspects such as the high analytical sensitivity required to detect the sub-nanogram per millilitre amounts in biological samples; the fact that the n-propoxy isomer of isotonitazene will result in very similar mass spectrometry fragmentation patterns; and that many 2-benzylbenzimidazoles have similar O-dealkylation biotransformation products (1). The UNODC EWA Tox-Portal and forensic toxicology reports from the USA (2) indicate that isotonitazene use has been associated with many deaths, although in most cases it was administered in combination with other opioids and benzodiazepines. In a study to quantify isotonitazene and its metabolites, the concentrations of isotonitazene were lower than those of fentanyl and approximately similar to those of carfentanil (1). Little information is available on online forums on usage, and there are few trip reports. Therefore, most of the information on isotonitazene comes from postmortem analyses and seizures reported to national and international monitoring organizations. Isotonitazene had been identified for only approximately 18 months at the time of writing this report, and the patterns of manufacture, distribution and usage are only just emerging.

1. Substance identification

A. International Nonproprietary Name (INN)

N,N-diethyl-2-[2-[(4-isopropoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]ethanamine

B. Chemical Abstract Service (CAS) Registry Number

14188-81-9 free base

119276-00-5 hydrochloride salt

*C. Other chemical names**N,N*-diethyl-2-[2-({4-[(propan-2-yl)oxy]phenyl)methyl}-5-nitro-1*H*-benzimidazol-1-yl]ethan-1-amine*N,N*-diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl)ethan-1-amine*N,N*-diethyl-2-[2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl]ethanamine*N,N*-diethyl-2-[2-[(4-isopropoxyphenyl)methyl]-5-nitro-benzimidazol-1-yl]ethanamine*N,N*-diethyl-2-[[4-(1-methylethoxy)phenyl)methyl]-5-nitro-1*H*-benzimidazole-1-ethanamine*N,N*-diethyl-2-[5-nitro-2-[(4-propan-2-yloxyphenyl)methyl]benzimidazol-1-yl]ethanamine*N,N*-diethyl-2-[5-nitro-2-({4-[(propan-2-yl)oxy]phenyl)methyl}-1*H*-benzimidazol-1-yl]ethan-1-amine1-[2-(diethylamino)ethyl]-2-(*p*-isopropoxybenzyl)-5-nitrobenzimidazole 1*H*-benzimidazole-1-ethanamine, *N,N*-diethyl-2-[[4-(1-methylethoxy)phenyl)methyl]-5-nitro-1-(*N,N*-diethylamino-ethyl)-2-benzyl-5-nitrobenzimidazolebenzimidazole, 1-[2-(diethylamino)ethyl]-2-(*p*-isopropoxybenzyl)-5-nitro (6CI,7CI,8CI)*N,N*-diethyl-2-[2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl]ethanamin (German)*N,N*-diéthyl-2-[2-(4-isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl]éthanamine (French)*D. Trade names*

Not applicable

E. Street names

Iso

Nitazene

Toni

F. Physical appearance

Yellow, brown or off-white powder

G. WHO review history

Isotonitazene has not been reviewed by the WHO ECDD.

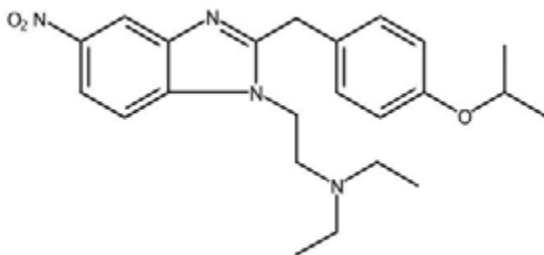
2. Chemistry

A. Chemical name

IUPAC name: *N,N*-diethyl-2-[2-[(4-isopropoxyphenyl)methyl]-5-nitrobenzimidazol-1-yl]ethanamine

CA Index name: 1*H*-benzimidazole-1-ethanamine, *N,N*-diethyl-2-[[4-(1-methylethoxy)phenyl]methyl]-5-nitro-

B. Chemical structure



Free base:

Molecular formula: $C_{23}H_{30}N_4O_3$

Molecular weight: 410.51

C. Stereoisomers

No isomers of isotonitazene have been described.

D. Methods and ease of illicit manufacture

Isotonitazene is a 5-nitro-2-benzylbenzimidazole belonging to the 2-benzylbenzimidazole group of compounds, which were originally developed as opioid analgesics. This group of compounds includes the closely related homologues etonitazene, metonitazene and clonitazene. The difference between isotonitazene, etonitazene and metonitazene is substitution at the para position of the benzyl moiety, with an isopropoxy group in isotonitazene, an ethoxy group in etonitazene and a methoxy group in metonitazene. The difference between isotonitazene and clonitazene is an ethereal isopropoxy group replacing the chloro halogen atom. Protonitazene is the n-propoxy isomer of isotonitazene (3).

As described in the EMCDDA technical report on isotonitazene, several methods have been developed for the synthesis of 2-benzylbenzimidazoles, including isotonitazene (4–6). In one method, 2-diethylaminoethylamine removes an activated chloro atom from 1-chloro-2,4-dinitrobenzene. Ammonium sulfide is used to selectively reduce the nitro function adjacent to the alkylamino moiety of the subsequent 2,4-dinitroaniline derivative. To obtain the final product, isotonitazene, the acquired orthophenylenediamine species is condensed with the imidate of 4-isopropoxyphenylacetic acid obtained from the corresponding

cyanide. Acid–base extraction is used for purification, followed by conversion of the free base into its hydrochloride salt if desired. It is unclear which method is currently being used for the manufacture of the isotonitazene that has appeared on the illicit drug market (3). One approach for synthesizing multiple 2-benzylbenzimidazole opioids is intended for the synthesis of etonitazene; it is apparently simpler and may be used for large-scale preparations (7). Alternatively, isotonitazene may be produced from desethyletonitazene, as described in the original patents (8, 9) and summarized in the EMCDDA report (3). Benzimidazoles were efficiently synthesized by three-component reactions of 2-haloanilines, aldehydes and NaN_3 in the presence of copper catalysts with commercially available starting materials and easy purification (10).

E. Chemical properties

Melting-point: 172–173 °C

Boiling-point: 584.7 ± 45.0 °C at 760 mm Hg

Solubility

Isotonitazene is predicted to be slightly soluble (1.0 g/L) at a temperature of 25 °C and pH 7. Because of its structural similarity to etonitazene, the free base could be expected to be sparingly soluble in water, whereas the hydrochloride salt could be expected to be more soluble. In a chemical characterization study, isotonitazene was solubilized in methanol for chromatographic analyses and assessment of biological activity, and in dimethyl sulfoxide for NMR spectroscopy (11). No definitive data on the solubility of salts of isotonitazene are available; however, as isotonitazene is similar to etonitazene, the salts are expected to be sufficiently water-soluble for administration of effective doses.

F. Identification and analysis

Analytical methods used for the characterization of isotonitazene in physical samples include HPLC, MS, ultraviolet spectroscopy, infrared spectroscopy, Raman spectroscopy, ^1H -NMR spectroscopy and ^{13}C -NMR spectroscopy (1, 11–14). A sample of white homogeneous powder sold online in June 2019 as etonitazene was compared with reference standard samples of isotonitazene by LC–TOF–MS, GC–MS, HPLC diode array detector, NMR spectroscopy and Fourier-transform infrared spectroscopy analysis. The sample sold as etonitazene was identified as isotonitazene (11).

Several factors should be taken into consideration when identifying and analysing samples suspected of containing isotonitazene. One is that high analytical sensitivity is necessary because the concentrations of isotonitazene in biological samples are typically low to sub-nanogram per millilitre (3). For example, in one forensic study, the average concentration in blood was 2.2 ± 2.1 ng/mL and could be as low as 0.4 ng/mL (1). A second factor is that GC–MS analysis of isotonitazene and its n-propoxy isomer, protonitazene, will result in similar MS fragmentation patterns (1, 11).

3. Ease of convertibility into controlled substances

At the time of writing this report, no information was available on whether isotonitazene is converted into other controlled substances. However, the synthesis of isotonitazene is similar to that of both etonitazene and clonitazene, as originally described in the patents (4–6, 8, 9).

4. General pharmacology

A. Routes of administration and dosage

Information from online forums (15–17) and forensic reports (1) indicates that the routes of administration of isotonitazene are vaping, intravenous, sublingual and intranasally via spray or insufflation. The doses reported on online forums vary, ranging from 1–10 mg intravenously, sublingually or via vaping; another report gave a dose of 100–200 µg via nasal spray. In one report, an isotonitazene user described feeling dependent on isotonitazene when consuming approximately 100 mg sublingually or intravenously per day. This variation probably reflects the nature of Internet self-reports and inability to verify that the substance consumed was really isotonitazene or how much of it was isotonitazene.

B. Pharmacokinetics

Isotonitazene was found to undergo de-alkylation to form *N*-desalkyl and *O*-desalkyl primary urinary metabolites, as determined from the finding of *N*-desethyl-isotonitazene and *N*-desethyl-*O*-desalkyl-isotonitazene in five of six urine specimens tested by Krotulski et al. (1). These authors reported that the nitro group was reduced to form the metabolite 5-amino-isotonitazene in only two urine samples, but in 15 of the 18 blood samples. These authors also noted that *O*-dealkylation biotransformation products are considered to be common metabolites of the three benzimidazole compounds – isotonitazene, metonitazene and etonitazene. This suggests that these metabolites could prove useful in monitoring these types of opioids. However, detection of metabolites alone would not indicate whether isotonitazene, metonitazene or etonitazene was the drug consumed (1).

In an ionization study of isotonitazene and other 2-benzylbenzimidazole analgesics, the apparent partition coefficient of isotonitazene in the aqueous buffer (pH 7.4)-cyclohexane system was observed to be greater than that of morphine. The differences were particularly extreme between morphine and isotonitazene. This suggested to the authors that isotonitazene, once administered, would be rapidly transported across lipid barriers to the site of action, i.e. it is a drug that penetrates the central nervous system rapidly (18). As isotonitazene has a calculated log *P* of 4.85, it would probably be absorbed easily and cross the blood–brain barrier (3).

C. Pharmacodynamics

In radioligand binding assays, the K_i values for isotonitazene were: 0.323 ± 0.094 nM for the μ -opioid receptor (MOR) with [^3H] [D-Ala $_2$, N-MePhe $_4$, Gly-ol]-enkephalin (DAMGO), 271 ± 83 nM for the κ -opioid receptor with [^3H] U69,593 and 115 ± 24 nM for the δ -opioid receptor with [^3H] [D-Pen $_2$,D-Pen $_5$] enkephalin. Therefore, isotonitazene selectively bound to μ -opioid receptors when [^3H]DAMGO was used as the radioligand (19).

Isotonitazene was tested *in vitro* in a human embryonic kidney 293 T (HEK293 T) cell-reporter assay and found to activate MOR by interaction with β -arrestin2 with a high potency EC_{50} of 11.1 nM and an efficacy that was 180% that of hydromorphone. This concentration-dependent response to stimulate MOR via β -arrestin2 was antagonized by naloxone (the authors did not publish these data) (11). In another study, isotonitazene was tested in MOR activation assays in HEK293 T cells with β -arrestin2, as in the previous study, or G protein (mini-Gi) recruitment. In the β -arrestin2 recruitment assay, the EC_{50} for isotonitazene was 6.64 nM (2.84–15.0) with an E_{max} of 159% (140–178); in the mini-Gi recruitment assay, the EC_{50} was 16.3 nM (10.6–25.5) with an E_{max} of 484% (444–525) relative to hydromorphone. In these studies, isotonitazene did not demonstrate any biased agonism (20).

When isotonitazene was evaluated in a [^{35}S]GTP γ S functional assay with preparations of transfected Chinese hamster ovary cells expressing human δ - and κ -opioid receptors and rat μ -opioid receptors, isotonitazene produced $114.6 \pm 7.5\%$, $87.7 \pm 3.5\%$ and $106.5 \pm 3.2\%$ maximum stimulation with EC_{50} potencies of 548.6 ± 8.1 nM, 344 ± 99 nM and 0.381 ± 0.076 nM, respectively. Importantly, isotonitazene fully stimulated all three opioid receptors and was more potent than DAMGO (25.2 ± 2.3 nM) and fentanyl ($27.9 + 4.2$ nM) at μ -opioid receptors. In summary, isotonitazene was most effective and most potent at μ -opioid receptors (19).

The only *in vivo* pharmacology study on isotonitazene was reported in the original patent of the 2-benzylbenzimidazole group of opioids. In a mouse tail-flick assay, subcutaneously administered isotonitazene was 500 times more potent than morphine as an analgesic (6, 8).

5. Toxicology

No preclinical acute or chronic toxicology studies of isotonitazene have been reported.

6. Adverse reactions in humans

The clinical toxicological properties of isotonitazene have not been studied directly, and there are few reports from user websites on the acute or chronic physical or psychological effects. Most of the information on adverse events

associated with isotonitazene is from postmortem, forensic toxicology studies. Toxicological case reports between 1 June and 23 September 2019 in the midwest USA indicated that isotonitazene was involved in several fatalities. These included one man aged between 25 and 44 years with 0.9 ng/mL isotonitazene alone; one man aged between 25 and 44 years with 1.7 ng/mL isotonitazene plus flualprazolam; two women with 1.0 and 4.4 ng/mL isotonitazene plus etizolam, one man aged > 64 years and one man aged between 25 and 44 years, both with 1.5–1.9 ng/mL isotonitazene plus etizolam; one man aged between 45 and 64 years with 4.4 ng/mL isotonitazene plus U-47700; and one person (sex not given) aged between 45 and 64 years with 0.4 ng/mL isotonitazene plus flualprazolam (21). Isotonitazene has been associated with many deaths, although in most cases it was administered in combination with other opioids and benzodiazepines.

Biological samples suspected of containing isotonitazene, which included cases reported to the UNODC EWA Tox-Portal, were submitted from NMS Laboratories to the Center for Forensic Science Research and Education (USA) for forensic analysis, characterization and metabolite identification (1). Isotonitazene was identified in blood, urine and vitreous fluid samples from 18 people who had died between August 2019 and January 2020 in four US states: Illinois, Indiana, Minnesota and Wisconsin. Twelve of the deceased were men and six were women, with an average age of 41 years (range, 24–66 years). Isotonitazene was the only opioid detected in half of the 18 samples, whereas the other samples also contained other opioids, such as fentanyl (six samples), heroin (three samples), tramadol (two samples) and U-47700 (one sample). Some of the samples included other benzodiazepine substances such as etizolam (six samples) and flualprazolam (seven samples) as well as other compounds. The average concentration of isotonitazene detected in blood samples was 2.2 ± 2.1 ng/mL (range, 0.4–9.5 ng/mL) (13). The National Forensic Laboratory Information System registered eight additional cases in which isotonitazene was involved: seven in Tennessee and one in California in 2019. The US Drug Enforcement Administration (DEA) reported another death, which occurred in January 2020 in Pennsylvania, in which isotonitazene was identified in a biological sample. However, the US DEA cautioned that use of isotonitazene is probably under-reported owing to its rapid appearance (2).

Toxicovigilance Canada reported a death in Alberta as early as March 2019 and two additional deaths in September and October 2019, although the role played by isotonitazene was not reported (22). A death involving isotonitazene was reported in Germany, but no details were available (1). The United Kingdom also reported the death of an individual with nanogram per millilitre concentrations of isotonitazene, butyrylfentanyl, despropionyl fentanyl and despropionyl fluorofentanyl. The extent to which isotonitazene contributed to this death is not known (3).

The case histories and autopsy findings relating to isotonitazene show similarities to those reported for use of traditional opioids, including heroin, such as scars from injecting and puncture wounds, consistent with intravenous drug use. Signs associated with suspected opioid overdose such as pulmonary and/or cerebral oedema were often noted in the autopsy reports (1).

No formal studies on the psychological and behavioural effects of isotonitazene have been reported. However, isotonitazene is likely to have the adverse effects commonly reported for other opioid analgesics, such as incoordination, dizziness, drowsiness, mental confusion, sedation and profound intoxication (23). Two users' reports on the online forums Drugs Forum and Reddit noted that the adverse effects were very dry eyes, constipation, joint "creakiness", sedation and mania at lower doses. However, very few self-reports about isotonitazene were available from Internet sites; moreover, it is not possible to verify that the substance consumed was isotonitazene.

7. Dependence potential

A. Animal studies

The dependence potential of isotonitazene had not been studied in animals at the time of this report. However, etonitazene, a closely related homologue to isotonitazene, has been studied for tolerance and dependence (24, 25) and found to have similar or greater potency and efficacy than morphine or fentanyl. These studies suggest that isotonitazene, a member of the 2-benzylbenzimidazole group of opioids, like etonitazene, can be predicted to have dependence-producing potential in animals.

B. Human studies

The dependence potential of isotonitazene has not been studied in humans to date. One person who reported frequent use of isotonitazene on Reddit described symptoms of physical dependence after taking up to 100 mg intravenously or sublingually for up to 5 months. The symptoms of dependence reported included withdrawal symptoms of fever, dizziness, flu-like feelings, blackouts, anxiety and panic attacks, according to two users on Reddit. Only one online forum thread described dependence related to isotonitazene use. Self-reports from Internet sites are limited and it is not possible to verify that the substance consumed was isotonitazene.

8. Abuse potential

A. Animal studies

The abuse liability of isotonitazene had not been studied in animals at the time of this report. However, etonitazene, a closely related homologue to isotonitazene, has been studied. Discriminative stimulus (26) and self-administration (27, 28)

occurred at similar or greater potency and efficacy as morphine or fentanyl. These studies suggest that isotonitazene, a member of the 2-benzylbenzimidazole group of opioids, like etonitazene, can be predicted to have abuse potential in animals.

B. Human studies

The abuse potential of isotonitazene has not been studied in humans.

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

There are currently no therapeutic applications or recorded medical uses of isotonitazene.

10. Listing on the WHO Model List of Essential Medicines

Isotonitazene is not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

No evidence is available that isotonitazene is being considered as a medicinal product. Furthermore, isotonitazene has never been granted a marketing authorization as a medicinal product for human or veterinary use and has not been the subject of an application for a marketing authorization as a medicinal product for human or veterinary use.

12. Industrial use

No potential industrial use was identified for isotonitazene besides as an analytical reference standard for scientific research and forensic applications. Isotonitazene is available for purchase from various chemical companies and is available in wholesale amounts and in consumer amounts.

13. Nonmedical use, abuse and dependence

No formal epidemiological reports have been published on the prevalence, abuse or dependence potential of isotonitazene. Only the toxicology case reports described above and the seizures described below indicate patterns or potential patterns of nonmedical use. However, the population likely to abuse isotonitazene appears to be the same as that which uses heroin, prescription opioid analgesics and other synthetic opioid substances (2). This is evidenced by the other types of drugs typically identified with isotonitazene in biological samples obtained from fatal overdose cases. Furthermore, a report from BlueLight described isotonitazene as having the “potency of fentanyl + duration of heroin, with actual euphoria to go with it”, and another report from Drugs Forum stated “This is my favorite drug I’ve ever done. A heavy rush similar to fentanyl, but with the euphoria of quality heroin. Extremely powerful, this dose would kill or at least incapacitate the average street user”. There are few descriptions of isotonitazene on

the readily available online forums (15–17). One user reported use for 5 months and another for 2 months on Reddit. Both described adverse effects such as extremely dry eyes, dehydration and constipation. The reported symptoms of dependence included withdrawal symptoms of fever, dizziness, flu-like feelings, blackouts, anxiety and panic attacks.

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

Toxicological case reports indicating that isotonitazene was involved in fatalities in midwestern USA (21) are discussed in section 6. In the 18 toxicological cases analysed at the Center for Forensic Science Research and Education (including the eight cases listed above) (see section 6), some of the people who died were regular heroin and opioid users, suggesting that isotonitazene may be a substitute for heroin or other opioids (1, 20). Indeed, the US Drug Enforcement Administration–Veterans Affairs reported the seizure of a powder mixture of isotonitazene, heroin and bromazolam (2). For the purpose of experimental analysis, “etonitazene” was purchased through an online supplier; however, it was found to be isotonitazene (11).

There have been no reports of impaired driving or harm to others. Isotonitazene is apparently the first of the 2-benzylbenzimidazole opioids to be identified on the current illicit drug market. Its novelty could increase accidental overdose or life-threatening poisoning if an individual is unfamiliar with how to dose the new substance (2). The risk is greater if isotonitazene is sold under another name or mixed with other drugs (2).

15. Licit production, consumption and international trade

The only licit production is of an analytical reference material classified as an opioid intended for research and forensic applications. It is synthesized by various chemical companies and is available in wholesale and consumer quantities. A labelled version, isotonitazene-d7 is also available for purchase through the same vendors for use with GC-MS or LC-MS methods for research and forensic purposes.

16. Illicit manufacture and traffic and related information

Isotonitazene is sold online as a powder, a ready-to-use nasal spray or in counterfeit pills (3). The size and scale of the manufacture and trafficking operations are not known. A Reddit user announced that a Chinese vendor would be preparing a new batch for distribution after the Chinese New Year in 2019, as reported in the online Filter Magazine (29). The first appearance of isotonitazene appears to have been in March 2019 in Alberta, Canada (22). In February and March 2020, law enforcement officials found isotonitazene in the form of triangular white tablets with an “M” logo on one side and an “8” on the other side and as a blue tablet in counterfeit Dilaudid pills (30).

In Europe, isotonitazene was found in a seizure in Estonia in April 2019. At the time of the technical report on isotonitazene published by the EMCDDA, isotonitazene had also been identified in Belgium, Germany, Latvia, Sweden and the United Kingdom (3). Seizures have been reported in Estonia ($n = 17$, isotonitazene in powder form), Germany ($n = 2$, 4.5 g isotonitazene in liquid form, one sample with a synthetic cannabinoid) and Latvia ($n = 4$, isotonitazene in powder form, one sample with fentanyl). A total of 109.6 g of isotonitazene powder was seized between April 2019 and January 2020. Other seizures in which isotonitazene was identified were reported by Sweden in a customs seizure (48.8 g), by Belgium as a collected sample and in the United Kingdom in biological samples following a death (3).

In the USA, isotonitazene in powder form has been identified as a single substance and in combination with other substances. According to the National Forensic Laboratory Information System database, isotonitazene had been identified in eight cases in the USA as of 5 March 2020. They occurred in 2019 in two states: seven cases in Tennessee and one in California. A seizure of 1.6 g of isotonitazene in California was reported in April 2019. In addition, Wisconsin State Crime Laboratories identified isotonitazene, bromazolam and heroin in a mixed seized powder. In Iowa, isotonitazene was found at the scene of investigation of a death (2).

Although isotonitazene has been identified in Canada, Europe and the USA, the extent of the illicit market is unknown. A user on Reddit claimed that the isotonitazene market may be limited. Anecdotal reports from February 2020 suggest that the presence of isotonitazene, at least in the USA, is not likely to increase because some manufacturers have allegedly discontinued production and have moved on to the production of other analogues (29).

17. Current international controls and their impact

Isotonitazene is not controlled under the Convention on Psychotropic Substances of 1971 or under Schedule I of the United Nations Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (31, 32). However, other drugs in the same class – etonitazene and clonitazene – are controlled under the United Nations Single Convention on Narcotic Drugs of 1961 (31, 33).

18. Current and past national controls

The US DEA placed a temporary order to schedule isotonitazene, including its isomers, esters, ethers, salts and salts of isomers, esters and ethers whenever they occur, in schedule I of the Controlled Substances Act on 18 June 2020 (34).

The United Kingdom controls isotonitazene through the legislation on NPS. Estonia, Latvia, Poland, Sweden and Turkey have placed isotonitazene under restrictive measures. Lithuania and Norway control isotonitazene through legislation on medicines. It is not known whether isotonitazene is controlled in China (3).

Isotonitazene is not subject to restrictive measures at national level by the Member States Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, the Netherlands, Portugal, Romania, Slovakia, Slovenia and Spain (3).

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

Limited pharmacological information is available on isotonitazene, which could increase the risk of harmful adverse events. There is no information on the social harm that may be caused by isotonitazene. It is likely, however, that the risks may be similar to those associated with the use of established opioids, especially etonitazene, metonitazene and clonitazene, which are derived from the same class of benzimidazole compounds.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of isotonitazene

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, seven in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. A total of 13 countries opted not to participate (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 29 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on isotonitazene

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	9	4
Eastern Mediterranean Region	8	3
European Region	22	16
South-East Asia Region	5	1
Western Pacific Region	4	4
Total 92	63	29

Legitimate use

No country reported approved human medical products or veterinary products containing isotonitazene.

One country (in the Region of the Americas) reported that isotonitazene was currently used in medical or scientific research (excluding use as an analytical standard), specifically in cell line studies (binding/functional assays) and animal studies.

One country (in the Region of the Americas) reported that isotonitazene was used in industrial or other non-medical or non-scientific applications.

No country reported approved therapeutic indications for isotonitazene.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Eight countries (two in the Region of the Americas, five in the European Region, one in the Western Pacific Region) reported that isotonitazene was misused or abused for its psychoactive properties or recreational use.

The most commonly reported route of administration was oral, followed by injection (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	3
Injection	2
Inhalation	0
Sniffing	1
Smoking	1
Don't know	18

The most commonly reported formulation of isotonitazene was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	4
Tablets	1
Liquid for oral use	1
Solution for injection	0
Don't know	16

Six countries reported the negative health impact of non-medical consumption of isotonitazene as “serious” or “substantial” (Table 4).

Table 4. Level of negative health impact

Serious	Substantial	Negligible	Don't know
5	1	8	14

One country (in the Region of the Americas) reported numerous seizures of isotonitazene and commented that, as isotonitazene is more potent than fentanyl, it may result in fatal overdoses. Another country (in the European Region) noted that, as there is no reporting obligation by hospitals, poison centres etc., there may be unreported cases of negative health impacts. One country (in the Region of the Americas) stated that isotonitazene caused adverse health effects including death and that isotonitazene has been positively identified in numerous non-fatal and fatal cases.

Two countries (in the European Region and in the Region of the Americas) reported emergency room admissions related to non-medical use of isotonitazene.

One country (in the Region of the Americas) listed the adverse effects with which patients have presented at emergency departments as opioid intoxication and central nervous system depression.

One country (in the European Region) reported that isotonitazene users had presented for drug dependence treatment.

Regarding mortality, four countries (two in the Region of the Americas and two in the European Region) reported deaths involving isotonitazene:

- one fatal case in which it was not known whether other substances were involved (2019)
- three fatal cases in which only the total number of cases was given (2020)
- 67 fatal cases in which other substances were involved (2020).

Status of national control and potential impact of international control

Eight countries (two in the Region of the Americas, five in the European Region, one in the Western Pacific Region) reported that the availability of isotonitazene is currently regulated under national legislation. One country (in the European Region) stated, “The substance Isotonitazene has been evaluated for scientific and healthy aspects and is under approval process by authorities for the inclusion in Table I of Narcotics and Psychotropic Substances”. Another country (in the European Region) noted that, “This substance is controlled as a narcotic drug from 21st September 2020 onwards”.

Table 5. Reported illicit activities involving Isotonitazene

Activity	Number of countries
Smuggling from other countries	1
Manufacture of substance by chemical synthesis	0
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	0
Trafficking	3
Diversion from legal supply chain	0
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	3
Internet sales – other, or location of sellers and website unknown	3
Direct sales to people who use the substance	1
Don't know	16

In addition to the above, countries added:

- trafficking through postal services
- assumed “dark web” sale from unknown origin.

Three countries (in the Region of the Americas and in the European Region) reported seizures (Table 6).

Table 6. Reported seizures of Isotonitazene

Year	No. of seizures
2020 ^a	41
2019	35
2018	0
Total	76
Smoking	1
Don't know	18

^a The country that reported 41 seizures stated that the data are for both 2019 and 2020.

Twenty-two countries have the forensic laboratory capacity to analyse Isotonitazene.

One country (in the European Region) noted that, “Forensic laboratories have the capacity to analyse Isotonitazene if reference material is available”.

Critical review report: MDMB-4en-PINACA

Executive summary

Methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1*H*-indazole-3-carboxamido)butanoate, MDMB-4en-PINACA (CAS not available) is a synthetic cannabinoid with an indazole core and a terminal alkene on the side-chain. It is structurally similar to 5F-ADB. MDMB-4en-PINACA has a chiral centre. The enantiomers have not been separated experimentally, but the S-enantiomer has been identified in samples. The compound is not readily converted into other controlled substances and has not been reviewed by the WHO ECDD.

The most likely routes of administration of MDMB-4en-PINACA in humans are inhalation by smoking the chemical after it has been sprayed onto plant material or vaping after formulation in liquid. It has been identified in seized material formulated for smoking. The dosage required to elicit pharmacological effects in humans is unknown. Only two studies have investigated MDMB-4en-PINACA, and both focused on identification of biomarker(s) that could serve in forensic investigations as indicators of use. Like many other synthetic cannabinoids, MDMB-4en-PINACA is extensively metabolized; however, unlike many other synthetic cannabinoids, the parent product has been identified in authentic urine samples. Analysis of human liver microsomes, hepatocytes and authentic urine samples showed that M3 (C₁₉H₂₇N₃O₅) was the most abundant metabolite.

MDMB-4en-PINACA binds to human cannabinoid type 1 (hCB₁) receptors with a K_i of 3.26 nM. Further, it is a full and potent agonist, decreasing forskolin-stimulated accumulation of cyclic adenosine monophosphate (cAMP) (EC₅₀ = 0.33 nM). No reports of in vivo pharmacological or toxicological effects of MDMB-4en-PINACA have been published. Unpublished data suggest that MDMB-4en-PINACA produces substantial lethargy and hypothermia at higher doses (1–10 mg/kg). No studies demonstrating its abuse or dependence potential were identified.

In humans, MDMB-4en-PINACA has been detected in postmortem femoral vein blood samples taken after two deaths; however, the degree to which the drug contributed to the deaths could not be determined. MDMB-4en-PINACA has also been detected in products marketed as heroin and cannabis in the USA and in Wales.

MDMB-4en-PINACA was first identified in Europe in 2017. Since then, the prevalence of use has increased dramatically, the largest number of seizures being reported in 2019 and a recent seizure in February 2020. Further, MDMB-4en-PINACA has been detected in Asia (three countries), the European Union

(17 countries), New Zealand, the Russian Federation and the USA. Currently, MDMB-4en-PINACA is not subject to international control under the 1971 United Nations Convention on Psychotropic Substances. It is under national control in Canada, Germany, Sweden and the United Kingdom.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available

B. Chemical Abstract Service (CAS) Registry Number

None available

C. Other chemical names

MDMB-PENINACA

MDMB-PINACA N1-pentyl-4-en isomer

5-CL-ADB-A

ADB-PINACA-A

D. Trade names

Not available

E. Street names

Reported in a product labelled “Heavy Weight” (unpublished certificate of analysis from the Massachusetts (USA) Department of State Police, February 2020). The product also contained other substances, including fentanyl.

F. Physical appearance

MDMB-4en-PINACA is described as a powder (1) or white powder (2, 3); a yellow or brown powder (3); a tan powder (unpublished certificate of analysis the Massachusetts Department of State Police, February 2020).

G. WHO review history

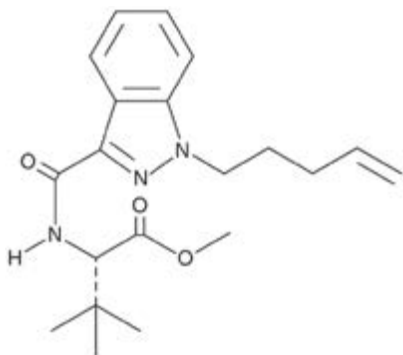
MDMB-4en-PINACA has not been reviewed by the WHO ECDD. It was classified as a high-priority submission for the 43rd annual meeting of the ECDD.

2. Chemistry

A. Chemical name

IUPAC name: methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate

CA Index name: Not available

B. Chemical structure

Molecular formula: C₂₀H₂₇N₃O₃
Molecular weight: 357.5 g/mol

C. Stereoisomers

MDMB-4en-PINACA has one chiral centre, with two enantiomers (*S* and *R*). The *S*-enantiomer has been synthesized as an in-house standard for forensic analysis (4); however, it was unclear whether the samples analysed contained only this enantiomer or the racemate.

D. Methods and ease of illicit manufacture

No information is available on methods of synthesis or ease of illicit manufacture.

E. Chemical properties

Melting-point: No data

Boiling-point: No data

Solubility: Soluble in CH₂Cl₂, MeOH and H₂O (1)

F. Identification and analysis

Various methods have been used to identify and/or analyse MDMB-4en-PINACA. They include GC-MS (1, 4), HPLC-TOF (1), ultra-high-pressure LC with photodiode array and quadrupole TOF-MS (4), NMR spectroscopy (4), LC and quadrupole TOF-MS (2), and LC-high-resolution MS (LC-HRMS) (5).

3. Ease of conversion into controlled substances

Convertibility into a controlled but non-cannabinoid substance is unlikely.

4. General pharmacology

A. Routes of administration and dosage

MDMB-4en-PINACA has been identified in herbal material obtained for research online or from law enforcement seizures (5). Most users who have posted on the effects of MDMB-4en-PINACA in online forums report that they smoked

or vaped the product containing the compound, and one reported sublingual administration (6).

Norman et al. (4) reported the analysis and identification of MDMB-4en-PINACA infused onto paper posted to inmates in Scottish prisons. Since a ban on smoking in prisons, inmates had been inserting small pieces of paper infused with MDMB-4en-PINACA and other synthetic cannabinoids into their e-cigarette devices for subsequent vaping. The concentration of MDMB-4en-PINACA on a single card ranged from <0.07 to 0.58 mg/cm². The dosage of MDMB-4en-PINACA required to elicit pharmacological effects in humans is unknown.

B. Pharmacokinetics

No information on the absorption and distribution of MDMB-4en-PINACA is available. Two studies have examined its metabolism, with an emphasis on the identification of biomarker(s) that could serve during forensic investigations as indicators of use. Like many other synthetic cannabinoids, MDMB-4en-PINACA is extensively metabolized; however, unlike many other synthetic cannabinoids, the parent product has also been detected in authentic urine samples (2, 5). Analysis of human liver microsomes revealed 14–31 phase-I metabolites resulting from various chemical reactions, including ester hydrolysis, double-bond oxidation and hydroxylation (2, 5). Follow-up analysis of authentic human urine samples showed that M3 (C₁₉H₂₇N₃O₅) was the most abundant metabolite (5).

C. Pharmacodynamics

MDMB-4en-PINACA binds to hCB₁ cannabinoid receptors (expressed in human embryo kidney cells), with K_1 (CB₁) = 3.26 ± 0.81 nM (7). When evaluated for functional activation of the CB₁ receptor, MDMB-4en-PINACA was shown to be a full and potent agonist, decreasing forskolin-stimulated accumulation of cAMP: EC₅₀ = 0.33 ± 0.11 nM; E_{max} = $112.7 \pm 5.5\%$ (7).

To date, no reports on the *in vivo* effects of MDMB-4en-PINACA have been published; however, the compound was tested in male ICR mice ($n = 6$) in an unpublished preclinical study (Wiley JL, Marusich JA. RTI International, Durham (NC), unpublished data). In this experiment, MDMB-4en-PINACA (0.1, 1 or 10 mg/kg) was injected intraperitoneally, and rectal temperature was measured 30, 45 and 60 min after injection with overt behaviour observed during the same period. Whereas the dose of 0.1 mg/kg did not reduce temperature at any time, 1 and 10 mg/kg decreased temperature, with maximal decreases of -4.6 ± 0.62 oC and -8.15 ± 0.41 oC, respectively. In addition, some mice that received either 1 or 10 mg/kg were lethargic and exhibited seizures upon handling. At 1 mg/kg, cage behaviour normalized within 2 h; however, at 10 mg/kg, mice were still lethargic 5 h after injection. The 10-mg/kg dose also led to gasping and aggression in some mice. These effects had worn off by 3 h after injection.

5. Toxicology

No preclinical toxicology studies on MDMB-4en-PINACA have been reported.

6. Adverse reactions in humans

Although adverse reactions to MDMB-4en-PINACA have not been widely reported, some information was available. For example, analysis of postmortem femoral vein blood samples by the Center for Forensic Science Research and Education (Willow Grove (PA); 12 September 2019) after two deaths revealed the presence of MDMB-4en-PINACA. However, the extent to which the drug contributed to the deaths could not be confirmed, as the circumstances related to the deaths were not reported. Bizarre and impulsive behaviour after consumption of heroin that had been cut with MDMB-4en-PINACA was reported in Holyoke (MA) (8). Although the UNODC Tox-Portal was searched, no cases related to MDMB-4en-PINACA were identified.

Of the user forums searched, Reddit (sub-reddit r/noids) contained the most information about user-reported effects (6). Users reported cannabis-like euphoria at moderate levels of intake, with dissociation at higher concentrations. Some users reported sedation, whereas others reported stimulation. Memory loss, confusion and agitation have also been reported (9).

7. Dependence potential

A. Animal studies

No in vivo animal studies of the dependence potential of MDMB-4en-PINACA have been reported.

B. Human studies

No human studies to evaluate the dependence potential of MDMB-4en-PINACA have been reported.

8. Abuse potential

A. Animal studies

No animal studies on the abuse potential of MDMB-4en-PINACA have been published. However, unpublished drug discrimination data (Wiley JL, Marusich JA, RTI International, Durham (NC)) showed that intraperitoneal MDMB-4en-PINACA substituted for Δ^9 -tetrahydrocannabinol (THC) in male ($n = 8$) and female ($n = 2$) C57/Bl6 mice trained to discriminate 5.6 mg/kg THC from vehicle in a two nose-poke drug discrimination procedure. Substitution was dose-dependent, with maximal substitution (97% THC-aperture responding) at 0.1 mg/kg, and was not accompanied by effects on response rates. The ED_{50}

for THC-like discriminative stimulus effects for MDMB-4en-PINACA was 0.071 $\mu\text{mol/kg}$.

B. Human studies

No human studies to evaluate the dependence potential of MDMB-4en-PINACA have been reported.

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

Not available

10. Listing on the WHO Model List of Essential Medicines

MDMB-4en-PINACA is not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

MDMB-4en-PINACA has no marketing authorizations as a medicinal product.

12. Industrial use

Not available

13. Nonmedical use, abuse and dependence

MDMB-4en-PINACA was first identified in Europe in 2017 (10). Since then, the prevalence of use has increased dramatically, with the largest number of seizures (143 seizures, representing 89% of all seizures) reported in 2019 and a recent seizure in February 2020 (10). As of August 2020, more than 70 product samples had been submitted and found to contain MDMB-4en-PINACA by WEDINOS (9). Whereas most samples contained only MDMB-4en-PINACA, a few samples contained additional substances, including nicotine, 5F-MDMB-BINACA, flubromazolam and pregabalin. No other specific information on MDMB-4en-PINACA use or abuse was found.

The prevalence of chronic use and dependence on MDMB-4en-PINACA has not been reported.

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

Specific information on the nature and extent of public health problems associated with use of MDMB-4en-PINACA is not available. Adverse effects reported by individual users are described in section 6 of this review.

15. Licit production, consumption and international trade

Not available

16. Illicit manufacture and traffic and related information

MDMB-4en-PINACA has been detected in 17 countries in the European Union – Austria, Belgium, Bulgaria, Cyprus, France, Germany, Hungary, Latvia, Lithuania, Poland, the Republic of Moldova, Romania, Slovakia, Slovenia, Spain, Sweden, Turkey – and in the United Kingdom (10, 11). Of these countries, 12 (70%) reported identification of the substance for the first time in 2019 (10). Identification of MDMB-4en-PINACA has also been reported in Asia (China, Kyrgyzstan and Singapore) (11), New Zealand (3), the Russian Federation (11) and the USA (11).

Information provided by the WHO ECDD confirmed traffic to the USA. For example, a situation report from the District of Columbia Department of Forensic Science (dated 16 December 2019) stated that MDMB-4en-PINACA had been identified for the first time in Washington DC. Similarly, a report from the Center for Forensic Science Research and Education (Willow Grove (PA); 12 September 2019) described analysis of postmortem biological fluid taken in July 2019 from two individuals in Indiana, in which MDMB-4en-PINACA was found.

17. Current international controls and their impact

MDMB-4en-PINACA is not currently under international control.

18. Current and past national controls

Sweden entered MDMB-4en-PINACA onto its list of controlled substances in 2018. It is also controlled in Canada, Germany and the United Kingdom.

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

MDMB-4en-PINACA has been detected as an adulterant in substances marketed as heroin or cannabis/THC (8, 9, 12).

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of MDMA-4en-PINACA

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, 7 in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. A total of 13 countries opted not to participate (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 35 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on MDMA-4en-PINACA

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	10	3
Eastern Mediterranean Region	6	5
European Region	18	20
South-East Asia Region	4	2
Western Pacific Region	4	4
Total 92	57	35

Legitimate use

No country reported approved human medical products or veterinary products containing MDMA-4en-PINACA.

One country (in the Region of the Americas) reported that MDMA-4en-PINACA was currently used in medical or scientific research (excluding use as an analytical standard), specifically in cell line studies (binding/functional assays) and animal studies.

No country confirmed that MDMA-4en-PINACA was used in industrial or other non-medical or non-scientific applications.

No country reported approved therapeutic indications for MDMA-4en-PINACA.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Sixteen countries reported that MDMB-4en-PINACA was being misused or abused for its psychoactive properties or recreational use.

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

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	1
Injection	0
Inhalation	2
Sniffing	0
Smoking	14
Don't know	18

The most commonly reported formulation of MDMB-4en-PINACA was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	9
Tablets	0
Liquid for oral use	2
Solution for injection	0
Don't know	16

To the above, countries added:

- herbal material or paper
- plant mixture sprayed with active substance
- solution for smoking, e-liquid
- blotters.

Eleven countries reported that the negative health impact of non-medical consumption of MDMA-4en-PINACA was “serious” or “substantial” (Table 4).

Table 4. Numbers of countries that reported levels of negative health impact of MDMA-4en-PINACA

Serious	Substantial	Negligible	Don't know
7	4	8	16

One country (in the Western Pacific Region) stated, “The social harm caused by MDMA-4en-PINACA is substantial”. Another country (in the European Region) reported “use by minors (15 years for the youngest) with electronic cigarettes (e-liquid)”. Another country (in the European Region) was concerned that “... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers etc.”. One country (in the European Region) reported, “Recent increase in use, reflected in increase in emergency room visits and increase in seizures. Mainly used by the population of ‘high-risk’ and homeless drug users in combination with other substances”. One country (in the Region of the Americas) stated, “MDMA-4en-PINACA has been identified in seized drug evidence both alone and mixed with fentanyl and/or heroin. It has also been associated with overdoses.”

Five countries (one in the Region of the Americas, four in the European Region) reported emergency room admissions related to non-medical use of MDMA-4en-PINACA.

Several countries reported specific adverse effects. One country (in the European Region) listed the adverse effects as “drowsiness, dizziness, nausea, pallor, derealization, euphoria, visual disturbances (‘zoom’)”; however, they also noted difficulty in specifying the adverse effects associated with MDMA-4en-PINACA because of multiple drug use. Another country (in the European Region) reported “agitation, anxiety, hallucination, convulsions, tachycardia and large pupils”. A third country (in the Region of the Americas) noted “body/muscle spasms similar to seizure, violence towards EMS personnel, tachycardia, PCP-like adverse effects, hypertension, erratic behavior”.

No country reported that users of MDMA-4en-PINACA presented for drug dependence treatment.

Regarding mortality, three countries (in the European Region) reported deaths involving MDMA-4en-PINACA:

- one fatal case in which other substances were also involved (2019)
- one fatal case in which MDMA-4en-PINACA was the only substance involved (2019).

Status of national control and potential impact of international control

Nineteen countries reported that the availability of MDMB-4en-PINACA is currently regulated under national legislation.

Table 5 shows the main reported activities involving MDMB-4en-PINACA.

Table 5. Reported illicit activities involving MDMB-4en-PINACA

Activity	Number of countries
Smuggling from other countries	8
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	2
Trafficking	5
Diversion from legal supply chain	0
Internet sales – seller or website located in country	2
Internet sales – from abroad to buyers in country	2
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	3
Don't know	20

In addition to the above, countries added:

- trafficking through postal services
- seizures in prisons.

Fifteen countries reported seizures (Table 6).

Table 6. Reported seizures of MDMB-4en-PINACA

Year	No. of seizures
2020	554
2019	1321
2018	13
Total	1888

Twenty-eight countries have forensic laboratory capacity to analyse MDMB-4en-PINACA.

Critical review report: CUMYL-PEGACLONE

Executive summary

CUMYL-PEGACLONE (SGT-151; CAS: 2160555-55-3), 5-pentyl-2-(2-phenylpropan-2-yl)pyrido[4,3-b]indol-1-one, is a synthetic cannabinoid derived by combining a cumyl group with pentyl and γ -carboline-1-one. It is structurally related to cumyl-PICA (SGT-56), which is covered by international patent WO 2014/167530 A1 (1). A synthesis method has been published for CUMYL-PEGACLONE. The compound is not readily converted into other controlled substances and has not been reviewed by the WHO ECDD.

CUMYL-PEGACLONE has been identified in seized material formulated for smoking. The dosage required to elicit pharmacological effects in humans is unknown. Apart from studies of its metabolism, investigation of the pharmacokinetics of CUMYL-PEGACLONE has been sparse. Like many other synthetic cannabinoids, CUMYL-PEGACLONE is extensively metabolized, and the presence of the parent product has not been reported in authentic urine samples. Of the identified metabolites, two monohydroxylated metabolites (M20 and M09) predominate and may serve as forensic markers of CUMYL-PEGACLONE use. A thermal degradation product of CUMYL-PEGACLONE has also been identified as N-pentyl- γ -carbolinone.

CUMYL-PEGACLONE binds to both human cannabinoid receptors, hCB1 and hCB2, with similar low nanomolar affinities. At CB1 receptors, it acts as a full and potent agonist, increasing [³⁵S]-GTP γ S binding and decreasing forskolin-stimulated accumulation of cAMP. CUMYL-PEGACLONE also produced pronounced biased agonism at the CB₁ receptor through recruitment of mini-Gai and β -arrestin2.

CUMYL-PEGACLONE has not been evaluated preclinically for pharmacological or toxicological effects, nor has its abuse or dependence potential been assessed. While the presence of CUMYL-PEGACLONE in postmortem femoral vein blood samples from six individuals has been reported, other drugs were also detected in these samples. Hence, the extent to which CUMYL-PEGACLONE contributed to the deaths could not be definitively stated. Two adolescents experienced seizures after smoking a herbal product laced with (analytically confirmed) CUMYL-PEGACLONE.

CUMYL-PEGACLONE was first identified in samples seized by authorities in Germany in 2016 as part of the European Union SPICE Profiling initiative. While the extent of its illicit manufacture and trafficking is unknown, its detection was reported in 16 countries in the European Union and in Japan between 2017 and 2019. Currently, CUMYL-PEGACLONE is not subject to international control under the 1971 United Nations Convention on Psychotropic Substances. In 2018, CUMYL-PEGACLONE became controlled under the German Narcotics Law.

The chemical is also federally controlled under the psychoactive substance laws of Canada, Sweden and the United Kingdom.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available

B. Chemical Abstract Service (CAS) Registry Number

2160555-55-3

C. Other chemical names

SGT-151

D. Trade names

Not available

E. Street names

CUMYL-PEGACLONE has been identified in products labelled Desert (2). In addition, it has been confirmed analytically in products labelled Spice Gold, Mary Joy, Mind Trip, Joker, K2, Karamel Sutra, CM, Monkees Go Bananas, Vertex, Crazy Monkees and KMA (3).

F. Physical appearance

CUMYL-PEGACLONE has been described as a crystalline solid (4) and a white powder (5).

G. WHO review history

CUMYL-PEGACLONE has not been reviewed by the WHO ECDD.

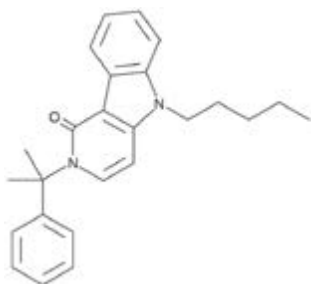
2. Chemistry

A. Chemical name

IUPAC name: 5-pentyl-2-(2-phenylpropan-2-yl)pyrido[4,3-b]indol-1-one

CA Index name: Not available

B. Chemical structure



Molecular formula: C₂₅H₂₈N₂O

Molecular weight: 372.5 g/mol

C. Stereoisomers

No stereoisomers of cumyl pegaclone have been identified.

D. Methods and ease of illicit manufacture

A synthesis method for CUMYL-PEGACLONE and derivatives was published by Janssens et al. (6)

E. Chemical properties

Melting-point: No data

Boiling-point: No data

Solubility: No data

F. Identification and analysis

Ultraviolet-visible spectrum: λ_{\max} at 252 nM (4).

Various methods have been used to identify and/or analyse CUMYL-PEGACLONE. These include GC-MS (2, 3, 7), GC-solid state infrared analysis (2), LC-ESI-quadrupole TOF-MS (2), NMR spectrometry (2, 7), HPLC-diode array detection (3), ultra-high-performance-quadrupole linear ion trap MS (UHPLC-QTRAP) (8) and LC-MS-MS (9).

3. Ease of convertability into controlled substances

Convertibility to a controlled but non-cannabinoid substance is unlikely.

4. General pharmacology

A. Routes of administration and dosage

The primary route of administration for CUMYL-PEGACLONE is presumed to be the same as that for other synthetic cannabinoids: inhalation by smoking or vaping after the chemical has been sprayed onto herbal material or solubilized in vehicle for vaping. Samples obtained for research from online purchases (3, 10) or law enforcement seizures (2, 7, 11) comprised “herbal material”, from which CUMYL-PEGACLONE was identified after extraction. Users have also reported formulation of an e-liquid form of CUMYL-PEGACLONE (12–14). The dosage of CUMYL-PEGACLONE required for pharmacological effects in humans is unknown, although forensic analysis of postmortem serum samples revealed concentrations ranging from 0.38 to 34.9 nM (0.14–13 ng/mL) (10).

B. Pharmacokinetics

No information on the absorption and distribution of CUMYL-PEGACLONE is available. Several studies have examined its metabolism, with emphasis on the identification of biomarker(s) that could serve in forensic investigations as indicators of use. Like many other synthetic cannabinoids, CUMYL-PEGACLONE is extensively metabolized, and the parent product is not detected in authentic urine samples (5, 8). Analysis of authentic urine samples revealed 22 distinct

phase-I metabolites resulting from various chemical reactions, including mono- and di-hydroxylation, dehydrogenation, N-dealkylation, degradation of the pentyl side-chain to a propionic acid metabolite and carbonyl formation at the pentyl side-chain (8). Of the metabolites, 16 were further confirmed in a pooled human liver microsome assay (8). Of these, two monohydroxylated metabolites were most abundant and may serve as forensic markers of use (8). A separate study identified three major metabolites by analysis of pooled human liver microsomes: OH-SGT-151, di-OH-SGT-151 and N-dealkyl SGT-151 (5).

In addition to metabolites, a thermal degradation product of CUMYL-PEGACLONE has been identified: *N*-pentyl- γ -carbolinone (15). Although its activity has not been investigated, the degradant may be present in biological samples after methods of use that involve high heat (e.g. smoking or vaping).

C. Pharmacodynamics

CUMYL-PEGACLONE binds to both hCB₁ and hCB₂ receptors (expressed in Chinese hamster ovary cells) with similar affinities: K_i (CB₁) = 1.37 ± 0.24 nM and K_i (CB₂) = 2.09 ± 0.33 nM (2). Binding affinity to hCB₁ receptors (expressed in human embryo kidney cells) was also reported to be in the low nanomolar range: K_i = 0.36 nM (16) and K_i = 4.57 (17). When evaluated for functional activation of the CB₁ receptor, CUMYL-PEGACLONE was shown to be a full and potent agonist and increased [³⁵S]-GTP-S binding (EC_{50} = 1.62 nM; E_{max} = 143% over basal activity) (16), and decreased forskolin-stimulated accumulation of cAMP (2), with EC_{50} = 0.114 nM; E_{max} = 109% (17). In two studies, CUMYL-PEGACLONE also produced pronounced biased agonism at the CB₁ receptor through recruitment of mini-G_{ai} (EC_{50} = 0.07 nM and E_{max} = 260.9% (18); EC_{50} = 0.17 nM and E_{max} = 194% (6)) and β -arrestin2 (EC_{50} = 0.09 nM; E_{max} = 655.1% (18); EC_{50} = 0.23 nM and E_{max} = 344% (6)). CUMYL-PEGACLONE has not been evaluated in vivo.

5. Toxicology

No preclinical toxicology studies on CUMYL-PEGACLONE have been reported.

6. Adverse reactions in humans

Although adverse reactions to CUMYL-PEGACLONE have not been widely reported (10), some information was available. For example, analysis of postmortem femoral vein blood samples from six individuals revealed the presence of CUMYL-PEGACLONE; however, the presence of other drugs (e.g. opioids, benzodiazepines, alcohol and/or other synthetic cannabinoids) was also noted in five of the six cases (10). Hence, the degree to which CUMYL-PEGACLONE contributed to the deaths could not be determined definitively.

Other cases in which CUMYL-PEGACLONE was identified in serum from dead people have been reported in Australia (19, 20). CUMYL-PEGACLONE was deemed to be a causal or contributory factor in 4 of the 12 reported deaths (20). Two adolescents experienced seizures after smoking a herbal product laced with (analytically confirmed) CUMYL-PEGACLONE (5).

7. Dependence potential

A. Animal studies

No in vivo studies to evaluate the dependence potential of CUMYL-PEGACLONE in animals have been reported.

B. Human studies

No studies to evaluate the dependence potential of CUMYL-PEGACLONE in humans have been reported.

8. Abuse potential

A. Animal studies

No in vivo studies to evaluate the abuse potential of CUMYL-PEGACLONE in animals have been reported.

B. Human studies

No studies to evaluate the abuse potential of CUMYL-PEGACLONE in humans have been reported.

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

Not available

10. Listing on the WHO Model List of Essential Medicines

CUMYL-PEGACLONE is not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

CUMYL-PEGACLONE has no marketing authorization as a medicinal product.

12. Industrial use

Not available

13. Nonmedical use, abuse and dependence

CUMYL-PEGACLONE began to appear on the German market in late 2016, shortly after enactment of the German law on NPS, which banned substances

based on generic structural features of previously identified synthetic substances of abuse. For cannabinoids, banned features included compounds with indole, indazole and benzimidazole cores. Because CUMYL-PEGACLONE contained a γ -carbolinone core that had not been observed previously, it is hypothesized that it was developed to circumvent the new German law (10). Within the first year of enforcement of these new legal restrictions, results of surveillance under the auspices of the European Union SPICE Profiling initiative revealed that, of the biological samples that contained any synthetic cannabinoid, CUMYL-PEGACLONE was identified in about 30% of urine samples between December 2016 and September 2017 (8) and in 29% of blood and serum samples between January and December 2017 (10). CUMYL-PEGACLONE was also present in 25% of product samples evaluated during the same period, second only to 5F-ADB in frequency of detection (10). While some biological and product samples contained other synthetic cannabinoids, CUMYL-PEGACLONE was the only synthetic cannabinoid identified in other samples.

A search of three user websites (Erowid, Bluelight and Reddit (subreddit/r/research_chemicals)) revealed only a few mentions of cumyl pegaclone (SGT-151). Most threads consisted of user queries about the substance. A single user's description of the effects was available: "The effects come on very fast and only last about 1 hour. It produces some euphoria, a relaxed but not 'out of it' – feeling. Some dissociation was also felt at the end of the experience. Also all the usual suspects: red eyes, dry mouth, munchies" (14).

The prevalence of chronic use and dependence on cumyl pegaclone has not been reported.

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

No specific information on the nature or extent of public health problems associated with use of CUMYL-PEGACLONE is available. In one case report, CUMYL-PEGACLONE was identified in samples obtained from two adolescents who experienced seizures after smoking a cigarette that had been laced with CUMYL-PEGACLONE without their knowledge, suggesting that the chemical could cause harm to others if administered without their knowledge or consent. Adverse effects experienced by individual users are described in section 6 of this review.

15. Licit production, consumption and international trade

Not available

16. Illicit manufacture and traffic and related information

CUMYL-PEGACLONE was first identified in samples seized by authorities in Germany in 2016 as part of the European Union SPICE Profiling initiative

(2). The extent of its illicit manufacture and trafficking is unknown. However, as for other synthetic cannabinoids, underreporting is likely, due to lack of routine screening for specific compounds. In addition to Germany (two reports in 2017; one report each in 2018 and 2019), the UNODC reported detection of CUMYL-PEGACLONE in the following countries between 2017 and 2019:

- Austria (two reports in 2019)
- Belgium (two reports in 2019)
- Croatia (one report in 2017)
- Denmark (one report each in 2017 and 2018)
- Finland (one report in 2019)
- France (one report each in 2017 and 2019)
- Hungary (one report each in 2017 and 2018)
- Japan (one report in 2019)
- Luxembourg (one report in 2018)
- Netherlands (one report each in 2017 and 2018)
- Poland (one report each in 2018 and 2019)
- Slovakia (one report in 2019)
- Slovenia (one report in 2018)
- Spain (two reports in 2019)
- Sweden (one report each in 2018 and 2019)
- Switzerland (one report each in 2017 and 2019) (21).

See Annex 1 for additional information on illicit manufacture and traffic in WHO Member States.

17. Current international controls and their impact

CUMYL-PEGACLONE is not currently under any international control.

18. Current and past national controls

In 2018, CUMYL-PEGACLONE became controlled under the German Narcotics Law. The chemical is also federally controlled under the psychoactive substance laws of Canada and the United Kingdom. Sweden entered CUMYL-PEGACLONE into its list of controlled substances in 2019.

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

None.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of CUMYL-PEGACLONE

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, 7 in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. A total of 13 countries opted not to participate (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 30 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on cumyl pegaclone

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	10	3
Eastern Mediterranean Region	7	4
European Region	21	17
South-East Asia Region	5	1
Western Pacific Region	4	4
Total 92	62	30

Legitimate use

No country reported approved human medical products or veterinary products containing CUMYL-PEGACLONE.

Two countries (in the European Region and the Region of the Americas) reported CUMYL-PEGACLONE being currently used in medical or scientific research (excluding use as an analytical standard).

No country reported CUMYL-PEGACLONE being used in industrial or other non-medical or non-scientific applications.

No country reported approved therapeutic indications for CUMYL-PEGACLONE.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Eight countries (six in the European Region, two in the Western Pacific Region) reported that CUMYL-PEGACLONE was being misused or abused for its psychoactive properties or recreational use.

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

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	1
Injection	0
Inhalation	2
Sniffing	0
Smoking	7
Don't know	15

To the above, one country added, “...most likely smoking”.

The most commonly reported formulation of CUMYL-PEGACLONE reported was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	4
Tablets	1
Liquid for oral use	1
Solution for injection	0
Don't know	14

To the above, countries added:

- tobacco leaves laced with substance
- herbal material or herbal plants for smoking.

Eight countries reported that the negative health impact of non-medical consumption of CUMYL-PEGACLONE was “serious” or “substantial” (Table 4).

Table 4. Numbers of countries that reported levels of negative health impact of CUMYL-PEGACLONE

Serious	Substantial	Negligible	Don't know
6	2	9	13

One country (in the European Region) reported, “... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers etc.”. Another country (in the European Region) noted the “Small magnitude of the problem. Extent increasing over the last years”.

One country (in the European Region) reported emergency room/department admissions related to non-medical use of CUMYL-PEGACLONE.

With regard to adverse effects, one country (in the European Region) noted, “Several severe intoxications; adverse reactions: can lead to sudden tiredness”.

No country reported that users of CUMYL-PEGACLONE presented for drug dependence treatment.

Regarding mortality, only one country (in the European Region) reported deaths involving CUMYL-PEGACLONE:

- three fatal cases in which other substances were also involved (2017).

Status of national control and potential impact of international control

Fourteen countries reported that the availability of CUMYL-PEGACLONE is currently regulated under national legislation.

Table 5 shows the main reported activities involving CUMYL-PEGACLONE.

Table 5. Reported illicit activities involving CUMYL-PEGACLONE

Activity	Number of countries
Smuggling from other countries	3
Manufacture of substance by chemical synthesis	0
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	0
Trafficking	3

Activity	Number of countries
Diversion from legal supply chain	0
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	2
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	0
Don't know	18

To the above, countries added:

- trafficking through postal services
- not currently, but trends suggest smuggling, production and Internet sales.

Table 6. Reported seizures of CUMYL-PEGACLONE

Year	No. of seizures
2020	32
2019	182
2018	1148
Total	1362

Twenty-four countries have forensic laboratory capacity to analyse CUMYL-PEGACLONE.

One country (in the European Region) noted, “Forensic laboratories have the capacity to analyse CUMYL-PEGACLONE if reference material is available”.

Critical review report: Flubromazolam

Executive summary

Flubromazolam is a novel or “designer” benzodiazepine that has not been subject to a clinical trial or registered for therapeutic use. It is a 1-4 triazolobenzodiazepine (similar to etizolam, triazolam and alprazolam) with a very high potency and long-lasting depressive effects on the central nervous system. The long half-life may result in increased risk of harm and more complicated clinical management than with shorter-acting benzodiazepines. Because of its high potency, the doses of flubromazolam are typically low (0.15–0.40 mg), and it is usually taken orally, as a liquid or tablet, although rectal, nasal, sublingual and inhaled routes of administration have also been described. The effects of flubromazolam are reversed by the benzodiazepine antagonist flumazenil, although, because of the long half-life of flubromazolam, patients can return to a comatose state when the effect of flumazenil wears off.

A single dose of 0.5 mg flubromazolam resulted in pharmacological effects (strong sedation and partial amnesia) lasting more than 24 h, with reports on online forums and in published case reports that the effects of a single dose can last for several days.

No preclinical or clinical studies were found of abuse liability or potential dependence on flubromazolam, although reports online describe severe withdrawal symptoms, loss of control over use and rapid onset of tolerance.

Limited information is available on the prevalence of use, and, as flubromazolam is often consumed in falsified medicines, it may often be consumed unintentionally. Nonmedical use of flubromazolam has been documented in many countries, including Australia, Denmark, Norway, Poland, Sweden, the USA and Wales, where published reports of both severe acute intoxication and fatal intoxication have appeared in recent years. Reports from online forums are consistent with scientific studies demonstrating high potency, amnesic and sedative effects, development of tolerance and severe withdrawal symptoms.

Flubromazolam is a controlled substance in Australia, Canada, Denmark, Finland, Sweden, Switzerland, Turkey, the United Arab Emirates, the United Kingdom and parts of the USA. It has not been pre-reviewed or critically reviewed by the ECDD, nor is it under international control.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available

B. Chemical Abstract Service (CAS) Registry Number

612526-40-6

C. Other chemical names

8-bromo-6-(2-fluorophenyl)-1-methyl-4*H*-(1,2,4)triazolo(4,3-*a*)(1,4)benzodiazepine

UNII-1BF1HN5GWD

1BF1HN5GWD

612526-40-6

4*H*-(1,2,4)triazolo(4,3-*a*)(1,4)benzodiazepine, 8-bromo-6-(2-fluorophenyl)-1-methyl-

SCHEMBL2841164

DTXSID40620266

VXGSZBZQCBNUIP-UHFFFAOYSA-N

MFCDD29036758

D. Trade names

None

E. Street names

Liquid Xanax

F. Physical appearance

Flubromazolam is a white powder, often sold as a liquid or as tablets (e.g. in falsified medicines). There are confirmed reports of flubromazolam being sold as alprazolam (1).

G. WHO review history

Flubromazolam has not been pre-reviewed or critically reviewed.

2. Chemistry

A. Chemical name

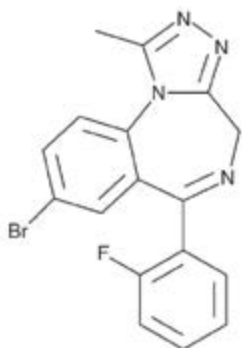
IUPAC Name: 8-bromo-6-(2-fluorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine

CA Index name:

Not available

B. Chemical structure

Flubromazolam is a 1-4 triazolobenzodiazepine containing a fluorine, a bromine and a methylated triazole substituent on the benzodiazepine skeleton (2). The fluorine in the R^{2'} position increases its potency (3).



Free base:

Molecular formula: C₁₇H₁₂BrFN₄

Molecular weight: 371.2

C. Stereoisomers

None

D. Methods and ease of illicit manufacture

No information on the methods or ease with which flubromazolam is manufactured was identified, although methods for one-pot synthesis of triazolobenzodiazepines have recently been published (4).

E. Chemical properties

Melting-point: Not found

Boiling-point: 520.6 ± 60.0 °C at 760 mm Hg

Solubility: Flubromazolam is sparingly soluble in an aqueous buffer; it can be dissolved in dimethylformamide before dilution in an aqueous buffer, with a solubility of 0.5 mg/mL in a 1:1 dimethylformamide:phosphate buffered saline solution (5).

F. Identification and analysis

Several publications report methods for the identification of flubromazolam. Flubromazolam cross-reacts with a range of commonly used urine immunoassays (6), and difficulty was reported in analysing a series of samples from impaired drivers, with negative responses reported in six of seven cases, despite later confirmation of the presence of flubromazolam by LC-MS-MS or GC-MS (7). Thus, some cases may be missed by screening with immunoassays, probably because of low concentrations of flubromazolam in blood, which reflect the low doses of this high-potency benzodiazepine that are typically used (7).

Confirmation of flubromazolam in urine samples by LC–MS–MS has been described, with direct injection after enzymatic hydrolysis (8). With this method, flubromazolam was identified in 96 of 390 patient samples collected between February 2014 and November 2015 that were positive in an immunoassay screen that tested negative for classical benzodiazepines. The concentration range of flubromazolam was 5.4–1500 ng/mL (8). LC–MS–MS has also been used to detect flubromazolam in other biological samples, including serum, urine and hair (9). More sensitive LC–MS methods have been used with ultra-high-performance LC) in a linear range of 0.5–1000 ng/mL and a limit of detection for flubromazolam of 0.1 ng/mL (10).

Novel LC–MS–MS methods have been developed to simultaneously identify and quantify flubromazolam and other novel benzodiazepines. They identify flubromazolam in serum at concentrations of 5–600 ng/mL, with a limit of detection of 1.5 ng/mL (11). A validation study with postmortem blood samples validated use of LC–MS–MS to detect flubromazolam. This technique also identified flubromazolam (at 40 ng/mL) in a postmortem sample in which only etizolam and lorazepam had been identified initially by GC–MS (12). LC–HRMS is also recommended as a sensitive method for identifying flubromazolam and other novel benzodiazepines (13).

A single dose could be detected in a hair sample 2 weeks after use of flubromazolam, indicating that the method could be useful in detecting substance use in drug-facilitated crimes (9).

UHPLC quadrupole TOF–MS was used to test a drug sample of pills identified as flubromazolam, which enabled subsequent identification of flubromazolam in the patient's urine (14).

Flubromazolam metabolites have been detected by triple quadrupole MS (15). LC–HRMS has also been used to study human metabolism of flubromazolam (16).

3. Ease of convertibility into controlled substances

No published information was available on the ease of conversion of flubromazolam into controlled substances.

4. General pharmacology

A. Routes of administration and dosage

Trip reports describe use of doses between 0.15 and 0.4 mg, 0.35 mg being a common dose (3, 17). Administration has been reported via rectal, nasal, sublingual and intravenous routes (18). Smoking and use of vaporized flubromazolam have also been described (18).

B. Pharmacokinetics

Consumption of a single 0.5-mg dose of flubromazolam led to multiple peaks in serum concentration. The first peak was reached after 5 h (7.4 ng/mL) and the second after 8 h (8.6 ng/mL, postprandial), possibly due to enterohepatic cycling of flubromazolam (9). The following day, sedative effects recurred, corresponding to a repeated rise in the serum flubromazolam concentration to 5.2 ng/mL (30 h after intake). A terminal elimination half-life of 10–20 h was estimated from this single-participant study with a single dose.

People who have taken flubromazolam report an onset of action after 20–45 min, an average duration of effects of 3–6 h and after-effects lasting 1–14 h (19). Longer duration is described in online forums; for example, reports from Sweden described effects lasting several days (18).

As the metabolism of flubromazolam involves CYP3A4/5 and UGT1A4 enzymes (16, 20), enzyme polymorphism may influence excretion and pharmacological effects. Major metabolites, formed predominantly by hydroxylation, dihydroxylation and O-glucuronidation, include α -hydroxy-flubromazolam (the most abundant metabolite), 4-hydroxy-flubromazolam, flubromazolam N-glucuronide, α -hydroxy-flubromazolam glucuronide and 4-hydroxy-flubromazolam glucuronide (2, 9, 16, 17). Use of flubromazolam hydroxy metabolites in urine as target metabolites has been suggested (21). Hepatic clearance of flubromazolam has been reported to be 0.42–0.43 mL/min/kg (16). Flubromazolam is 89% plasma protein-bound (10, 22).

A median blood concentration of 0.012 mg/L (0.00048–0.10 mg/L) was reported for flubromazolam in a study of 25 impaired drivers (23). Two cases involved only flubromazolam. In the first, the blood concentration was 0.10 mg/L, and the driver was assessed as “considerably impaired”. In the second, the concentration was 0.00048 mg/L, and the driver was assessed as mildly impaired. In a later study, a median blood concentration of 0.0056 mg/L flubromazolam (range, 0.0004–0.0036 mg/L) was measured in 20 samples obtained predominantly from intoxicated drivers. However, none of the cases involved flubromazolam alone, so that the blood concentration associated with impairment could not be determined (24). One autopsy case in the same study had a flubromazolam blood concentration of 0.052 mg/L.

C. Pharmacodynamics

A single 0.5-mg dose of flubromazolam induced strong sedative effects that lasted more than 10 h and partial amnesia over more than 24 h (9).

Like other benzodiazepines, flubromazolam achieves its pharmacological effect by allosteric potentiation of chloride currents induced by GABA in GABA_A receptors.

5. Toxicology

No studies of acute and preclinical toxicology were identified.

6. Adverse reactions in humans

Acute intoxication

The cases described below are from reports of acute nonfatal intoxication ($n = 21$) and fatal intoxication ($n = 11$) with flubromazolam. Patients commonly presented in severely drowsy or comatose states, often with protracted symptoms, due to the long half-life of flubromazolam. The benzodiazepine antagonist flumazenil is used to manage acute symptoms in some cases (25). If long-term benzodiazepine use is likely to increase the risk of withdrawal and seizures or a patient is on other proconvulsant medications, flumazenil may not be used because of a risk of seizures (26). Some patients who have taken flubromazolam have been admitted to intensive or critical care units, with effects lasting 8–24 h or more (27).

Australia

- A 32-year-old man in treatment for opioid dependence (taking methadone, 50 mg daily) fell from his chair after taking “pink and purple tablets like lollies” (14). He required supplemental oxygen to maintain an oxygen saturation of $> 94\%$ and had a score of 10 on the GCS. Initial screening of his urine for drugs was positive for benzodiazepines, and further investigation identified doxylamine, clonidine, oxazepam, temazepam, methadone and a methadone metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), which were not considered to explain the presentation. Additional analysis by UHPLC-QTOF revealed that the pills contained 16 mg clonazepam and 0.18 mg flubromazolam. Flubromazolam was subsequently detected in the patient’s urine. The patient was discharged after 15 days of hospitalization, including a lengthy stay in intensive care.

Poland

- A 27-year-old man was found in a comatose state, and urinalysis showed that benzodiazepines were involved (28). Toxicological analysis detected flubromazolam (59 ng/mL in serum and 105 ng/mL in urine). Urinalysis and thin-layer chromatography were negative for substances other than benzodiazepines. The patient improved after administration of the benzodiazepine antagonist flumazenil (1.0 mg for about 30 min) before returning to the previous state, thus confirming the involvement of benzodiazepines. The patient was mechanically ventilated for 4 days and transferred to the neurology department after 9 days. Severe, long-lasting

central nervous system depression with cardiorespiratory failure and brain hypoxic–ischaemic changes were attributed to an estimated dose of 3.0 mg (0.043 mg/kg body weight).

Sweden

- Seventeen cases in which the presence of flubromazolam in urine was confirmed were described. In 15 of the cases, flubromazolam was the only benzodiazepine involved, and 2 involved flubromazolam with meclonazepam (25). Most of the cases were in young people (from 17 years), although the age range extended to 65 years. Several cases required admission to an intensive care unit for up to 72 h. Common symptoms included central nervous system depression, drowsiness, disorientation, slurred speech, hypotension and both dilated and miotic pupils. In each case, the presence of flubromazolam was confirmed in the urine, usually after an initial positive screening for benzodiazepines. Flumazenil (0.1–0.6 mg) was administered in seven cases, and responses were documented in all seven. In this report, which covered a range of novel benzodiazepines, flubromazolam was identified as both the most prevalent and the most hazardous.

United Kingdom

- A 25-year-old man was reported to have been mute and apparently having visual hallucinations before loss of consciousness in his home, and later had seizures during his hospital admission (29). He had a history of mental health conditions and had been prescribed analgesia for back pain. He reported use of flubromazolam (purchased online from China), in addition to oxycodone, ketamine, cannabis and possibly heroin. His urine tested positive for benzodiazepines (consistent with self-reported flubromazolam use) and cannabis, although confirmatory toxicology was not described.

USA

- A 36-year-old man with a history of mental health conditions and substance use disorder experienced prolonged bradycardia after use of 0.4 mg flubromazolam purchased on the Internet to self-manage his anxiety (26). He was monitored in intensive care and treated with supportive fluids before being transferred for management of his sedative dependence. Flumazenil was not administered because of the risk of seizures, given the patient's long-term benzodiazepine use and concurrent proconvulsant medications. Benzodiazepines were detected in routine screening of urine for drugs, although further confirmatory testing was not described.

Deaths

Denmark

- Analysis of two unrelated forensic samples (from a 41-year-old man and a 47-year-old man) identified flubromazolam, in addition to various other pharmaceuticals and substances (16). Methadone intoxication was recorded as the cause of death in both cases. The concentration of flubromazolam in femoral blood was 0.0080 mg/kg in one case and 0.0044 mg/kg in the other.

United Kingdom

- The Advisory Council on the Misuse of Drugs reported a death in 2015 in which flubromazolam was implicated (30). No further details were reported.

USA

- A 24-year-old man who took flubromazolam (purchased online and posted to him while he was an inpatient in a treatment facility for substance use disorder) was attributed to complications of overdose after an extended hospital stay (31). His urine tested positive for benzodiazepines; further confirmatory testing for flubromazolam was not described. Flumazenil was administered, but the patient did not respond to this treatment.
- An autopsy report on a 34-year-old man with a history of depression and suicidal ideation who was found dead in his home revealed the presence of 3-FPM, flubromazolam, U47700, delorazepam, amitriptyline, nortriptyline, methamphetamine, amphetamine, diazepam, nordiazepam and temazepam in femoral blood and 3-FPM in the urine (32). Death was attributed to accidental multiple drug toxicity (diazepam, U-47700, temazepam, flubromazolam, delorazepam, methamphetamine, 3-FPM and amitriptyline).

7. Dependence potential

A. Animal studies

No studies on the dependence potential of flubromazolam in animals were identified.

B. Human studies

No studies on the dependence potential of flubromazolam in humans were identified. People who used flubromazolam reported severe withdrawal symptoms, loss of control over use and rapid onset of tolerance (18).

8. Abuse potential

A. Animal studies

No studies on the abuse potential of flubromazolam in animals were identified.

B. Human studies

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

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

No therapeutic applications of flubromazolam were identified.

10. Listing on the WHO Model List of Essential Medicines

Flubromazolam is not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

Flubromazolam does not have any marketing authorization as a medicinal product.

12. Industrial use

Flubromazolam has no known industrial use.

13. Nonmedical use, abuse and dependence

Nonmedical use of flubromazolam has been documented in many countries, including Australia, Denmark, Norway, Poland, Sweden, the USA and Wales, although limited data on the prevalence of use are available.

The US National Poisons Data System reported 13 cases of single-agent flubromazolam poisoning in 2016 ($n = 2$) and 2017 ($n = 11$). It is therefore less common in single-agent exposure than etizolam ($n = 106$ cases over the same period) (27). The poisonings typically involved young men (85% males; median age, 24 years, range 18–36 years), most cases representing acute exposure in the context of “abuse” (77%).

WEDINOS has published details of reports, between 2015 and 2020, of more than 70 samples in which flubromazolam was the main drug detected (33). In recent years, almost all the flubromazolam sold was as falsified medicines (usually as diazepam and less often as alprazolam or zolpidem), whereas in earlier years flubromazolam tended to be sold as “reagents”, packaged with warnings such as “not for human use”. One sample that tested positive for flubromazolam in the WEDINOS programme, which was sold as Xanax®, also contained MDMA-4en-PINACA.

An analysis of 197 trip reports from online forums described use of flubromazolam, commonly ingested as a liquid and associated with long-lasting effects (3). The main effects were hypnosis and amnesia, which were reported more often than anxiolytic and euphoric effects. Of the 10 novel benzodiazepines examined, flubromazolam scored equal second-highest for potency. The high potency score is consistent with the binding affinity predicted from quantitative structure–activity relationship (QSAR) models (3, 34).

The first reported seizure involving flubromazolam in Sweden occurred in September 2014 (25). The Swedish STRIDA study identified 92 confirmed cases involving flubromazolam intoxication, making it the most prevalent novel benzodiazepine in the report. Clinical data were available for 24 cases in which intoxication with novel benzodiazepines was analytically confirmed. Of these, 15 cases involved flubromazolam as the only benzodiazepine. Most cases were detected in late 2014 and in 2015.

In its second quarter 2020 report, the US Center for Forensic Science Research and Education described eight cases in which flubromazolam use was detected. These included forensic samples from cases linked to illicit drug investigations, medicolegal death investigations and/or investigations of driving under the influence of drugs (35).

Co-intoxication with flubromazolam was identified in five of 52 nonfatal cases of acute intoxication with 3-MeO-PCP and/or 4-MeO-PCP (collected between 2013 and 2015) that were analysed as part of the STRIDA project (36).

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

Reports from an online forum in Sweden by people who used flubromazolam indicated that the withdrawal syndrome associated with flubromazolam was more severe than those with other benzodiazepines. They mentioned rapid development of tolerance, and “worse and longer” withdrawal symptoms, including muscle aches, sleeping disorders, panic attacks, dissociative symptoms, perceptual distortions, cramping, vomiting and seizures (18).

Cases of impaired driving associated with flubromazolam have been reported. It was the most commonly detected novel benzodiazepine in a study of samples from impaired drivers in Norway (between July 2013 and May 2016) (23). In a later study (June 2016–September 2019), however, flubromazolam was less commonly detected than other novel benzodiazepines (24).

A study of 12 drivers in the USA stopped for impaired driving identified flubromazolam in 9 (7). The mean blood concentration of flubromazolam was 16.3 ng/mL (range 7.0–31 ng/mL). The drivers were typically young (17–35 years) and had consumed many substances, including cannabis and cocaine.

In August 2020, the UNODC Tox-Portal identified 129 reports involving flubromazolam. Most ($n = 103$) cases involved driving under the influence of

drugs; 20 were postmortem reports; and 5 related to clinical admissions. Most reports involved men ($n = 107$, mainly aged 15–24 years ($n = 48$) and 35–44 years ($n = 31$)). Most reports were from the USA ($n = 113$), with 14 from Canada, one from Finland and one from the United Kingdom.

The National Board of Forensic Medicine in Sweden identified 41 autopsy cases that had been confirmed to involve flubromazolam and 27 nonfatal cases from contexts such as traffic incidents, violent crimes or probation control in which flubromazolam consumption was confirmed (2).

The long half-life of flubromazolam may contribute to overdose when it is combined with other drugs such as opioids. This may also make the drug prone to accumulation with repeated dosing, which may also contribute to the risk of overdose (9). People who use flubromazolam substances may not be aware of these risks. Characteristics of flubromazolam such as its high potency and its potential to cause strong sedation and amnesia at low oral doses are thought to increase its potential danger. High doses may be taken because of difficulty in measuring doses from bulk materials. It has potential use in drug-facilitated crimes (37).

15. Licit production, consumption and international trade

Flubromazolam is currently sold online as a research chemical.

16. Illicit manufacture and traffic and related information

No descriptions of illicit manufacture of flubromazolam were found. However, Moosmann and Auwärter (17) reported that synthesis of triazolo analogues such as flubromazolam is feasible with available 1,4-benzodiazepines and that a large number of doses of flubromazolam can be made from a given amount of 1,4-benzodiazepines, with relatively low synthesis effort.

17. Current international controls and their impact

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

18. Current and past national controls

Flubromazolam is on Schedule 1 in Virginia (USA) (38).

In 2017, flubromazolam was added to Schedule 2 of the Misuse of Drugs Act 1971 in the United Kingdom (39).

Flubromazolam would be captured under a group listing for benzodiazepines as Schedule IV substances in Canada (40).

Flubromazolam is under international control in Denmark, Finland, Sweden, Switzerland, Turkey and the United Arab Emirates (19).

Flubromazolam was captured under benzodiazepines as a group listing in Schedule 4 (prescription only) listing in Australia. The Australian Therapeutic Goods Administration increased its rating to Schedule 9, which came into effect in 2016 (41). The decision was based on an assessment that flubromazolam has no therapeutic use, carries risks of undetected “spiking” because of the low doses required, has high potential nonmedical use and a risk of overdose, and that local attempts to illegally import the drug had resulted in seizures.

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

None

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of flubromazolam

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, 7 in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. A total of 13 countries opted not to participate (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 34 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on flubromazolam

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	9	4
Eastern Mediterranean Region	7	4
European Region	19	19
South-East Asia Region	5	1
Western Pacific Region	3	5
Total 92	58	34

Legitimate use

No country reported approved human medical products or veterinary products containing flubromazolam.

One country (in the Region of the Americas) reported that flubromazolam was currently used in medical or scientific research, specifically in cell line studies (binding/functional assays) and animal studies.

One country (in the Region of the Americas a) reported that flubromazolam was used in industrial or other non-medical or non-scientific applications.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Twelve countries reported that flubromazolam was being misused or abused for its psychoactive properties or recreational use.

The most commonly reported route of administration was oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	7
Injection	0
Inhalation	0
Sniffing	0
Smoking	0
Don't know	21

The most commonly reported formulation of flubromazolam was tablets (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	4
Tablets	7
Liquid for oral use	1
Solution for injection	0
Don't know	19

To the above, countries added:

- blotting paper (blue)
- trips.

Eight countries reported that the negative impact of non-medical consumption of flubromazolam was “serious” or “substantial” (Table 4).

Table 4. Level of negative health impact

Serious	Substantial	Negligible	Don't know
5	3	9	15

One country (in the European Region) stated, "... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers etc". Another (in the European Region) added, "Flubromazolam is sometimes mixed in fake 'street benzos'. There has been a small increase in the last year in the number of tablets containing it, but numbers are still small. The first emergency room visits (5) have been reported recently". A third country (in the Region of the Americas) reported, "Flubromazolam has been identified in an increasing number of law enforcement seizures. It is abused by a broad range of groups including youths, young adults and older adults. In 2018 flubromazolam was identified by law enforcement in driving under the [influence] ...".

Four countries (three in the European Region, one in the Region of the Americas) reported emergency room admissions after non-medical use of flubromazolam.

With regard to reported adverse effects, one country (in the European Region) commented, "In combination with other drugs: reduced conscience, meiosis, bradycardia, tachycardia, hypertension, agitation, confusion". Another country (in the European Region) noted, "Addiction. Difficulty naming side effects attributed to flubromazolam because context of polyconsumption (opioids, benzodiazepines in particular)".

No country reported that users of flubromazolam presented for drug dependence treatment.

Regarding mortality, three countries (two in the European Region and one in the Region of the Americas) reported deaths involving flubromazolam:

- two fatal cases in which other substances were also involved (2017)
- one fatal case in which other substances were also involved (2020)
- six fatal cases in which it was not reported whether other substances were also involved (two in 2019, four in 2020).

Status of national control and potential impact of international control

Sixteen countries reported that the availability of flubromazolam was currently regulated under national legislation.

Table 5 shows the main reported activities involving flubromazolam.

Table 5. Reported illicit activities involving flubromazolam

Activity	Number of countries
Smuggling from other countries	2
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	0
Trafficking	6
Diversion from legal supply chain	0
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	3
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	2
Don't know	18

To the above, countries added:

- trafficking through postal services
- Internet sales without other information.

Eleven countries reported seizures (Table 6).

Table 6. Reported seizures of flubromazolam

Year	No. of seizures
2020	58
2019	390
2018	477
Total	925

Twenty-six countries have the forensic laboratory capacity to analyse flubromazolam.

One country (in the European Region) noted, “Forensic laboratories have the capacity to analyse flubromazolam if reference material is available”.

Critical review report: Clonazolam

Executive summary

Clonazolam is the most potent of a series of 1-4 triazolobenzodiazepines. It was first synthesized in 1971 but was not licensed for therapeutic use. Clonazolam is a triazolo analogue of the registered drug clonazepam. Clonazolam is sold in powdered form as well as in blotter, liquid and tablet forms. Clonazolam has increasingly been sold as falsified benzodiazepines (commonly as diazepam and alprazolam).

Clonazolam cross-reacts with common benzodiazepine immunoassays. It can be detected in blood by LC–MS–MS and in urine and serum by LC–HRMS. Clonazolam is typically found in urine at low concentrations as the parent compound. Use of low cut-offs and screening for the parent metabolite is recommended.

The doses are generally low, because of its high potency (e.g. 0.2–0.4 mg). Adverse reactions include severe sedation, which sometimes requires flumazenil treatment. Toxicological studies on large groups of impaired drivers have identified clonazolam, albeit less frequently than other novel benzodiazepines. In recent years, many more seizures of clonazolam have been reported in the USA.

Clonazolam is under national control in Sweden and the United Kingdom and has been classified as a Schedule I drug in Virginia (USA). Clonazolam has not been pre-reviewed or critically reviewed by the ECDD, nor is it under international control.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available

B. Chemical Abstract Service (CAS) Registry Number

33887-02-4

C. Other chemical names

UNII-HJH52YYC1X

HJH52YYC1

33887-02-4

SCHEMBL11681332

XJRGLCAWBRZUFC-UHFFFAOYSA-N

DTXSID301014166

ZINC39206261

DB14716

Q19607410

4*H*-(1,2,4)triazolo(4,3-*a*)(1,4)benzodiazepine, 6-(2-chlorophenyl)-1-methyl-8-nitro-6-(2-chlorophenyl)-1-methyl-8-nitro-4*H*-[1,2,4]triazolo[4,3-*a*]

[1,4]benzodiazepine

6-(2-chlorophenyl)-1-methyl-8-nitro-4*H*-s-triazolo[4,3-*a*][1,4]

benzodiazepine

8-nitro-1-methyl-6-(*o*-chlorophenyl)-4*H*-s-triazolo-[4,3-*a*][1,4]

benzodiazepine

8-nitro-6-(*o*-chlorophenyl)-1-methyl-4*H*-s-triazolo[4,3-*a*]

[1,4]-benzodiazepine

6-(2-Chlorophenyl)-1-methyl-8-nitro-4*H*(1,2,4)triazolo(4,3-*a*)(1,2,4)

triazolo(4,3-*a*)(1,4)benzodiazepine

D. Trade names

Reported also to be sold as clonitrazolam (1).

E. Street names

Clon

Clam, C-lam (2)

F. Physical appearance

Clonazolam is sold in powdered, blotter, liquid and tablet forms (3, 4). It is often sold as falsified pharmaceutical benzodiazepine products in tablets and it is also taken in liquid form (5, 6).

G. WHO review history

Clonazolam has not been pre-reviewed or critically reviewed by the ECDD.

2. Chemistry

A. Chemical name

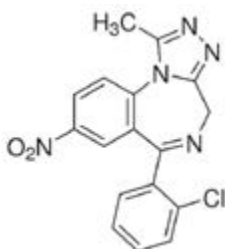
IUPAC name: 6-(2-Chlorophenyl)-1-methyl-8-nitro-4*H*-[1,2,4]

triazolo[4,3-*a*][1,4]benzodiazepine

CA Index name: Not available

B. Chemical structure

Clonazolam is a triazolobenzodiazepine, with a 1-methylated triazole ring fused to the diazepine ring. It is a potent derivative of clonazepam and alprazolam (7).



Free base:

Molecular formula: C₁₇H₁₂ClN₅O₂

Molecular weight: 353.9 g/mol

C. Stereoisomers

None

D. Methods and ease of illicit manufacturing

Methods of small scale-synthesis for forensic use have been published (3). No information was found on illicit manufacture, although purchase as a research chemical is commonly described.

Methods of synthesis of triazolo analogues from available 1-4 benzodiazepines have been described (8, 9).

E. Chemical properties

Melting-point: Not reported

Boiling-point: 576.0 ± 60.0 °C at 760 mm Hg

Solubility: 0.0426 mg/mL in water

F. Identification and analysis

Clonazolam has sufficient cross-reactivity to trigger a positive result on urine screening in common commercial benzodiazepine immunoassays. Those immunoassays cannot, however, distinguish between prescribed benzodiazepines and clonazolam (10).

Clonazolam has been detected in blood samples by LC-MS-MS (11, 12) and in urine and serum by LC-HRMS (13-15). The metabolite 7-aminoclonazolam has been identified in urine by nano-LC-HRMS/MS (16). Clonazolam is typically found in urine at low concentrations as the parent compound (e.g. 7-23 ng/mL) (17). For this reason, screening for the metabolite is recommended (16, 18). A lower cut-off of 10 ng/mL has been recommended (13).

A case report described testing of a drug sample (unconsumed tablets). Clonazolam was identified in the tablets by ultra-HPLC quadrupole TOF-MS (19). Neither clonazolam nor its metabolites were identified in the patient's urine; however, it is unclear whether this was due to limitations of the testing procedure or because the contents of the unconsumed tablet were different from those of the consumed tablet.

A study of femoral blood and urine from an autopsy identified clonazolam and other novel benzodiazepines in the urine but not in femoral blood using QTRAP®, a technology that includes triple quad LC-MS-MS in addition to linear ion trap (20).

3. Ease of convertability into controlled substances

No information was found on the ease with which clonazolam is converted into a controlled substance.

4. General pharmacology

A. Routes of administration and dosage

Oral administration of common doses of 0.2–1.0 mg has been reported (6, 9).

B. Pharmacokinetics

The elimination half-life of clonazolam is estimated to be 3.6 h (14). Clonazolam is extensively metabolized and is mainly excreted as its amino and acetamino metabolites (16). It has a medium-length onset of action (20–60 min) (7). The main metabolites are 7-aminoclonazolam, hydroxycloazolam and 7-acetamidoclonazolam (4). Both metabolites and parent compound are eliminated in the urine. No information was available on the volume of distribution (4). A serum concentration of 6.8 ng/mL was identified in a person intoxicated with multiple substances (15).

C. Pharmacodynamics

Clonazolam is a triazolo analogue of the registered drug clonazepam (21). As with all benzodiazepines, clonazolam achieves its pharmacological effect by allosterically potentiating chloride currents induced by GABA in GABA_A receptors. Clonazolam produces sedation, muscle relaxation, loss of motor control and amnesia (7).

5. Toxicology

Initially synthesized in 1971 in a series of 1-4 triazolobenzodiazepines with high central nervous system depressant activity, clonazolam was found to be the most active substance in the series. It was effective at test doses of less than 10 µg/kg in mice, death occurring at an ED₅₀ of 0.005 mg/kg; the ED₅₀ for antagonism of foot shock was 0.031 mg/kg (22). In these preclinical studies, high potency was demonstrated in tests for loss of righting reflex, antagonizing pharmacological effects of drugs like nicotine and strychnine as well as electric shock and foot shock, in addition to potentiating effects of alcohol and pentobarbital (22).

A QSAR approach showed that clonazolam has a much higher binding affinity at the GABA_A receptor than “classic” benzodiazepines (23). Clonazolam was the second most potent benzodiazepine tested in the study.

6. Adverse reactions in humans

Common clinical effects of clonazolam poisoning identified by the US National Poisons Data System include drowsiness/lethargy (68% of cases), slurred speech (16%) and tachycardia (14%) (24). In most cases (80%), the effects were assessed to be mild to moderate, usually lasting up to 24 h (24). Most of the cases were managed with fluids (34%), although three cases were managed with the benzodiazepine antagonist flumazenil.

Nine case reports (eight emergency department or intensive care admissions and one autopsy) involving clonazolam were identified.

Australia

- A case report described a 32-year-old man in treatment for opioid dependence (taking methadone, 50 mg daily) who had fallen from his chair after taking “pink and purple tablets like lollies” (19). He required supplemental oxygen to maintain an oxygen saturation of > 94%, and had a GCS score of 10. An initial screening of urine for drugs was positive for benzodiazepines. Further investigation identified doxylamine, clonidine, oxazepam, temazepam, methadone and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, but it was considered that these did not explain the presentation. Additional analysis of the tablets by UHPLC-QTOF showed that each tablet contained 16 mg of clonazolam and 0.18 mg of flubromazolam. Flubromazolam was subsequently detected in the patient’s urine; clonazolam was not detected, either because the amount was below the detection level, it had been excreted or it was not consumed. The patient was discharged after 15 days in intensive care.

Czechia

- A 26-year-old man was found unconscious (GCS, 3) and required admission to intensive care with artificial ventilation (15). He was extubated after 12 h and discharged after 40 h. The substances identified in the serum and urine were clonazolam, U-47700, tetrahydrocannabinol, citalopram and midazolam.

France

- Injecting material and several small plastic bags labelled as deschloroetizolam, clonazolam, diclazepam and pyrazolam were identified at the scene where a dead 31-year-old man was found (20). The autopsy revealed multiple organ congestion. Testing of femoral blood and urine revealed the presence of clonazolam and also of flubromazolam, deschloroetizolam and meclonazepam, diclazepam, flubomazepam, nixofepam and etizolam.

Poland

- A 26-year-old woman was admitted to hospital after intentional consumption of clonazolam powder (10 mg) to treat poor sleep due to a persistent cough (25). The patient was unconscious (GCS score, 3) on admission and tachycardic, possibly due to underlying infection and fever associated with bronchitis. A high concentration of clonazolam in

the blood (0.077 mg/L) was measured. After 24 h, the patient still fell asleep when unstimulated, but no flumazenil was required. She was discharged after eight days. No mental health or substance use disorder was identified.

USA

- Two presentations at an emergency department in Ohio were described. Laboratory analysis of the samples of the tablets involved confirmed that they were clonazolam (26):
 - A 20-year-old man was found slumped in his car after taking 2.1 mg of clonazolam (three 0.7 mg tablets). He became hypotensive and bradycardic and responded to intravenous fluids. His urine showed benzodiazepines only.
 - An 18-year-old man in the same car fell asleep after taking 1.4 mg clonazolam. He had tachycardia and hypertension (in contrast to the first case). His urine tested positive for opioids, cannabis and benzodiazepines.
- A 28-year-old man presented to an emergency department with somnolence after ingesting approximately 15 mL of a product labelled as clonazolam 0.5 mg/mL in ethyl alcohol and propylene glycol (4). He was observed in the emergency department, where his vital signs were normal, and he returned to baseline mental status after 6 h.
- A 25-year-old man with a long history of polysubstance use was treated for confusion, visual hallucinations, acute agitation and aggressive behaviour during a hospital stay (1). He reported recent use of benzodrine inhalers and had taken 100 mg of clonazolam over two days before hospital admission.
- A 34-year-old man attended an emergency department in a state of somnolence and confusion that lasted for more than 6 h (14). Samples of tablets he had taken contained clonazolam (the tablet contained 1.1 mg, although marked 0.5 mg) and etizolam (2.4 mg, although marked 1.2 mg).

An unpublished communication to WHO (2020) referred to at least 21 ante- and postmortem overdose events that involved clonazolam in the USA since 2012. Seizure events involving clonazolam were noted to have been increasing at a faster rate than those associated with other substances. The same communication

indicated that the Center for Forensic Science Research and Education in the USA has identified at least nine forensic events, such as postmortem toxicology and human performance testing, that have involved clonazepam since 2018.

7. Dependence potential

A. Animal studies

No published studies were identified.

B. Human studies

No published studies were identified.

C. Abuse potential

A. Animal studies

No published studies were identified.

B. Human studies

No published studies were identified.

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

Clonazepam has never been licensed for therapeutic use.

9. Listing on the WHO Model List of Essential Medicines

Clonazepam is not on the WHO Model List of Essential Medicines.

10. Marketing authorizations (as a medicinal product)

None

11. Industrial use

Clonazepam is sold as a research chemical and reagent (21, 27).

12. Nonmedical use, abuse and dependence

Clonazepam was first detected on the drug market in 2014 (9), and the first reported seizure occurred in Sweden in October 2014 (28). The Swedish STRIDA study identified 16 confirmed cases involving clonazepam intoxication in Sweden, most of which occurred in 2015. The US National Poisons Data System reported 50 cases of clonazepam poisoning during 2016 ($n = 14$) and 2017 ($n = 36$), making it the second most common single-agent exposure after etizolam (24). Poisonings typically occurred in young men (84% males; median age, 26 years, range 15– 50 years), most cases occurring after acute exposure in the context of “abuse” (60%) and suspected suicide (20%) (24).

WEDINOS published details of 24 samples in which clonazepam was the main drug detected (5). Of these, 13 samples were purchased as diazepam or alprazolam. Most of the samples tested were blue, green, red or white “brick”-like tablets sold as falsified alprazolam.

An analysis of 197 trip reports from online forums that described use of clonazepam mentioned hypnotic, amnesic and anxiolytic effects. Users rated clonazepam as having a short-term effect and a high potency score. These effects are consistent with the binding affinity predicted in QSAR models (6, 23).

Online forums describe clonazepam as a strong benzodiazepine, and people who reported recreational and nonmedical use noted strong anxiolytic effects, tolerance, withdrawal and blackouts (29, 30). In discussions in these forums, clonazepam is considered to be one of the most potent benzodiazepines, and a number of forum users warn against its use.

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

In a study of samples of blood from intoxicated drivers between 2013 and 2016, seven samples contained clonazepam, but there were none in which clonazepam was the sole intoxicant. In this study, clonazepam first appeared in early 2016. The median concentration of clonazepam in blood was 0.0053 mg/L (range, 0.0019–0.011 mg/L) (11). In a study of intoxicants, samples from impaired drivers in Norway between June 2016 and September 2019 were examined. Clonazepam was detected in 22 samples, but it was not the sole substance present, and impairment could not be attributed to clonazepam. None of 6500 autopsy reports in this study identified clonazepam (31).

The propensity for clonazepam to potentiate the effects of alcohol and pentobarbital was demonstrated in preclinical studies, indicating that it is likely to contribute to overdose when combined with other sedative drugs (22).

The UNODC Tox-Portal contained 29 reports involving clonazepam, all in the USA, during the period 2017–2019. About half of the cases involved driving under the influence of drugs, one was a postmortem analysis, and four report related to a clinical admission. Males were involved in 20 of the 29 cases, and 25 of the 29 cases involved clonazepam as the sole substance. Most ($n = 16$) cases were in people aged 15–24 years, while 11 reports involved people aged 25–44 years.

15. Licit production, consumption and international trade

Clonazepam was first synthesized in 1971 (22). No products were subsequently marketed, and no clinical trials of clonazepam have been registered. Clonazepam can currently be purchased from many chemical vendors.

16. Illicit manufacture and traffic and related information

Clonazepam is sold in liquid, tablet, capsule, pellet or blotter form on a number of European and US websites, the prices for different preparations being € 10–12 or US\$ 30 for a 30-mL vial. Bulk quantities are available from US websites at higher prices (4).

Domestic seizures of clonazepam have been reported in five US states: Florida, Hawaii, Idaho, Montana and Texas (unpublished communication to WHO from the US Drug Enforcement Administration, Diversion Control Intelligence Division). The cases involved clonazepam in falsified medicines or products purchased from Internet sites (e.g. selling research chemicals) that were labelled as clonazepam.

Preliminary, incomplete data from US law enforcement datasets indicate that clonazepam was involved in more than 570 independent seizure events domestically and/or at US points of entry in 2019 and 2020 (unpublished communication to WHO, 2020). The communication described this as a “dramatic increase” over previous years.

17. Current international controls and their impact

Clonazepam is not currently under international control.

18. Current and past national controls

Clonazepam is on Schedule 1 in Virginia and Louisiana (USA) (32) and is classified as a hazardous substance in Sweden (33).

In 2017, clonazepam was added to Schedule 2 of the United Kingdom Misuse of Drugs Act 1971 (34). Clonazepam would be included in a group listing for benzodiazepines as a Schedule IV substance in Canada (35).

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

None

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of clonazepam

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, 7 in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. A total of 13 countries opted not to participate (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 36 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on clonazepam

Region	Number of countries with no information	Number of countries with information on substance
African Region	12	4
Region of the Americas	8	5
Eastern Mediterranean Region	7	4
European Region	20	18
South-East Asia Region	5	1
Western Pacific Region	4	4
Total 92	56	36

Legitimate use

No country reported that it approved human medical products or veterinary products containing clonazepam.

One country (in the Region of the Americas) reported that clonazepam was currently used in medical or scientific research, “specifically in cell line studies (binding/functional assays) and animal studies”.

Two countries (one in the Region of the Americas and one in the Western Pacific Region) reported that clonazepam was used in industrial or other non-medical or non-scientific applications.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Fifteen countries reported that clonazepam was being misused or abused for its psychoactive properties or recreational use.

The most commonly reported route of administration was oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	12
Injection	0
Inhalation	0
Sniffing	1
Smoking	0
Don't know	20

The most commonly reported formulation of clonazepam was tablets (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	7
Tablets	10
Liquid for oral use	3
Solution for injection	0
Don't know	19

To the above, countries added:

- capsules
- blotter
- stamps.

Nine countries reported that the negative health impact of non-medical consumption of clonazepam was “serious” or “substantial” (Table 4).

Table 4. Numbers of countries that reported levels of negative health impact of clonazepam

Serious	Substantial	Negligible	Don't know
5	4	8	17

One country (in the Western Pacific Region) noted, “The social harm caused by clonazepam is substantial”. Another country (in the European Region) stated, “... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centres etc.”. A third country (in the European Region) wrote, “Clonazepam is sometimes mixed in fake ‘street benzos’. There has been a small increase in the last year in the number of tablets containing it but numbers are still small. The first emergency room visits (two) have been reported recently.” One country (in the Region of the Americas) commented, “Clonazepam has been identified in an increasing number of law enforcement seizures and has contributed to at least two fatal and 19 non-fatal overdose events. It is abused by a broad range of groups, including youths, young adults and older adults.”

Five countries (one in the Region of the Americas and four in the European Region) reported emergency room admissions related to non-medical use of clonazepam.

With regard to reported adverse effects, one country (in the European Region) noted “difficulty listing the side-effects associated with clonazepam because most often polyconsumption contexts”. Another country (in the Region of the Americas) reported, “Clonazepam has been identified in an increasing number of law enforcement seizures and has contributed to at least two fatal and 19 non-fatal overdose events. It is abused by a broad range of groups including youths, young adults and older adults.”. One country (in the European Region) reported the adverse side-effects as “fatigue and relatively low respiratory rate”.

No country reported that users of clonazepam presented for drug dependence treatment.

Regarding mortality, only three countries (one in the Region of the Americas and two in the European Region) reported deaths involving clonazepam:

- one fatal case in which other substances were also involved (2016)
- two fatal cases in which it was not known whether other substances were involved (2018)
- one fatal case in which this substance was the only substance involved (2019)
- two fatal cases in which other substances were also involved (2019).

Status of national control and potential impact of international control
Fifteen countries reported that the availability of clonazepam is currently regulated under national legislation.

Table 5 shows the main reported activities involving clonazepam.

Table 5. Reported illicit activities involving clonazepam

Activity	Number of countries
Smuggling from other countries	4
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	1
Trafficking	5
Diversion from legal supply chain	1
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	4
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	2
Don't know	19

To the above, countries added:

- trafficking through postal services
- Internet sales (without other information).

Twelve countries provided information on seizures (Table 6).

Table 6. Reported seizures of clonazepam

Year	No. of seizures
2020	369
2019	848
2018	768
Total	1985

Twenty-seven countries have the forensic laboratory capacity to analyse clonazepam.

One country (in the European Region) commented, “Forensic laboratories have the capacity to analyse clonazepam if reference material is available”.

Critical review report: Diclazepam

Executive summary

Diclazepam is a 2-chloro derivative of the benzodiazepine diazepam. It consists of a benzene ring fused to a diazepine ring, with an R1 methyl group substitution and two substituted chlorine groups. Diclazepam was first synthesized in the 1960s but was never registered as a therapeutic product.

Diclazepam was first notified to the EMCDDA Early Warning System in 2013. It is commonly sold online as a research chemical. It is taken in doses of 1–4 mg (1–2 mg being a typical dose). It is increasingly sold as falsified diazepam (or “street diazepam”).

Diclazepam has a long elimination half-life of 42 h and is metabolized into the pharmaceutical benzodiazepines delorazepam, lorazepam and lormetazepam. It has similar pharmacological effects to the structurally similar diazepam, causing sedation and impairment of motor activity.

Reports from online forums describe diclazepam as having anxiolytic and hypnotic but not euphoric effects. It is commonly described as used to self-medicate anxiety, as a sleep aid or to self-manage benzodiazepine and stimulant withdrawal. Diclazepam has long-acting effects, with reports of people having “blacked out” for many days after use. It is considered to have lower recreational value than other benzodiazepines.

Diclazepam has been increasingly identified in blood samples from impaired drivers and has also been identified in samples in cases of drug-facilitated sexual assaults in China.

Diclazepam is monitored by the EMCDDA Early Warning System, and 19 European Union countries have reported detection of diclazepam. The UNODC Early Warning System holds data on diclazepam from 23 countries in four regions, with 62 reports between 2015 and 2019. Diclazepam is under national control in Denmark, Finland, Germany, the Republic of Korea, the Russian Federation, Switzerland, Turkey, the United Arab Emirates and the United Kingdom. Diclazepam has not been pre-reviewed or critically reviewed by the ECDD, nor is it under international control.

1. Substance identification

A. International Nonproprietary Name (INN)

Not available

B. Chemical Abstract Service (CAS) Registry Number

2894-68-0

C. Other chemical names

7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one

chlorodiazepam

2'-chloro-diazepam

Ro 5-3448

2-chlorodiazepam

2'-chlorodiazepam

2*H*-1,4-benzodiazepin-2-one, 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1-methyl- (ACD/Index Name)

7-chlor-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-on (German) (ACD/IUPAC Name)

7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin- 2-one

7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin- 2-one (ACD/IUPAC Name)

UNII-070818R7PB

HSDB 6959

C. Trade names

No registered products

D. Street names

None found

E. Physical appearance

Diclazepam is a white powder. It is commonly sold as tablets, pellets and as a liquid and online as a research chemical (1).

F. WHO review history

Diclazepam has not been pre-reviewed or critically reviewed by the ECDD.

2. Chemistry

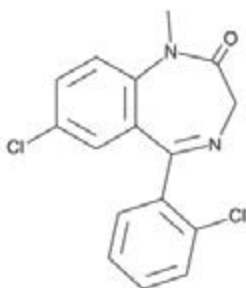
A. Chemical name

IUPAC name: 7-chloro-5-(2-chlorophenyl)-1-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one

CA Index name: Not available

B. Chemical structure

Diclazepam consists of a benzene ring fused to a diazepine ring, with an R1 methyl group substitution and two substituted chlorine groups.



Free base:

Molecular formula: $C_{16}H_{12}Cl_2N_2O$

Molecular weight: 319.2

C. Stereoisomers

None

D. Methods and ease of illicit manufacturing

Diclazepam is manufactured by several laboratories for research purposes and is readily available on the Internet (1). Methods of synthesis have been described (2, 3); however, no information was found on the methods and ease of illicit manufacture.

E. Chemical properties

Melting-point: 217–219 °C

Boiling-point: 524.6 ± 50.0 °C at 760 mm Hg

Solubility: 20.5 mg/L at 25 °C

F. Identification and analysis

Diclazepam is detectable with various immunoassays commonly used for screening urine and blood samples for drugs (4–6). With 200 ng/mL in serum and urine, 72% cross-reactivity was reported in the cloned enzyme donor immunoassay and 75% cross-reactivity in the fluorescence polarization immunoassay, indicating that not all cases of diclazepam use would be detected with these methods (7). Furthermore, a risk has been identified of classification as false-positive for diazepam or of attribution of a positive result to a pharmaceutical benzodiazepine, because diclazepam breaks down into commonly used benzodiazepines, which can complicate interpretation of assay results (8).

A number of approaches have been developed and validated for the detection of diclazepam. Blood and urine samples can be tested for diclazepam by LC–MS–MS (9, 10), and urine can be tested by reversed-phase LC separation with HRMS (11). A microextraction technique based on ultrasound-assisted

low- density solvent dispersive liquid–liquid microextraction coupled with GC–triple quadrupole MS has also been used for the determination of diclazepam in urine samples (12).

Diclazepam has been analysed in an LC–MS–MS system with UHPLC–MS–MS) (13–17). A novel non-aqueous capillary electrophoresis–MS–MS method for simultaneous separation, identification and quantification of diclazepam (and eight other designer benzodiazepines) down to concentrations of 1.5 ng/mL in humans has also been developed and validated (18).

In a study of femoral blood and urine from an autopsy case, diclazepam and other novel benzodiazepines blood were identified with QTRAP® (a technology that includes triple quad LC–MS–MS in addition to linear ion trap) (19). Diclazepam was identified by detecting its phase I metabolites lormetazepam and lorazepam.

Portable methods such as handheld Raman spectroscopic techniques have also been used to identify diclazepam (20).

A case report described use of full-scan high-resolution MS to reanalyse samples after a library was updated with additional novel psychoactive substances. Diclazepam was identified in this retrospective screen, although it had not initially been identified as a contributing drug (21). The report highlighted the usefulness of retrospective screening for identifying novel benzodiazepines and other psychoactive substances. In this case, metabolites of diclazepam – lormetazepam (hydroxy-diclazepam), delorazepam (desmethyl diclazepam) and lorazepam (hydroxy-desmethyl diclazepam) – were initially identified in both blood and urine, but the presence of diclazepam was not confirmed until later.

3. Ease of convertability into controlled substances

No information was found on the ease with which diclazepam can be converted into other controlled substances.

4. General pharmacology

A. Routes of administration and dosage

Diclazepam is taken orally or sublingually. It is sold as a research chemical in 1-, 5- and 10-mg pellets. Common doses reported in online forums were 2–4 mg (22).

B. Pharmacokinetics

Data from a self-experiment with a single 1-mg dose showed that diclazepam has an elimination half-life of 42 h, and its three pharmacologically active metabolites (delorazepam, lorazepam and lormetazepam) can be detected in urine for 6, 19 and 11 days, respectively (7). Diclazepam is a 2-chloro derivative

of diazepam that is metabolized into the prescription drugs benzodiazepines delorazepam, lorazepam and lormetazepam (7).

The metabolic pathways and processes (dealkylation and hydroxylation), with biotransformation via a two-compartment model, are similar to those of diazepam (8). A median blood concentration of 0.025 mg/L diclazepam was associated with impairment (23).

When administered acutely, diclazepam can reduce oxycodone metabolism. When it was administered chronically, increased production of oxymorphone (a more toxic metabolite of oxycodone), rather than the usual metabolic pathway to noroxycodone, was detected (24). No effect of oxycodone on diclazepam metabolism was seen in this study. The study shows that diclazepam can contribute to oxycodone overdose if the two are used together.

Diclazepam has a plasma protein binding value of 93.8%, suggesting that it is less lipophilic than benzodiazepines such as phenazepam, which has a value of 98.3% (25). Its experimental pKa1 is 2.31 ± 0.07 .

C. Pharmacodynamics

Diclazepam has similar effects to diazepam, and people who use diclazepam report comparable tolerance and withdrawal symptoms (26).

The estimated potency of diclazepam as compared with diazepam differs by species. For example, diclazepam was more potent than diazepam in terms of impairment of motor activity and reducing conflict behaviour (e.g. choosing between food and avoiding punishment) in studies with Sprague-Dawley rats (27). Diclazepam was observed to be more potent than diazepam in measures of sedation and muscle relaxation in cats but not in mice (28). In studies with monkeys, the potency of diclazepam was not significantly different from that of diazepam at comparable doses of 1, 2 and 10 mg/kg, suggesting equivalent potency in this species (29).

User reports suggest that the effects last for 5–12 h (30).

5. Toxicology

No studies were identified of the acute or chronic preclinical toxicology of diclazepam.

6. Adverse reactions in humans

The long half-life of diclazepam (42 h) may increase the risk of accumulation and intoxication (7). Published case reports of acute nonfatal intoxication ($n = 7$) and death ($n = 19$) were identified, although it could not be concluded that diclazepam contributed in every case.

Acute intoxication

France

A series of 18 cases of intoxication with diarylethylamines (ephedrine, diphenidine and methoxphenidine) included three cases in which diclazepam was also identified as an intoxicant (31). These were:

- a 34-year-old man who experienced tachycardia, agitation, fever, sweating and obtundation;
- a 20-year-old man admitted to hospital after a suicide attempt, in whom methoxphenidine, diphenidine, 1P-LSD, pyrazolam, diclazepam, metizolam, flubromazepam ethanol and heroin were identified; and
- a 53-year-old man admitted to hospital with asthenia and somnolence in whom methoxphenidine, ephedrine, 1-(benzofuran-6-yl)-*N*-ethylpropan-2-amine, 3-methylmethcathinone, 2-amino-1-(4-bromo-2,5-dimethoxyphenyl)ethan-1-one, α -methyltryptamine and diclazepam were identified.

Italy

- A 30-year-old man with a history of substance use was found in a confused, agitated, uncommunicative state with a GCS score of 9 (32). A small plastic bag containing a few milligrams of a white powder, labelled “Diphenidine 1 g”, was found with him. Toxicological testing confirmed diphenidine in plasma and urine and methylphenidate and diclazepam in plasma, in addition to hospital-administered drugs and their metabolites in urine and plasma. The authors concluded from the toxicological results that the drugs were likely to have been taken together within a short time. The plasma concentration of diclazepam was 3.5 ng/mL.

Sweden

- A 39-year-old man who reported taking 3:4-dichloromethylphenidate and unknown tablets and powder spent 4 h under medical observation with initial signs of agitation, pupil dilation and tachycardia; some of the symptoms might have been attributable to stimulant use. Diclazepam was identified in his urine (33).
- A 45-year-old man was admitted to intensive care after reporting taking 2 mg diclazepam and 8 mg flubromazepam. He was febrile, with agitation, dilated pupils and tachycardia. Flubromazepam was the only novel benzodiazepine detected in a urine sample taken 9 h after admission, although the patient was prescribed zuclopenthixol, which may cause tachycardia. The authors noted that diclazepam might not have been identified because only its metabolites are detectable (33), and unmetabolized diclazepam is not detected in all samples (7).

USA

- A 30-year-old man who was found unresponsive (GCS score, 3) was admitted to an emergency department with non-reactive dilated pupils and required mechanical ventilation (34). Initial screening of his urine for drugs revealed lorazepam and cannabis. He improved over several days, although his condition was complicated by agitation and withdrawal symptoms, which were managed with antipsychotics and benzodiazepines. He was extubated after 10 days. He reported use of 240 mg of diclazepam in liquid form purchased online for research use. Lack of routine testing for diclazepam was identified as a barrier to identification of its use in this case.

Deaths

Australia

- A 28-year-old man with a history of substance use (methamphetamine and a “benzo”) was found dead. His death was attributed to aspiration and mixed drug toxicity (21). Initial screening suggested that U-47700 was involved in the death. Retrospective screening identified additional compounds, namely diclazepam, flubromazepam and 2,5-dimethoxy-4-chloroamfetamine.

Cyprus

- A 42-year-old man with a history of serious mental illness was found unresponsive and could not be resuscitated (35). White powder and a series of tablets were found at the scene. The powder was found to contain etizolam and diclazepam (based on matching mass spectral library information), while the tablets contained mirtazapine and olanzapine.

France

- A 41-year-old man with a well-established history of polydrug use and recent carfentanil intoxication was found dead. Autopsy specimens of blood and urine contained multiple substances, including carfentanil, benzoylfentanyl, 4-fluobutyrylfentanyl ethylhexedrone, diclazepam and methoxetamine. Death was considered to be attributable to carfentanil (36).
- A 31-year-old man was found dead with injecting equipment and several small plastic bags labelled deschloroetizolam, clonazolam, diclazepam and pyrazolam (19). Autopsy revealed multiple organ congestion. Testing of femoral blood and urine revealed diclazepam, with flubromazolam, deschloroetizolam, clonazolam, meclonazepam, flubomazepam, nifoxipam and etizolam. Diclazepam was detected from the presence of its metabolites (lormetazepam and lorazepam), which were found at high concentrations in urine. Diclazepam was not present in blood or urine.

Germany

- A 21-year-old man with a history of substance use was found dead in the bath (37). Urine and femoral blood samples obtained postmortem contained metabolites of diclazepam, in addition to methoxphenidine, 4-fluoroamphetamine and evidence of alcohol consumption.
- A 27-year-old man was found dead, with plastic bags at the scene labelled as containing diclazepam 2 mg, pyrazolam, 3F-phenmetrazine, 1-(2-fluorophenyl) propan-2-amine and diphenhydraminhydrochloride, as well as one unlabelled plastic bag. The sample labelled as diclazepam was confirmed to contain diclazepam, and its metabolites were identified in blood, urine and pericardial and cerebrospinal fluid at autopsy, although at concentrations that were not likely to have been lethal. Death was attributed to positional asphyxia promoted by polysubstance intoxication.

Norway

- A study of samples from intoxicated drivers and other offenders included 13 autopsy cases in which diclazepam was identified. The median concentration of diclazepam in blood was 0.0032 mg/L (range 0.0018–0.032 mg/L).

The UNODC Tox-portal identified four reports involving diclazepam. Two cases involved males aged 15–24 years driving under the influence of drugs (in 2018–2019). Two further cases were reported from Finland and France, both postmortem samples, in which diclazepam was considered to have made little or no contribution.

With the exception of one case in which a high dose of diclazepam was consumed, most cases in which diclazepam has been detected in adverse events have involved consumption of multiple substances, and there is no clear evidence that diclazepam had a contributory role.

7. Dependence potential

A. Animal studies

No published studies were identified.

B. Human studies

No published studies were identified.

8. Abuse potential

A. Animal studies

No published studies were identified.

B. Human studies

No published studies were identified.

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

Diclazepam was developed by a pharmaceutical company but never tested in clinical trials (38).

10. Listing on the WHO Model List of Essential Medicines

Diclazepam is not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

Diclazepam was synthesized and patented in 1961 (3) but has never been marketed as a medicinal product.

12. Industrial use

Diclazepam has no known industrial use.

13. Nonmedical use, abuse and dependence

Diclazepam was first notified to the EMCDDA Early Warning System in August 2013 in a report from Germany (39).

Two samples containing diclazepam were identified in the Swedish STRIDA study in 2013 and 2014 (40).

Content analysis of text from websites such as Drugsforum showed that diclazepam began to appear on the illicit marketplace between 2010 and 2015 (41). Increasing numbers of reports of cases involving novel benzodiazepines (including diclazepam) have been made in France (42).

In an analysis of a convenience sample (in the Global Drug Survey) of 2282 US respondents aged 16–60 years who had attended a nightclub in the previous year, 12 respondents (0.53%) reported use of diclazepam in their lifetime (43).

WEDINOS has published details of more than 70 samples in which diclazepam was the main drug detected (44). The reports, published between 2014 and 2020, confirmed the presence of diclazepam in the samples. The first samples were predominantly tablets packaged and labelled diclazepam, usually sold as reagents labelled “not for human use”. Towards 2018, the frequency of samples increased, and the more recent products were predominantly falsified diazepam and occasionally contained more than one benzodiazepine (e.g. diclazepam with either alprazolam or etizolam).

The US National Poisons Data System reported four cases of diclazepam poisoning in 2016 ($n = 1$) and 2017 ($n = 3$) (45). The US National Forensic

Laboratory Information System reported 203 instances in which diclazepam was identified in reports, increasing from 4 in 2014 to 63 in 2018 and 62 in 2019 (communication to WHO by Cassandra Proileau). The UNODC Early Warning System reported data on diclazepam from 23 countries in four regions, with a total of 62 reports recorded between 2015 and 2019 (46).

An analysis of 197 trip reports from online forums was published. Use of diclazepam was associated with anxiolytic and hypnotic effects and amnesia but not euphoria (22). People who reported using diclazepam assigned it a high potency score, consistent with its binding affinity predicted in QSAR models (22, 47).

In Ireland, samples from 200 participants receiving opioid agonist treatment (i.e. an opioid dependence treatment sample) were examined (48). Two pharmaceutical benzodiazepines that are also metabolites of diclazepam (lorazepam and lormetazepam) were identified. The report did not reach a conclusion about the prevalence of diclazepam use, most likely because of difficulties in differentiating between use of lorazepam and lormetazepam and diclazepam.

Diclazepam has been described on consumer discussion forums as commonly purchased as a sleep aid, to treat anxiety, for sedation and to self-treat benzodiazepine withdrawal or stimulant withdrawal (1).

People on online forums describe diclazepam as inducing less euphoria than other, faster-onset benzodiazepines like alprazolam and perceived it as being less potent than other benzodiazepines in inducing psychoactive effects. They also described cases in which people have blacked out for several days, due to its long half-life (49). Erowid.org had 17 reports on diclazepam; one described suicidal and psychotic symptoms after self-administration (50), although most reports described diclazepam as similar to other benzodiazepines, like diazepam and lorazepam, but longer-acting.

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

User reports suggest that diclazepam is of low recreational value as it causes minimal cognitive impairment (30). The variable amounts of diclazepam contained in non-pharmaceutical products may contribute to public health problems, as larger doses than intended may be consumed due to this variation (7). For example, 1-mg tablets were shown to contain 0.59–1.39 mg diclazepam per tablet.

Reports of impaired driving after consumption of diclazepam appear to be increasing. An initial study of samples associated with driving under the influence of drugs and other criminal offences (July 2013–May 2016) identified 77 samples containing novel benzodiazepines; diclazepam was identified in 15 samples (14). The mean blood concentration was 0.013 mg/L (range, 0.0021–0.057 mg/L). In

a case in an 18-year-old man, diclazepam was the only drug detected, at a blood concentration of 0.057 mg/L. The driver was assessed as “considerably impaired” (the highest rating possible).

A later study reported the results of analysis of 575 samples taken between June 2016 and September 2019, predominantly from intoxicated drivers and other criminal offenders in Norway. Of these samples, 334 contained diclazepam, making it the most frequently detected novel benzodiazepine (23). The median blood concentration was 0.0096 mg/L (range, 0.0016–0.25 mg/L). In 16 cases, all involving driving under the influence of drugs, diclazepam was the only novel benzodiazepine identified. Tests on half ($n = 8$) of the samples identified other substances, including ethanol, nitrazepam and tetrahydrocannabinol or lorazepam, although the latter is likely to have been present as a metabolite of diclazepam. In most cases, impairment was assessed to be moderate to considerable, with diclazepam as the main contributor to impairment. The median blood concentration in individuals judged to be impaired (0.025 mg/L) was higher than that in cases in which the individual was judged not to be impaired (0.0083 mg/L).

Diclazepam has been reported to have been involved in drug-facilitated sexual assaults in China (51). In a study of 31 cases of drug-facilitated sexual assault, for which 31 samples were available, diclazepam was identified in 6 of the 27 biological samples and 6 of the 9 alcohol samples studied. A further report of a case of sexual assault involving diclazepam was published in an abstract (52).

The EMCDDA Early Warning System Network reported 34 deaths in which diclazepam was identified in biological samples (53).

Four deaths involving diclazepam were reported in the United Kingdom between 2014 and 2016 (54).

15. Licit production, consumption and international trade

Diclazepam is commonly sold online as a research chemical, labelled as not for human consumption (26).

16. Illicit manufacture and traffic and related information

An analysis of the content of Internet search engines detected a small increase in the number of websites selling diclazepam between 2014 and 2016 (from 49 to 55) (1). The price of diclazepam sold as a research chemical dropped over time, with considerable discounts for bulk purchasing. Bulk purchases were assumed to be for dealing or supplying friends (1).

In Thailand, 99 850 tablets in a seizure were found to contain diclazepam (official communication to the WHO ECDD).

Diclazepam is monitored as an NPS by the EMCDDA through the European Union Early Warning System. Nineteen European Union countries

have reported detection of diclazepam to the EMCDDA, 17 of the countries reporting approximately 2380 seizures, representing approximately 353 400 units of diclazepam, predominantly in tablet form (53). In 2018, seizure data from the European Union Early Warning System showed that novel benzodiazepines (etizolam, flubromazolam phenazepam and diclazepam) accounted for most (80%) seizures of novel benzodiazepine, although the proportions accounted for by each were not reported (55).

17. Current international controls and their impact

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

18. Current and past national controls

Diclazepam is not currently listed as a Schedule IV substance in the Controlled Substances Act in the USA (26). Diclazepam would be covered in a group listing for benzodiazepines as a Schedule IV substance in Canada, although it is not listed individually (56).

Diclazepam is under national control in Denmark, Finland, the Republic of Korea, Switzerland, Turkey and the United Arab Emirates (57). It is listed under the Misuse of Drugs Act 1971 in the United Kingdom as a Class C drug (58) and in the Law on the Traffic of Narcotics in Germany (59) and is a Schedule III controlled substance in the Russian Federation (60).

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

None

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of diclazepam

Data were obtained from 105 Member States (19 in the African Region, 16 in the Region of the Americas, 13 in the Eastern Mediterranean Region, 40 in the European Region, seven in the South-East Asia Region and 10 in the Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire is 13 (three in the African Region, three in the Region of the Americas, two in the Eastern Mediterranean Region, two in the European Region, one in the South-East Asia Region and two in the Western Pacific Region), leaving 92 active countries. Of these, 32 countries had information on the substance (Table 1).

Table 1. Numbers of countries that provided information on diclazepam

Region	Number of countries with no information	Number of countries with information on substance
African Region	15	1
Region of the Americas	9	4
Eastern Mediterranean Region	7	4
European Region	21	17
South-East Asia Region	4	2
Western Pacific Region	4	4
Total 92	60	32

Legitimate use

No country reported approved human medical products or veterinary products containing diclazepam.

Two countries (one in the Region of the Americas and one in the European Region) reported that diclazepam was currently used in medical or scientific research (excluding use as an analytical reference standard), specifically “in cell line studies (binding/functional assays) and animal studies”.

Two countries (one in the Region of the Americas and one in the Western Pacific Region) reported that diclazepam was used in industrial and other non-medical and non-scientific applications.

Epidemiology of non-medical, non-scientific use – use for psychoactive purposes or recreational drug use

Twelve countries reported that diclazepam was being misused or abused for its psychoactive properties or recreational use.

The most commonly reported route of administration was oral (Table 2).

Table 2. Common routes of administration

Oral	11
Injection	1
Inhalation	0
Sniffing	1
Smoking	0
Don't know	18

The most commonly reported formulation of diclazepam was tablets (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	8
Tablets	10
Liquid for oral use	1
Solution for injection	0
Don't know	16

To the above, countries added:

- trips, capsules
- green capsules.

Eleven countries reported that the negative health impact of non-medical consumption of diclazepam was “serious” or “substantial” (Table 4).

Table 4. Numbers of countries that reported levels of negative health impact of diclazepam

Serious	Substantial	Negligible	Don't know
5	6	7	13

Four countries (in the European Region) reported emergency room admissions related to non-medical use of diclazepam.

With regard to reported adverse effects, one country (in the European Region) noted “lowering consciousness”. Another country (in the European Region) noted, “Difficulty listing the side-effects attributed to diclazepam because context of polyconsumption the most often”.

No country reported that users of diclazepam presented for drug dependence treatment.

Regarding mortality, three countries (in the European Region) reported deaths involving diclazepam:

- two fatal cases in which other substances were also involved (2016)
- one fatal case in which other substances were also involved (2019)
- eight fatal cases in which it was not reported whether other substances were also involved (five in 2019, three in 2020).

Status of national control and potential impact of international control

Fifteen countries reported that the availability of diclazepam was currently regulated under national legislation.

Table 5 shows the main reported activities involving diclazepam.

Table 5. Reported illicit activities involving diclazepam

Activity	Number of countries
Smuggling from other countries	5
Manufacture of substance by chemical synthesis	1
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	1
Trafficking	4
Diversion from legal supply chain	0

Activity	Number of countries
Internet sales – seller or website located in country	2
Internet sales – from abroad to buyers in country	2
Internet sales – other, or location of sellers and website unknown	4
Direct sales to people who use the substance	2
Don't know	18

To the above, countries added:

- trafficking through postal services
- Internet sales (with no other information).

Eleven countries reported seizures (Table 6).

Table 6. Reported seizures of diclazepam

Year	No. of seizures
2020	13
2019	138
2018	131
Total	282

Twenty-seven countries have the forensic laboratory capacity to analyse diclazepam.

One country (in the European Region) commented, “Forensic laboratories have the capacity to analyse diclazepam if reference material is available”.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The Public Health Dimension of the World Drug Problem: How WHO works to prevent drug misuse, reduce harm and improve safe access to medicines.

Geneva: World Health Organization; 2019 (WHO/MVP/EMP/2019.02). Licence: CC BY-NC-SA 3.0 IGO (12 pages)

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children)

WHO Technical Report Series, No. 1021, 2019, ISBN 978-92-4-121030-0 (681 pages)

WHO Expert Committee on Drug Dependence

Forty-first report

WHO Technical Report Series, No. 1018, 2019, ISBN 978-92-4-121027-0 (68 pages)

WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents

Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

WHO Expert Committee on Drug Dependence

Fortieth report

WHO Technical Report Series, No. 1013, 2018, ISBN 978-92-4-121022-5 (60 pages)

WHO Expert Committee on Drug Dependence

Thirty-ninth report

WHO Technical Report Series, No. 1009, 2018, ISBN 978-92-4-121018-8 (48 pages)

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children)

WHO Technical Report Series, No. 1006, 2017, ISBN 978 92 4 121015 7 (604 pages)

WHO Expert Committee on Drug Dependence

Thirty-eighth report

WHO Technical Report Series, No. 1005, 2017, ISBN 978 92 4 1210140 (44 pages)

WHO Expert Committee on Drug Dependence




Thirty-seventh report

WHO Technical Report Series, No. 998, 2016, ISBN 978 92 4 120998 4 (34 pages)

WHO Expert Committee on Drug Dependence

Thirty-sixth report

WHO Technical Report Series, No. 991, 2015, ISBN 978 92 4 120991 5 (62 pages)



This report presents the recommendations of the forty-third Expert Committee on Drug Dependence (ECDD). The ECDD is responsible for the assessment of psychoactive substances for possible scheduling under the International Drug Control Conventions. The ECDD reviews the therapeutic usefulness, the liability for abuse and dependence, and the public health and social harm of each substance. The ECDD advises the Director-General of WHO to reschedule or to amend the scheduling status of a substance. The Director-General will, as appropriate, communicate the recommendations to the Secretary-General of the United Nations, who will in turn communicate the advice to the Commission on Narcotic Drugs.

This report summarizes the findings of the forty-third meeting at which the Committee reviewed 11 psychoactive substances:

- 5-Methoxy-N,N-diallyltryptamine (5-MeO-DALT)
- 3-Fluorophenmetrazine (3-FPM)
- 3-Methoxyphencyclidine (3-MeO-PCP)
- Diphenidine
- 2-Methoxydiphenidine (2-MeO-DIPHENIDINE)
- Isotomitazene
- MDMB-4en-PINACA
- CUMYL-PEGACLONE
- Flubromazolam
- Clonazolam
- Diclazepam

The report also contains the critical review documents that informed recommendations made by the ECDD regarding international control of those substances.

