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1046

WHO Expert Committee on Drug Dependence

Forty-fifth report

World Health Organization

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Contents

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Bromazolam: Giuseppe Cannazza[1], Cinzia Citti[2], Jenny Wiley[3]
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Executive summary

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

At its forty-fifth meeting, the ECDD critically reviewed nine new psychoactive substances, comprising one synthetic cannabinoid receptor agonist (ADB-BUTINACA), two benzodiazepines (adinazolam, bromazolam) four novel synthetic opioids (protonitazene, etazene, etonitazepyne, 2-methyl-AP-237) and two cathinones/stimulants (α-PiHP and 3-Methylmethcathinone). A critical review was undertaken of data on the use of each substance and its effects, so that the Expert Committee could determine whether the information available on these substances justified scheduling in the 1961 or 1971 Convention. In addition, the meeting pre-reviewed zopiclone, to determine whether the current information justified a critical review.

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

	Substance name	**International Union of Pure and Applied Chemistry (IUPAC) name**
To be added to Schedule I of the Single Convention on Narcotic Drugs (1961)	2-Methyl-AP-237	1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone
	Etazene	*2-[(4-Ethoxyphenyl)methyl]-N,N-diethyl-1H-benzimidazole-1-ethanamine*
	Etonitazepyne	2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1H-benzoimidazole
	Protonitazene	*N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine
To be added to Schedule II of the Convention on Psychotropic Substances (1971)	ADB-BUTINACA	*N*-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide
	α-PiHP	4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one
	3-Methylmethcathinone	2-(Methylamino)-1-(3-methylphenyl)propan-1-one)

	Substance name	International Union of Pure and Applied Chemistry (IUPAC) name
To be kept under surveillance	Adinazolam	8-Chloro-*N*,*N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4] benzodiazepine-1-methanamine)
	Bromazolam	8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4] benzodiazepine
	Zopiclone	6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate

1. Information session

On 10 October 2022, before the Expert Committee convened, an information session was held so that the Committee could hear presentations and questions from representatives of interested parties about data that had been provided on the substances under review.

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

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

The 45th ECDD information session received one written statement for consideration.

2. Meeting report of the 45th Expert Committee on Drug Dependence

The forty-fifth meeting of the WHO Expert Committee on Drug Dependence (ECDD) was convened on 10–13 October 2021, coordinated from WHO headquarters in Geneva, Switzerland.

Mariangela 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[8] and the 1971 Convention on Psychotropic Substances[9], 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.

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[10] and the guidance on WHO review of psychoactive substances for international control[11]. The functions of the ECDD are therefore to review the information available to it on the substances being considered for international control and for exemptions and to advise the Director-General on such control. Dr Nannini also reminded participants of the confidentiality of the ECDD's deliberations.

Competing interests in health care may result in conflicts of interest, in biased generation or assessment of evidence and in misinformed health-care policies. WHO has a stringent policy on avoiding conflicts of interest, particularly in the preparation of official guidance documents that affect health care. As a declaration of conflicts of interest is insufficient to neutralize potentially harmful effects, the

[8] Single Convention on Narcotic Drugs, 1961. Vienna: United Nations Office on Drugs and Crime; 1961 (https://www.unodc.org/pdf/convention_1961_en.pdf).
[9] Convention on Psychotropic Substances, 1971. Vienna: United Nations Office on Drugs and Crime; 1971 (https://www.unodc.org/pdf/convention_1971_en.pdf).
[10] Regulations for expert advisory panels and committees: Report by the secretariat. Geneva: World Health Organization; 1998 (http://apps.who.int/iris/bitstream/handle/10665/79146/ee21.pdf?sequence=1&isAllowed=y).
[11] Guidance on the WHO review of psychoactive substances for international control. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/bitstream/handle/10665/44454/9789241500555_eng.pdf?sequence=1&isAllowed=y).

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 45th meeting of the ECDD considered that one member's interest was in conflict with discussions to take place regarding one substance to be reviewed by the Expert Committee. Therefore, Sandra Comer was recused from discussions on zopiclone. No other interests declared by members of the Expert Committee or temporary advisers were deemed relevant to the work of the group.

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

2.1 Updates on ECDD meeting recommendations and outcomes

2.1.1 Recommendations from the 44th ECDD

The 44th Expert Committee on Drug Dependence, which convened on 11–15 October 2021, made the following recommendations.

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

- Brorphine
- Metonitazene

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

- Eutylone

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

- 4F-MDMB-BICA
  Benzylone
- Kratom, mitragynine, 7-hydroxymitragynine
- Phenibut

The WHO Director General communicated these recommendations to the United Nations Secretary General.

Subsequently, on 16 March 2022, the Commission on Narcotic Drugs decided by 49 votes to none, with no abstentions, to include brorphine in Schedule I of the 1961 Convention.

At the same meeting, the Commission decided by 49 votes to none, with no abstentions, to include metonitazene in Schedule I of the 1961 Convention.

The Commission decided by 49 votes to none, with no abstentions, to include eutylone in Schedule II of the 1971 Convention

Therefore, all recommendations made by the 44th ECDD were accepted by the Commission on Narcotic Drugs, effectively placing three new psychoactive substances under international control.

2.1.2 Recommendations by the 10th ECDD Working Group

The ECDD Working group met in March, May, and July 2022 in preparation for the 45th ECDD.

ECDD substance prioritization process

In preparation for the 45th ECDD, the Secretariat initiated a substance prioritization process by requesting information on harmful psychoactive substances from international agencies and a select group of geographically representative Member States with established NPS monitoring systems. This information was reviewed by the Secretariat and the ECDD Working Group.

A total of 10 substances were recommended by the working group for prioritized ECDD review. This included 7 substances for which the Secretariat received nominations from Member States or international agencies for review.

Substance surveillance system

The Working Group also considered data collection priorities for substances that have been recommended for surveillance by the ECDD.

Three substances that have been under WHO ECDD Surveillance (2-Methyl-AP-237, 3-MMC and Zopiclone) were prioritized for consideration by the ECDD given new information provided by Member States and international agencies through the substance prioritization process. These substances will be reviewed by the 45th ECDD.

The ECDD Working Group also recommended to add fluonitazene (flunitazene), AP-238, and *N,N*-Dimethylpentylone (dipentylone) to surveillance for enhanced data collection.

As part of its ongoing substance surveillance work, the Working Group considered additional data collection measures that may be required for substances that have been recommended in the past for surveillance by the ECDD.

This includes tramadol, which has been under ECDD surveillance and was most recently reviewed by the 41st ECDD in 2018. The 41st ECDD recommended continued surveillance, in which regard the Secretariat is seeking to intensify data collection surrounding the medical and extent of non-medical use of tramadol.

Ketamine

The Working Group requested the Secretariat to collect additional information about the medical and non-medical use of ketamine.

2.1.3 Other related priority areas of work

WHO has continued in its efforts to address the inadequate access and availability of opioid pain medication in low-income countries. In 2020 WHO released guidelines on the management of chronic pain in children and we are also developing guidelines on balanced national policies to ensure controlled medicines are available where needed while also minimizing harms caused by their overuse and misuse.

2.2 Recommendations for international control of psychoactive substances

At its 126th session, in January 2010, the WHO Executive Board approved the publication "Guidance on the WHO review of psychoactive substances for international control" *(4)*. In accordance with that document, WHO 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.

According to the Guidance *(4)*, a critical review is initiated by the Expert Committee in any of the following cases:

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

2.2.1 ADB-BUTINACA

Substance identification

ADB-BUTINACA (IUPAC chemical name: *N*-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) is an indazole-derived synthetic cannabinoid. It is described as a crystalline solid or a beige or yellowish powder and has also been found sprayed onto plant material and paper. It is commonly smoked or vaped, although isolated cases of oral use have also been reported.

WHO review history

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

Similarity to known substances and effects on the central nervous system

ADB-BUTINACA is a synthetic cannabinoid that binds to CB_1 and CB_2 receptors with high affinity and is a potent full agonist at both receptors. Its effects are similar to those of other potent CB_1 agonists that are currently controlled under Schedule II of the Convention on Psychotropic Substances of 1971.

No controlled studies of the effects of ADB-BUTINACA have been reported. Online self-reports describe euphoria, appetite stimulation, sedation and paranoia after its use. These effects are consistent with the known effects of cannabinoid agonists.

Dependence potential

No controlled studies of the dependence potential of ADB-BUTINACA in animals or humans have been reported. Its effects at the CB_1 receptor suggest that it would be expected to produce dependence similar to other synthetic cannabinoids.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, ADB-BUTINACA had effects similar to the CB_1 receptor agonist *delta*-9-tetrahydrocannabinol. No studies have been conducted to determine the likelihood of abuse of ADB-BUTINACA in humans; however, CB_1 receptor agonists have known abuse potential.

A number of countries in various regions have reported use of ADB-BUTINACA and harm related to its use, including multiple deaths and presentations of patients to emergency departments with altered consciousness and loss of consciousness. Other substances were usually also involved in these cases, although a number of deaths involved only ADB-BUTINACA.

Therapeutic usefulness

ADB-BUTINACA is not known to have any therapeutic use.

Recommendation

ADB-BUTINACA (*N*-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) is a potent synthetic cannabinoid receptor agonist with a mechanism of action and effects similar to those of a number of other synthetic cannabinoids that are controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Its mode of action suggests the likelihood of abuse and potential for dependence. Use of ADB-BUTINACA has been associated with severe adverse effects, including fatal intoxications. ADB-BUTINACA has no known therapeutic use.

Recommendation: The Committee recommended that ADB-BUTINACA (*N*-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.2.2 Adinazolam

Substance identification

Adinazolam (IUPAC chemical name: 8-Chloro-*N*,*N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine) is a triazolobenzodiazepine. Adinazolam appears as a white or yellow powder and is also sold as tablets and capsules.

WHO review history

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

Similarity to known substances and effects on the central nervous system

Adinazolam is a short-acting benzodiazepine with moderate affinity for the benzodiazepine receptor. It is a chemical analogue of alprazolam and triazolam.

Consistent with its benzodiazepine receptor action, adinazolam showed anticonvulsant, anxiolytic and antidepressant properties in animals. In humans, adinazolam (and its metabolite *N*-desmethyladinazolam) produced a dose-dependent decrease in psychomotor performance and increased sedation and amnesia. It also had some subjective effects similar to those of benzodiazepines such as diazepam and lorazepam, which are controlled under Schedule IV of the 1971 Convention on Psychotropic Substances.

Dependence potential

No studies have been conducted in animals or humans on the dependence potential of adinazolam. In view of its mechanism of action, however, it would be expected to produce typical benzodiazepine dependence.

Actual abuse and/or evidence of likelihood of abuse

In animals, adinazolam shows behavioural effects consistent with those of drugs with abuse liability. In controlled studies in humans, adinazolam produced sedation, and, in one controlled study, adinazolam produced a self-reported "high" feeling, with a greater estimated street value than placebo.

Currently, there is insufficient evidence that adinazolam is being abused to such an extent as to constitute a public health problem. Seizures of adinazolam have been reported in a few countries in two regions. Adinazolam has been identified in falsified pharmaceutical benzodiazepine products, such as falsified alprazolam.

Adinazolam was identified in a few drug-related deaths in combination with other psychoactive substances, including opioids and other benzodiazepines; however, there was no evidence that adinazolam played a causative role in these deaths.

Therapeutic usefulness

Adinazolam is not known to have any therapeutic uses and is not listed on the WHO Model List of Essential Medicines.

Recommendation

Adinazolam (IUPAC chemical name: 8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4] triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine) has effects similar to those of substances listed under Schedule IV of the Convention on Psychotropic Substances of 1971. There is, however, insufficient evidence that its use is a public health and social problem to justify its placement under international control.

Recommendation: The Committee recommended that adinazolam (IUPAC chemical name: 8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*] [1,4]benzodiazepine-1-methanamine) be kept under surveillance by the WHO Secretariat.

2.2.3 Bromazolam

Substance identification

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

WHO review history

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

Similarity to known substances and effects on the central nervous system

There is currently insufficient information on the pharmacological profile of bromazolam from controlled studies in animals or humans to conclude that it has effects similar to those of benzodiazepines, which are controlled under the 1971 Convention on Psychotropic Substances.

Online self-reports by people who claim to have used bromazolam describe benzodiazepine-like effects, including hypnotic, sedative, muscle relaxant and euphoric effects. There are, however, no clinical reports or analytical confirmation of bromazolam to confirm these effects.

Dependence potential

No controlled studies in animals or humans have been reported on the dependence potential of bromazolam. Online self-reports describe withdrawal symptoms after cessation of chronic use.

Actual abuse and/or evidence of likelihood of abuse

No controlled studies in animals or humans have been reported on the abuse liability of bromazolam. In self-reports online, people have described using the drug for its euphoric and other benzodiazepine-like effects; however, there is no confirmation that that the substance used was bromazolam.

Seizures of bromazolam have been reported in multiple countries in several regions.

Bromazolam has been analytically confirmed in a number of deaths, non-fatal intoxications and instances of driving under the influence of drugs. Because of the presence of other drugs, especially other benzodiazepines, however, the contribution of bromazolam cannot be determined.

Therapeutic usefulness

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

Recommendation

While the chemical structure of bromazolam (8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine) is similar to those of other benzodiazepines listed under the Convention on Psychotropic Substances of 1971, its mechanism of action and effects are yet to be confirmed. Although there is increasing evidence of its use, no studies in animals or humans have been reported

on the effects or abuse potential of bromazolam. The limited information on its effects provides insufficient evidence to justify placement of bromazolam under international control.

Recommendation: The Committee recommended that bromazolam (8-bromo-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine) be kept under surveillance by the WHO Secretariat.

2.2.4 Protonitazene

Substance identification

Protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl) methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, is a 5-nitro-2-benzylbenzimidazole synthetic opioid. Protonitazene has been described as a white, yellow or brown powder and as a crystalline solid.

WHO review history

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

Similarity to known substances and effects on the central nervous system

Protonitazene is a chemical analogue of metonitazene and etonitazene, which are controlled under Schedule I of the Single Convention on Narcotic Drugs of 1961. Studies in animals have demonstrated that protonitazene is a full agonist at μ-opioid receptors, with greater potency than morphine and similar potency to fentanyl. Its effects are blocked by the opioid antagonist, naltrexone.

Dependence potential

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

Actual abuse and/or evidence of likelihood of abuse

In animals, protonitazene showed potent opioid effects and abuse potential, similar to those of morphine and fentanyl. Its abuse potential has not been studied in humans; however, online self-reports indicate typical opioid effects, including sedation and euphoria.

Protonitazene is relatively new on the illicit drug market, and there is limited information on the prevalence of its use or of its harm. Several fatalities have occurred in which the presence of protonitazene was confirmed, usually with other substances. The number of deaths may be underreported because of limitations in testing, including difficulty in differentiating this substance from isotonitazene. Protonitazene is reported to be administered through various routes, including intranasally and intravenously.

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

Therapeutic usefulness

Protonitazene is not known to have any therapeutic use.

Recommendation

Protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl) methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, is a synthetic opioid that is liable to abuse and to produce ill effects similar to other 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 protonitazene (IUPAC chemical name: *N,N*-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine), also known as propoxynitazene, be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.2.5 Etazene

Substance identification

Etazene (IUPAC chemical name: 2-[(4-Ethoxyphenyl)methyl]-*N,N*-diethyl-1*H*-benzimidazole-1-ethanamine), also known as etodesnitazene, is a benzimidazole-derived synthetic opioid. Etazene has been described as a grey crystalline, light-yellow, white or beige powder. It has also been identified in liquid form and in falsified pharmaceutical opioids.

WHO review history

Etazene has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this

substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

Etazene binds to the μ-opioid receptor with a potency greater than that of morphine. In studies of analgesia in animals, etazene had full agonist effects, with a potency between those of morphine and fentanyl, which are both controlled under Schedule I of the Single Convention on Narcotic Drugs, 1961. The effects of etazene are reversed by the opioid antagonist, naltrexone.

Dependence potential

No controlled studies of the dependence potential of etazene in animals or in humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similar to other opioids, such as morphine and fentanyl. Online self-reports described tolerance with repeated use of etazene.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, etazene had effects similar to those of morphine. No controlled studies have been conducted of the abuse potential of etazene in humans, 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. Online self-reports support its euphoric and other opioid effects.

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

A number of deaths have occurred in which the presence of etazene was confirmed analytically and in which it was considered to have contributed to death, although other substances were also identified in these cases.

Therapeutic usefulness

Etazene is not known to have any therapeutic use.

Recommendation

Etazene (IUPAC chemical name: 2-[(4-Ethoxyphenyl)methyl]-*N*,*N*-diethyl-1*H*-benzimidazole-1-ethanamine), also known as etodesnitazene, is a synthetic opioid that is liable to abuse and produces ill effects similar to other 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 poses a significant risk to public health.

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

2.2.6 Etonitazepyne

Substance identification

Etonitazepyne (IUPAC chemical name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1Hbenzoimidazole), also known as *N*-pyrrolidino etonitazene, is a benzimidazole-derived synthetic opioid. Etonitazepyne is found as a yellow powder and crystalline solid and has been identified in falsified pharmaceutical opioid tablets.

WHO review history

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

Similarity to known substances and effects on the central nervous system

Studies in animals have demonstrated that etonitazepyne is a potent, full agonist at μ-opioid receptors. In animals, it produces effects similar to those of opioids such as morphine, fentanyl and isotonitazene but with greater potency. There is limited information about the effects of etonitazepyne alone in humans.

Dependence potential

No controlled studies of the dependence potential of etonitazepyne in animals or humans have been reported. As it is a potent μ-opioid receptor agonist, it would be expected to produce dependence similarly to other opioids, such as morphine and fentanyl. Online self-reports describe tolerance and withdrawal after repeated etonitazepyne use.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, etonitazepyne was shown to produce effects that indicated greater potency compared to morphine and fentanyl, and these effects were reversed by the opioid antagonist, naltrexone.

Seizures of etonitazepyne have been reported in multiple countries in two regions. It is reported to be administered by various routes, including snorting, sniffing

and oral administration. Etonitazepyne has been identified in falsified medicines, suggesting that its use may sometimes be unintentional.

Etonitazepyne is a relatively new drug on the illicit market, and there is limited information on the prevalence of its use and of its harm, although non-fatal and fatal intoxications have been documented in a number of countries. The number of deaths involving etonitazepyne has increased over a relatively short time but may be underreported because of its recent, rapid appearance.

Therapeutic usefulness

Etonitazepyne is not known to have any therapeutic use.

Recommendation

Etonitazepyne (IUPAC chemical name: 2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1Hbenzoimidazole), also known as *N*-pyrrolidino etonitazene, is a synthetic opioid that is liable to abuse and to produce ill effects similar to other 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 poses a significant risk to public health.

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

2.2.7 2-methyl-AP-237

Substance identification

2-Methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) is a methyl derivative of the opioid analgesic AP-237 (or bucinnazine).

2-Methyl-AP-237 has been described as a white crystalline powder, a crystalline solid and a white solid.

WHO review history

2-Methyl-AP-237 has not been formally reviewed by WHO and is not currently under international control. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

2-Methyl-AP-237 is an opioid analgesic with a rapid onset of action and a potency and analgesic effects similar to those of fentanyl, which is listed under Schedule I of the Single Convention on Narcotic Drugs, 1961. In animals, it produces acute toxic effects typical of opioids, including respiratory depression. Limited research has been reported on the effects of 2-methyl-AP-237 in humans, although its respiratory depressant effects have been observed, which can be reversed by the opioid antagonist, naloxone.

Dependence potential

No controlled studies of the dependence potential of 2-methyl-AP-237 have been reported in animals or humans. As it is a μ-opioid receptor agonist, it would be expected to produce dependence similar to that induced by other opioids, such as morphine and fentanyl. Online self-reports described tolerance and withdrawal.

Actual abuse and/or evidence of likelihood of abuse

In an animal model predictive of abuse potential, 2-methyl-AP-237 was shown to produce opioid-like effects with a potency between those of morphine and fentanyl. These effects were blocked by the opioid antagonist, naltrexone.

No controlled studies on the abuse potential of 2-methyl-AP-237 in humans have been reported, but, as it is a μ-opioid receptor agonist, it would be expected to produce euphoria and other effects predictive of high abuse liability. Online self-reports support its euphoric and other opioid effects.

Seizures of 2-methyl-AP-237 have been reported in multiple countries in two regions.

A number of deaths in which 2-methyl-AP-237 has been found have been reported, often with multiple substances involved. The deaths occurred in a number of countries and regions.

Therapeutic usefulness

2-Methyl-AP-237 is not known to have any therapeutic use.

Recommendation

2-Methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) is a synthetic opioid that is liable to abuse and to have ill effects similar to those of other 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 2-methyl-AP-237 (IUPAC chemical name: 1-[2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-1-butanone) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.2.8 α-PiHP

Substance identification

α-Pyrrolidinoisohexanophenone (IUPAC chemical name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as α-PiHP, is a synthetic cathinone. It has been described as an off-white solid, a white powder and a crystalline solid.

WHO review history

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

Similarity to known substances and effects on the central nervous system

α-PiHP is an isomer of α-PHP, which is controlled under Schedule II of the Convention on Psychotropic Substances of 1971. Laboratory studies suggest that α-PiHP can inhibit the uptake of dopamine and norepinephrine more potently than substances with known abuse potential, including methcathinone, cocaine and methamphetamine. Studies in animals have shown that α-PiHP is a psychomotor stimulant, with effects comparable to those of cocaine and methamphetamine.

Online self-reports by people who use α-PiHP describe stimulant effects similar to those of α-PVP and α-PHP.

Dependence potential

No controlled studies of the dependence potential of α-PiHP in animals or humans have been reported. In view of its actions and effects on the central nervous system, it would be expected to produce dependence similarly to other psychostimulants such as methamphetamine.

Actual abuse and/or evidence of likelihood of abuse

Studies in animals predictive of abuse liability indicate that α-PiHP produces effects similar to those of methamphetamine and cocaine. No controlled studies of the abuse potential of α-PiHP in humans have been reported.

Seizures of α-PiHP have been described in multiple countries in three regions. α-PiHP has been identified in a number of serious adverse events and drug-related deaths. As it is usually detected with other substances, including opioids and benzodiazepines, the role of α-PiHP is unclear in some instances.

Therapeutic usefulness

α-PiHP is not known to have any therapeutic use.

Recommendation

α-Pyrrolidinoisohexanophenone (IUPAC chemical name: 4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as α-PiHP, is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants, such as methamphetamine, that are listed under Schedule II of the Convention on Psychotropic Substances of 1971. There is evidence that its abuse is likely to constitute a substantial public health and social problem. It has no known therapeutic use.

Recommendation: The Committee recommended that α-pyrrolidinoisohexanophenone (IUPAC chemical name: 4-methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one), also known as α-PiHP, be added to Schedule II of the 1971 Convention on Psychotropic Substances.

2.2.9 3-MMC

Substance identification

3-Methylmethcathinone (IUPAC chemical name: 2-(Methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, is a synthetic cathinone. 3-Methylmethcathinone has been found as a white or off-white powder, a white, yellow or orange solid and a crystalline solid. It has been detected in tablet, capsule and liquid forms.

WHO review history

3-Methylmethcathinone was critically reviewed by the Committee at its 38th meeting, in 2016, when it decided to request a further critical review

once more information became available and to consider it at a subsequent meeting. Information was brought to the attention of WHO that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use. Information from international agencies suggests that there has been a significant increase in the availability of and harm due to 3-methylmethcathinone in recent years.

Similarity to known substances and effects on the central nervous system

3-Methylmethcathinone is an isomer of 4-methylmethcathinone (mephedrone), which is a synthetic cathinone listed under Schedule II of the Convention on Psychotropic Substances of 1971.

3-Methylmethcathinone has a typical psychostimulant profile, similar to that of 4-methylmethcathinone, including inhibition of the reuptake of dopamine, norepinephrine and serotonin and increased release of dopamine and serotonin.

Clinical features of 3-methylmethcathinone intoxication are consistent with those produced by other stimulants and include tachycardia, hypertension, agitation, aggression, hallucinations, rhabdomyolysis and kidney failure.

Dependence potential

No controlled studies of the dependence potential of 3-methylmethcathinone in animals or humans have been reported. Withdrawal symptoms indicative of physical dependence have been documented in people who use 3-methylmethcathinone. In view of its actions and effects on the central nervous system, 3-methylmethcathinone would be expected to produce dependence similar to other psychostimulants, such as methamphetamine.

Actual abuse and/or evidence of likelihood of abuse

In animal models predictive of rewarding effects, 3-methylmethcathinone produced effects that were similar to those of methamphetamine. 3-Methylmethcathinone also produced behavioural (stimulant) effects similar to methamphetamine. No controlled studies in humans have examined the abuse potential of 3-methylmethcathinone.

3-Methylmethcathinone has been seized in multiple countries in several regions.

Many fatal and non-fatal intoxications involving 3-methylmethcathinone have been reported. Other substances were commonly involved in these cases, although severe intoxication and death have been reported in cases in which 3-methylmethcathinone was the only substance identified.

Therapeutic usefulness

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

Recommendation

3-Methylmethcathinone (IUPAC chemical name: 2-(Methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, is a synthetic cathinone with effects similar to those of other synthetic cathinones and other psychostimulants such as methamphetamine that are listed under Schedule II of the Convention on Psychotropic Substances of 1971. There is evidence that its abuse is likely to constitute a substantial public health and social problem. It has no known therapeutic use.

Recommendation: The Committee recommended that 3-methylmethcathinone (IUPAC chemical name: 2-(Methylamino)-1-(3-methylphenyl)propan-1-one), also known as 3-MMC, be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.3 Recommendations on preliminary reviews (pre-reviews)

2.3.1 Zopiclone

Substance identification

Zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) is a sedative hypnotic drug of the cyclopyrrolone class. Zopiclone has been reported as a white or slightly yellowish powder. Zopiclone is available as pharmaceutical products in tablet form for oral use. Eszopiclone (the S-enantiomer of zopiclone) is marketed as a pharmaceutical product in some countries.

WHO review history

Zopiclone was pre-reviewed by the Committee at its 29th meeting, when it recommended that surveillance be continued but that a critical review was not required. In view of the abuse liability of the drug and the significant number of reports of adverse drug reactions related to zopiclone abuse sent to the WHO international drug monitoring programme, however, zopiclone was pre-reviewed by the Committee at its 33rd meeting, when it recommended a critical review. Zopiclone was critically reviewed at the 34th meeting, in 2006, when the Committee rated its abuse liability as low and its therapeutic usefulness considerable and recommended continued surveillance by WHO. A pre-review was initiated after a proposal was received from an international agency that

suggested a significant increase in the reported number of trafficking cases and seizures involving zopiclone.

Similarity to known substances and effects on the central nervous system

Zopiclone binds to the benzodiazepine receptor that forms part of the $GABA_A$ receptor complex. It may bind to different parts of the receptor or cause different changes in the $GABA_A$ receptor complex than benzodiazepines.

In animals, zopiclone has sedative, anxiolytic, anticonvulsant and muscle relaxant properties similar to those of benzodiazepines. In studies in humans, it was less effective than benzodiazepines for treatment of anxiety.

Dependence potential

Studies in animals show evidence of zopiclone tolerance and withdrawal, indicating the development of physical dependence. A number of published reports have described physical dependence associated with zopiclone use in humans. Withdrawal symptoms such as increased anxiety and insomnia have been described in people who cease zopiclone use, usually after prolonged use and dose escalation from clinical use. Tolerance and withdrawal have also been reported in clinical trials. Dependence is documented in databases on adverse events associated with use of pharmaceutical drugs.

Actual abuse and/or evidence of likelihood of abuse

Studies in animals suggest that zopiclone may have abuse liability similar to that of benzodiazepines such as midazolam, diazepam, nitrazepam and alprazolam. The effects indicative of abuse liability were blocked by the benzodiazepine antagonist flumazenil, indicating a mechanism of action involving the benzodiazepine receptor.

No controlled studies in humans have been reported on the abuse potential of zopiclone. Published reports support its abuse potential, its use with alcohol and other drugs, excessive use and escalation to high-dose use. The extent of harm related to the use of zopiclone is, however, unclear.

Zopiclone is widely used therapeutically in many countries and regions, and it is also listed in databases of adverse events associated with pharmaceutical use. Zopiclone is most likely to be misused by individuals to whom it is prescribed for long periods, who are using other psychoactive drugs or in those with psychiatric comorbidities. While seizures of zopiclone have been reported in multiple countries in several regions, the prevalence of non-medical use of zopiclone by

the general population is unknown. Furthermore, there is insufficient evidence that significant public health and social problems related to abuse can be directly attributed to sole use of zopiclone.

Therapeutic usefulness

Zopiclone is a widely used medicine primarily indicated for the short-term treatment of insomnia.

Recommendation

Zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate) is a sedative hypnotic drug of the cyclopyrrolone class. The Committee noted that concern has been expressed in several countries regarding non-prescription use of zopiclone. While there have been reports of adverse effects, overdose, withdrawal symptoms and an increased number of seizures of the substance, there is still insufficient evidence that zopiclone is or is likely to be abused to such an extent as to constitute a public health and social problem.

The Committee also noted that zopiclone is widely used therapeutically in many countries.

Recommendation: The Committee recommended that zopiclone (IUPAC chemical name: 6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl4-methylpiperazine-1-carboxylate) not proceed to critical review but be kept under surveillance by the WHO Secretariat.

3. Critical review and pre-review reports

3.1 Critical review reports

3.1.1 ADB-BUTINACA

1. Substance identification

A. International nonproprietary name

Not available.

B. Chemical Abstracts Service registry number

2666932-43-8 ((*N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide)

2682867-55-4 ((*S*)-enantiomer) (*N*-[(1S)-1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide)

C. Other chemical names

N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-benzyl-1H-indazole-3-carboxamide

N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-benzylindazole-3-carboxamide

2-[(1-Butyl-1*H*-indazol-3-yl)formamido]-3,3-dimethylbutanamide

N-[1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-butyl-1*H*-indazole-3-carboxamide

ADB-BUTINACA

ADB-BINACA

The name ADB-BINACA has been used to refer to ADB-BUTINACA (*N*-[1-amino-3,3-dimethyl-1-oxobutan-2-yl]-1-butyl-1*H*-indazole-3-carboxamide), the analogue with the 1-butyl substituent on the indazole ring instead of the 1-benzyl substituent (ABD-BINACA). ADB-BINACA is the name used for the analogue with the benzyl substituent on the indazole ring as the tail portion (*N*-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-

benzyl-1*H*-indazole-3-carboxamide), while ADB-BUTINACA contains a butyl moiety as its tail *(1–3)*.

D. Trade names

The (S)-enantiomer (*N*-[(1S)-1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide) is sold by Cayman Chemicals as an analytical standard under the trade name "ADB-BUTINACA" *(4)*.

E. Street names

Although no specific information was available on the street names for ADB-BUTINACA, it is likely that the substance is sold under the name "Spice", which is typically used for smoking mixtures containing synthetic cannabinoid receptor agonists. Other common names for such mixtures depend on the country, region, product type, brand name and user groups *(5)*.

F. Physical appearance

The (*S*)-enantiomer of ADB-BUTINACA has been described as a crystalline solid *(4)*. Pure ADB-BUTINACA is typically available as a beige or yellowish powder, but it is easily blended into other street drugs. Thus, small amounts of ADB-BUTINACA in a sample may be difficult to identifiy, as other components can mask its colour, smell and taste. Moreover, solutions of synthetic cannabinoids such as ADB-BUTINACA are usually sprayed onto plant material or into blotting paper and smoked, vaped or consumed orally *(6)*.

G. WHO review history

ADB-BUTINACA has not previously been reviewed by the WHO Expert Committee on Drug Dependence.

2. Chemistry

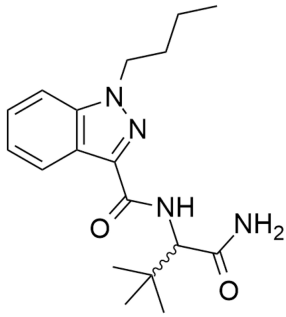
A. Chemical name

IUPAC name:
N-[1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide

Chemical Abstracts index name:
1*H*-Indazole-3-carboxamide, *N*-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-butyl- (ACI)

B. Chemical structure

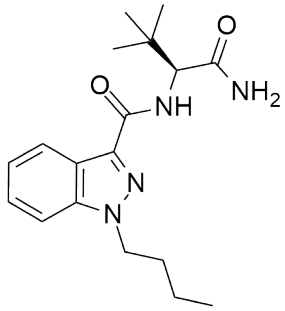
Free base:



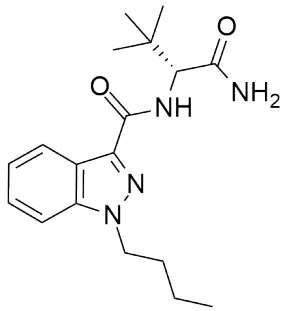
Molecular formula: $C_{18}H_{26}N_4O_2$
Molecular weight: 330.43 g/mol

C. Stereoisomers

The presence of an asymmetric carbon atom gives rise to the (*R*)- and (*S*)-enantiomers of ADB-BUTINACA. Although structurally related synthetic cannabinoid receptor agonists typically show the (*S*) configuration, the same substance with either (*R*)-configuration or the racemic mixture may be present in seized samples. Although structurally related synthetic cannabinoid receptor agonists typically show the (*S*) configuration, the same substance with either (*R*)-configuration or as the racemic mixture may be present in seized samples.



N-[(1S)-1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide



N-[(1R)-1-(Aminocarbonyl)-2,2-dimethylpropyl]-1-butyl-1*H*-indazole-3-carboxamide

D. Methods and ease of illicit manufacture

No information was available on the manufacture of ADB-BUTINACA seized or collected on the market. Preparation of this substance is, however, straightforward and follows standard procedures with cheap, readily available reagents. Two examples are the synthetic procedures for obtaining (*S*)-ADB-BUTINACA in three steps, starting from methyl indazole-3-carboxylate, described by Cannaert et al. *(7)* and Sparkes et al. *(8)*. Although the process is simple, it requires the equipment of a chemical synthetic laboratory and qualified personnel.

E. Chemical properties

Melting-point
148.2–148.4 °C (7)

Boiling-point
No information was found.

Solubility
ADB-BUTINACA is soluble in dimethylformamide at 20 mg/mL and in dimethyl sulfoxide at 10 mg/mL. In ethanol, it is soluble at 20 mg/mL *(4)*.

F. Identification and analysis

Synthetic ADB-BUTINACA was characterized by proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR), mass spectrometry (MS), ultraviolet spectrophotometry and infra-red spectroscopy *(2, 7)*. ADB-BUTINACA and two of its metabolites, ADB-BUTINACA *N*-butanoic acid and ADB-BUTINACA *N*-(4-hydroxybutyl), are available as reference materials from commercial suppliers for use in forensic and clinical investigations *(4, 9, 10)*.

Analytical methods for identification of ADB-BUTINACA in seized samples have been published. They include gas chromatography (GC)–MS), GC–infra-red spectroscopy, liquid chromatography (LC)-MS, ionic chromatography, ^{1}H NMR and ^{13}C NMR *(11, 12)*.

ADB-BUTINACA and its major metabolites were identified and quantified in human hepatocytes, liver microsomes, hair, urine, blood and post-mortem kidney and liver samples by LC coupled with high-resolution MS and LC coupled with triple-quadrupole MS *(1, 13, 14)*.

No information was available on the enantiomeric composition of ADB-BUTINACA, but the substance available on the market is most likely to be the (*S*)-enantiomer, like most other closely related synthetic cannabinoids. The (*S*)-enantiomer has not, however, been identified in analysed samples, and the presence of the (*R*)-enantiomer (including as an impurity) cannot be excluded.

3. Ease of conversion into controlled substances

No information was available in the literature.

4. General pharmacology

A. Routes of administration and dosage

Posts on online forums by people who use drugs indicate that ADB-BUTINACA has been inhaled by vaping after solubilization *(15–17)*. Oral and sublingual use have also been reported *(17)*. ADB-BUTINACA has been found in seizures of various products: adulterated cannabis or hemp plant material prepared for smoking *(18–20)*, paper infused with the chemical (used mainly to smuggle material into controlled environments such as prisons) *(2)* and powders for making formulations and products *(18, 19)*. In many cases, ADB-BUTINACA was not the sole substance identified in tested samples.

The dosage required for intoxication is unclear. One person reported vaping a 500-µg/mL solution of ADB-BUTINACA, while others reported smoking 1 mg and taking 75 µg sublingually *(17)*. The duration of effects ranged from 30 min to 3 h *(16)*. These online forum posts should be considered anecdotal, as there was no analytical confirmation of the purity of ADB-BUTINACA.

B. Pharmacokinetics

Like many synthetic cannabinoids, ADB-BUTINACA undergoes extensive hepatic biotransformation in the body, with an estimated half-life after exposure to human liver microsomes of < 30 min *(1)*. The parent compound is not usually found in urine samples from live humans *(1, 13)* but may be found in post-mortem samples *(13)*. The parent compound has also been reported in human blood samples and in tissue (kidney and liver) samples *(13)*. The number of identified phase-I and -II metabolites ranged from 21 to 40, depending on the assay (urine samples, human hepatocytes or human liver microsomes), but three published studies concur in specifying mono-hydroxylation as a dominant phase I reaction,

resulting in some of the most abundant metabolites *(1, 2, 13)*. While Kavanagh et al. *(13)* and Kronstrand et al. *(2)* recommended use of the dihydrodiol metabolite as a primary urinary biomarker, Sia et al. *(1)* reported that this metabolite is not abundant and recommended one of the hydroxylated metabolites as the most stable urinary biomarker, with half-lives of 48–190 min. Kavanagh et al. *(13)* suggested that the mono-hydroxylated metabolites (or the parent compound) would be the most reliable biomarker in blood. Three isoforms of CYP450 (CYP2C19, CYP3A4 and CYP3A5) appear to be the predominant enzymes involved in the metabolism of ADB-BUTINACA *(1)*.

C. Pharmacodynamics

ADB-BUTINACA binds to both human type 1 cannabinoid (hCB1) and hCB2 receptors (expressed in HEK-293 cells), with a three times greater affinity (K_i) for hCB1 than for hCB2 receptors: pK_i (CB1) = 9.52 ± 0.05 M (K_i = 0.299 nM) and pK_i (CB2) = 9.04 ± 0.16 M (K_i = 0.912 nM) *(8)*. In an evaluation of functional activation of the CB1 receptor (8), ADB-BUTINACA was found to be a full, potent agonist at both cannabinoid receptors in a fluorescence-based membrane assay in AtT20 cells, with greater potency for activation of CB1 than of CB2 receptors: half maximal effective concentration (EC_{50}) = 0.67 nM, E_{max} = 113% ± 3 (compared with CP55,940) for the CB1 receptor and EC_{50} = 4.1 nM, E_{max} = 101% ± 3 (compared with CP55,940) for the CB2 receptor. Using the same assay, Cannaert et al. *(7)* reported that ADB-BUTINACA was almost 10 times less potent (EC_{50} = 6.36 nM, 95% confidence interval: 2.88 nM; 11.9 nM) at CB1 than CB2 receptors *(8)* but had greater efficacy (E_{max} = 290%), although efficacy was compared with that of JWH-018 rather than CP55,940. A third study *(2)* found a potency (EC_{50}) of 11.6 nM (95% CI: 9.8 nM; 13.4 nM) for increasing calcium flux in recombinant Chinese hamster ovary cells expressing hCB1 receptors. ADB-BUTINACA also showed pronounced biased agonism at the CB1 and CB2 receptors through recruitment of β-arrestin 2, with EC_{50} = 19 nM (E_{max} = 728% when compared with CP55,940) and EC_{50} = 1.79 nM (E_{max} = 83% when compared with CP55,940) for the CB1 and CB2 receptors, respectively (8).

ADB-BUTINACA has been evaluated in one in-vivo assay in mice, in which it caused a pronounced, dose-dependent decrease in core body temperature (maximum ~ 6.5 °C decrease at 3 mg/kg intraperitoneally), with maximal effects 45 min after injection and dissipation of the effect by 135 min after injection *(8)*. A decrease in temperature of this magnitude is commonly observed after administration of synthetic cannabinoids to mice *(21)*.

5. Toxicology

No preclinical studies or systematic studies of human toxicology with ADB-BUTINACA were identified.

6. Adverse reactions in humans

Summary information from the US Drug Enforcement Administration provided to the ECDD Secretariat indicates that analytically confirmed use of ADB-BUTINACA has been implicated in at least six fatal poisonings and at least eight non-fatal poisonings that required medical treatment. By the time most patients came to the attention of medical personnel, they were minimally responsive or unconscious. In two of the non-fatal poisonings, patients were reported to be "excitable" before becoming lethargic. Most of the patients were given naloxone, which had no notable effect on their symptoms. Five of the non-fatal and five of the fatal poisonings were in people who were incarcerated at the time of the poisoning. All the deceased were men, as were four of the six people involved in nonfatal poisonings. The age range for all poisoning cases was 27–60 years. The cause of death of one person was listed as cardiac arrest, while the causes of death of the other patients were not available. Several patients had a history of non-cannabinoid substance use, and one had high cholesterol and schizophrenia. While ADB-BUTINACA and/or its metabolites were detected in serum or urine in each case, the effects of ADB-BUTINACA in these poisonings could not be specified because of the presence of other substances in the blood or urine of all but one patient. This non-fatal case had been observed using other substances (alcohol and cocaine contaminated with fentanyl) the night before the poisoning, complicating attribution of his symptoms to ADB-BUTINACA, as the serum or urine concentrations of the other substances might have dissipated overnight.

In addition, a recently published study of patients presenting to the emergency departments of hospitals in the United Kingdom reported ten patients who tested positive for ADB-BUTINACA from February to October 2021 *(22)*. ADB-BUTINACA was the second most commonly identified synthetic cannabinoid in the tested samples. Of the ten cases, samples from seven patients tested positive for other substances whereas ADB-BUTINACA was the sole substance identified in samples from the remaining three patients. Each of these three patients (and six of the seven patients with multiple substance use) exhibited reduced levels of consciousness. All ten patients recovered and left the hospital.

Phrases used to describe the sensations experienced after intentional use of ADB-BUTINACA at doses that did not result in unresponsiveness include: "it gets me mad stoned, very sedating and warm and pleasant", "giggle euphoria munchies warmth, and then sleep with higher doses" and "It is quite a nice high, warm, fuzzy, euphoric and a little rushy. It is my favourite noid so far" *(17)*. In cases in which use of ADB-BUTINACA was unintentional (also see section 19), users reported sensations such as "extreme paranoia", "felt like K2/Spice", "tripping sensation", "got an allergy-like reaction at injection site", "out-of-body experience", "blacked out for 5 h, didn't remember anything" *(18)*. These user posts should be considered anecdotal, as sole use of ADB-BUTINACA was not analytically confirmed.

7. Dependence potential

A. Studies in experimental animals

No studies were available.

B. Studies in humans

No studies were available.

8. Abuse potential

A. Studies in experimental animals

No published studies on the abuse potential of ADB-BUTINACA in experimental animals were available; however, unpublished studies of drug discrimination provided by the US Drug Enforcement Administration *(23)* showed that intraperitoneal ADB-BUTINACA substituted for THC in six male Sprague-Dawley rats trained to discriminate 3 mg/kg THC (intraperitoneally) from vehicle in a two-lever discrimination test. The substitution was dose-dependent, with maximal substitution (100% THC-lever response) at 0.1 mg/kg but no effect on the response rates. The ED_{50} for THC-like discriminative stimulus effects for ADB-BUTINACA was 0.038 mg/kg.

B. Studies in humans

No studies were available.

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

ADB-BUTINACA has no known therapeutic applications and is not used medically.

10. Listing on the WHO Model Lists of Essential Medicines

ADB-BUTINACA is not listed on the 22nd WHO Model List of Essential Medicines or on the 8th Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

There are no known marketing authorizations for ADB-BUTINACA.

12. Industrial use

ADB-BUTINACA has no known industrial use.

13. Non-medical use, abuse and dependence

ADB-BUTINACA appeared on the European drug market in September 2019 in Sweden *(20)*. Reports on online forums by people who use drugs provide evidence that ADB-BUTINACA has been used intentionally for its intoxicating effects (see section 6), and this substance has been detected in seized and biological samples in 11 countries (see section 16 for listing) and as an adulterant in substances marketed as cannabis *(18, 19, 24, 25)*.

No information was found on the prevalence of chronic use of ADB-BUTINACA and dependence.

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

ADB-BUTINACA has been detected in infused paper in post sent to prison inmates in Scotland. Between January and June 2021, ADB-BUTINACA was one of the most prevalent synthetic cannabinoids seized in Scottish prisons, with a total of 76 (60.3%) samples positive for this substance *(2)*. In 2021, the United Nations Office on Drugs and Crime Tox Portal included 23 cases in Singapore in which ADB-BUTINACA was detected in biological samples *(26)*. No other substances were detected in four post-mortem samples, and ADB-BUTINACA was designated high on the causality scale used in the system. ADB-BUTINACA was also designated as high on the causality scale for 16 of the clinical admissions and as contributory (medium) for the other three cases. No details of the

nature of the symptoms or the clinical course were available. The Republic of Korea reported seven additional detections, and France and the United States each reported one case, again with no information on the nature of the symptoms. At least six deaths in which ADB-BUTINACA was found toxicologically post-mortem have occurred in the USA, and at least eight non-fatal poisonings severe enough to require emergency medical attention were reported in a summary document provided by the US Drug Enforcement Administration to the Secretariat of the Expert Committee on Drug Dependence; however, as noted in section 6, ADB-BUTINACA was not the only substance ingested.

15. Licit production, consumption and international trade

ADB-BUTINACA is not legally produced, consumed or in international trade.

16. Illicit manufacture and traffic and related information

The first documented seizure of ADB-BUTINACA in Europe was in Sweden in September 2019 *(20)*. Since that report, ADB-BUTINACA has been detected in seized products or biological samples in 11 countries: Austria *(19, 23)*, China *(13, 27)*, France *(26)*, Republic of Korea *(26)*, Russian Federation *(13)*, Singapore *(1, 25)*, Slovenia *(24)*, Sweden *(24)*, Switzerland *(19)*, the United Kingdom *(2, 28)* and the USA *(19, 26)*. Most of the reports were made during 2020 and 2021.

17. Current international controls and their impact

Currently, there are no international controls specifically for ADB-BUTINACA.

18. Current and past national controls

ADB-BUTINACA does not appear to be controlled under the national regulations of any country, although it may be covered by generic or analogue legislation or regulations. Although a summary document provided by the US Drug Enforcement Administration to the Secretariat of the Expert Committee on Drug Dependence stated that ADB-BUTINACA has been designated as schedule I in the USA, a search for the compound in the *Federal Register* did not confirm a current status of "schedule I" for ADB-BUTINACA.

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

No information was available.

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3.1.2 Adinazolam

1. Substance identification

A. International Nonproprietary Name (INN)

Adinazolam

B. Chemical Abstracts Service registry number

37115-32-5 (free base)

57938-82-6 (methanesulfonate (1:1))

57561-75-8 (lithium salt)

867019-46-3 (carbonic acid, dilithium salt)

C. Other chemical names

Free base:

8-Chloro-*N*,*N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4] benzodiazepine-1-methanamine (ACI)

8-Chloro-1-[(dimethylamino)methyl]-6-phenyl-4*H*-s-triazolo[4,3-a][1,4] benzodiazepine

Adinazolam

U 41123

Methanesulfonate:

4*H*-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine-1-methanamine, 8-chloro-*N*,*N*-dimethyl-6-phenyl-, monomethanesulfonate (9CI)

Adinazolam mesylate

Adinazolam methanesulfonate

Adinazolam monomethanesulfonate

Deracyn

U 41123F

D. Trade names

The trade name Deracyn has been registered for adinazolam methanesulfonate, but the product has never been marketed.

E. Street names

Adinazolam is sold as tablets or powders under the chemical name Adinazolam.

Novel psychoactive substances (NPS) belonging to the benzodiazepines class can be purchased mainly on the online drug market under various street names, such as "legal benzodiazepines", "designer benzodiazepines" and "research chemicals" *(1)*.

F. Physical appearance

White or yellowish powder *(2)*

Adinazolam was identified in seized sample of white powder and in white tablets marked "D/CD" *(1)*.

G. WHO review history

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

4. Chemistry

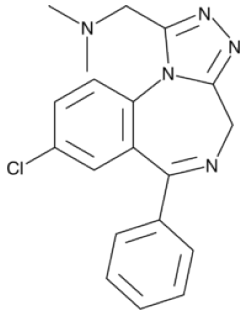
A. Chemical name

IUPAC name:
1-(8-Chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-1-yl)-*N,N*-dimethylmethanamine

Chemical Abstracts Index name:
4*H*-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine-1-methanamine, 8-chloro-*N,N*-dimethyl-6-phenyl- (9CI, ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{19}H_{18}ClN_5$
Molecular weight: 351.83 g/mol

C. Stereoisomers

No stereoisomers of adinazolam have been described.

D. Methods and ease of illicit manufacture

Several synthetic procedures for the preparation of adinazolam have been reported in the literature since the early 1970s (e.g., *3–8*).

A convenient synthesis would include introduction of a triazole ring into 1,4-benzodiazepine precursors, such as nordazepam, which are readily available as pure substances because of their pharmaceutical use. Alternatively, adinazolam can be prepared by cyclization of 2-amino-5-chlorobenzophenone with methyl 2-aminoacetate *(9)*. Treatment of nordazepam with phosphorous pentasulfide gives 7-chloro-l,3-dihydro-5-phenyl-2*H*-l,4-benzodiazepin-2-thione, and subsequent cycloaddition of *N,N*-dimethyl-acetyl hydrazine gives adinazolam free base *(6)*.

A high-yielding one-step synthesis route for adinazolam involves the reaction of estazolam (a readily available marketed pharmaceutical substance) with dimethyl(methylene)ammonium chloride (a cheap, readily available marketed reagent) *(10)*.

No information was available on the routes of synthesis used for the adinazolam products circulating on the market. All the syntheses reported in the literature, although simple, require the equipment of a chemical synthetic laboratory and qualified personnel.

E. Chemical properties

Melting-point
171–172.5 °C (7)

Boiling-point
No information was found.

Solubility
Soluble in dichloromethane and methanol *(2)*.

The free base of adinazolam is insoluble in water, while the salt (mesylate) is soluble in water (> 100 mg/mL) *(11)*.

F. Identification and analysis

Synthetic adinazolam was characterized by proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR), mass spectrometry (MS) and infra-red spectroscopy (IR) *(10)*.

Adinazolam and two of its metabolites, α-hydroxy alprazolam and estazolam, are available as reference materials from commercial suppliers for routine analysis in forensic and clinical investigations *(12)*.

Analytical methods for identification of adinazolam in seized sample matrices include gas chromatography (GC)-MS); GC-IR; liquid chromatography (LC)–MS, ionic chromatography, ^{1}H-NMR and ^{13}C-NMR *(2)*. Biological fluids have also been analysed by radioimmunoassay, fluorescence polarization immunoassay and enzyme immunoassay; however, presumptive detection by immunoassay must be confirmed with chromatographic techniques *(13, 14)*. GC-MS and high-performance LC coupled with ultraviolet detection have been used for identification and quantification of adinazolam and its major metabolites in human liver microsomes and human urine and blood *(13, 15, 16)*. Urine, serum and plasma samples were also analysed by LC coupled with either high-resolution MS or triple–quadrupole MS for quantification of adinazolam *(17, 18)*. These platforms were also used to quantify adinazolam in post-mortem femoral blood and urine *(19)* and to assess adinazolam metabolism in human liver microsomes *(20)*.

Two metabolites of adinazolam, estazolamand α-hydroxyalprazolam, are licensed benzodiazepines. In order to detect adinazolam use, both the parent drug and any metabolites should be assessed *(13, 20, 21)*.

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

A. Routes of administration and dosage

Adinazolam is usually administered orally, often in tablet or capsule form but sometimes as a powder *(9, 22)*. Recreational dosages range from 5 to > 50 mg, the most common being 15–30 mg *(9, 23)*. The onset of effects occurs within 10–25 min, while acute effects last 2–5 h and after-effects for up to 16 h *(23)*. Adinazolam was tested at doses up to 90 mg/day (average, 50 mg/day) in controlled clinical trials when it was under consideration as a candidate antidepressant medication *(24, 25)*.

B. Pharmacokinetics

Because adinazolam was originally investigated as a possible antidepressant with a novel site of action, studies were conducted to determine its pharmacokinetics. In humans, the bioavailability of adinazolam is estimated to be 40%, intestinal metabolism playing a significant role before hepatic metabolism *(26, 27)*. After oral administration and absorption, adinazolam is quickly and almost completely metabolized to a primary metabolite, *N*-desmethyladinazolm (NDMAD) *(26, 27)*, the isoenzyme CYP 3A4 playing a major role in its biotransformation *(28)*. Psychoactivity was found to be more closely associated with plasma levels of NDMAD rather than of adinazolam, and the investigators suggested that adinazolam is actually a prodrug *(27)*. Subsequent studies in which NDMAD was evaluated directly in humans support the earlier hypothesis that NDMAD is more potent than its parent compound *(26, 29)*. NDMAD is subsequently metabolized to didesmethyladinazolam (DDMAD) *(28)*; however, this metabolite is considered not to be clinically significant in mediating the behavioural effects of adinazolam. Consistent with identification of these metabolites after administration in vivo, NDMAD and DDMAD were also identified as primary metabolites of adinazolam in incubated pooled human liver microsomes *(20)*. NDMAD is eliminated mainly via the renal route *(28)*. Pharmacokinetic parameters of acute intravenous adinazolam in humans were as follows: volume of distribution (L), 106; elimination half-life (h), 2.9; and clearance (mL/min), 444 *(27)*. After acute oral administration of 10-50 mg doses of adinazolam, half-life ranged from 2.24 – 3.07 h *(26)*. Similarly, after acute oral administration of 20-60 mg doses of adinazolam, the average half-life of NDMAD was 3.8 h, with peak plasma levels at an average of 1.16 h *(30)*.

C. Pharmacodynamics

Adinazolam and NDMAD bind to benzodiazepine receptors, as measured by displacement of [^{3}H]flunitrazepam (k_i = 208 and 6.96 nM, respectively) *(31)*. Further, modelling predicted moderate binding affinity of adinazolam at the $GABA_A$ receptor (log 1/c = 7.18) *(9)*. In contrast, adinazolam has negligible binding affinity for histamine H_1, muscarinic, α1- and α2-adrenergic, 5-HT_{1A}, 5-HT_2 or dopamine D_2 receptors *(32, 33)*. In vivo, adinazolam was an effective, potent anticonvulsant in rodent models *(31, 32)* and suppressed increases in stress-induced plasma corticosteroid concentrations in rats, which was deemed indicative of anxiolytic activity *(32)*. It was also effective in several rodent models of depression *(32)*. The results of a voltammetry study in anaesthetized rats showed that adinazolam (10 mg/kg) significantly decreased hippocampal norepinephrine and serotonin release via a pre-synaptic mechanism, an effect that the author hypothesized is related to its putative antidepressant effects *(34)*.

Adinazolam has been studied clinically for its potential therapeutic effects in the treatment of depression, anxiety and panic disorder *(24, 25, 35, 36)*. While one study found that adinazolam was moderately effective as an antidepressant *(24)*, another indicated that the antidepressant effect was transient and had dissipated by day 7 of a 6-week study *(25)*. The US Food and Drug Administration has not issued regulatory approval for use of adinazolam in any therapeutic indication.

5. Toxicology

Although there have been no systematic studies of the toxicology of adinazolam, some of the clinical trials in which adinazolam pharmacokinetics was evaluated in healthy volunteers included measurement of physiological parameters. Acute oral doses of up to 50 mg adinazolam and its major metabolite NDMAD did not alter blood pressure, pulse or respiration, and neither substance substantially affected values in undefined "safety laboratory tests" *(26)*. Furthermore, no abnormal laboratory values were found in a clinical trial of individuals with depression given adinazolam for 6 weeks (average daily dose, 50 mg orally) *(25)*. Oral and intravenous administration of either adinazolam or NDMAD was associated with decreased serum concentrations of uric acid, suggesting increased clearance of this substance *(26, 37)*. Adinazolam given at 2.5 or 5 mg/kg to rats did not affect blood pressure or heart rate *(38)*.

6. Adverse reactions in humans

Few user reports of recreational use of adinazolam are available, and most of the information on adverse reactions in humans is derived from controlled clinical trials of the drug and its major metabolite, NDMAD. The incidence of adverse effects after acute administration of adinazolam at doses up to 50 mg orally or 20 mg intravenously was consistently higher than in the placebo group *(26, 36, 39)*, although the effects were usually mild or moderate. Sedation and drowsiness were the untoward effects most often mentioned.

One case report described a shift to mania in three individuals with bipolar disorder who were receiving adinazolam in a clinical trial *(40)*; however, another study did not support this finding *(24)*.

Several clinical trials included measurement of psychomotor and/or cognitive parameters, which indicated that adinazolam and NDMAD each induced dose-dependent decrements in psychomotor performance in card-sorting tasks and increased amnesia and sedation *(26, 29, 30, 39)*.

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found.

8. Abuse potential

A. Studies in experimental animals

Conditioned place preference procedures are sometimes used to assess the rewarding effects of a drug according to the principles of classical conditioning. Adinazolam (at 2 and 4 mg/kg) induced conditioned place preference (as compared with the vehicle) in male hooded Lister rats in a two-compartment procedure *(41)*.

Adinazolam was also evaluated in two groups of rats trained to discriminate 1 or 10 mg/kg diazepam from vehicle. In each group, adinazolam fully and dose-dependently substituted for the training drug *(42)*, showing that adinazolam shares discriminative stimulus effects with diazepam.

No studies have been conducted of self-administration.

B. Studies in humans

Bird et al. *(43)* evaluated dependence on adinazolam (30 and 50 mg) in a double-blind placebo-controlled study with recreational drug users. Dependence was measured from items in the Addiction Research Center Inventory. Both doses of adinazolam induced significant increases in items related to "mental high" and "physical high". The 50-mg dose also induced significant increases in "street value" over that with placebo. Adinazolam at 50 mg induced more physical and mental sedation than lorazepam (2–4 mg) or diazepam (20 mg), but it also induced greater "mental unpleasantness" than placebo up to 4 h after ingestion.

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

Although adinazolam was investigated as a putative antidepressant or anti-anxiety agent in early studies *(24, 25)*, investigation of the compound was discontinued for unspecified reasons. There is no approved therapeutic use of adinazolam.

10. Listing on the WHO Model Lists of Essential Medicines

Adinazolam is not listed on the 22nd WHO Model List of Essential Medicines or the 8th Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Adinazolam has no known marketing authorization.

12. Industrial use

Adinazolam has no known industrial use.

13. Non-medical use, abuse and dependence

Adinazolam appeared on the European recreational drug market in 2015 in Germany, Slovenia and Sweden *(1, 9)*. Adinazolam has been detected in formulations containing combinations of benzodiazepines (e.g., tablets, capsules, powders), including falsified pharmaceutical preparations labelled as a legal prescription drugs (e.g., "Xanax") *(22)*. Little information on its non-medical use is available, and it is rarely mentioned in online forums on substance use.

No information was available on the prevalence of chronic use or dependence on adinazolam.

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

Little information is available on fatal and non-fatal poisonings with analytically confirmed use of adinazolam. Investigators in Poland described a fatality in which a woman ingested adinazolam in combination with opioids and a selective serotonin reuptake inhibitor *(13)*. The concentrations of adinazolam in post-mortem blood and urine samples were 18.0 and 82.1 ng/mL, respectively. The role of adinazolam in her death is unknown, although the authors speculated that the combination of adinazolam (a benzodiazepine) and U-47700 (an opioid) may have contributed. In the USA, three fatal cases have been reported since April 2022 in which adinazolam was detected in post-mortem blood samples; however, as adinazolam was only one of several benzodiazepines present in the samples, its contribution to the deaths cannot be determined *(44)*.

15. Licit production, consumption and international trade

No information was available.

16. Illicit manufacture and traffic and related information

The first documented seizure of adinazolam in Europe was in Germany in 2015, which was followed shortly thereafter by detection in samples collected in Slovenia and Sweden *(1, 9)*. Samples containing adinazolam that were submitted to an anonymous testing site (since 2019) were received from Austria (n=1), China (n=1) and the USA (n=4) *(22)*. As submission of samples was voluntary, the distribution of sites is not expected be representative of the distribution or trafficking of adinazolam in the world. Between January 2021 and March 2022, adinazolam was also detected in 19 samples submitted to the Welsh Emerging Drugs and Identification of Novel Substances Project *(45)*. In Canada, adinazolam was detected in seized samples (tablets) that "appeared to be Xanax" *(46)*.

17. Current international controls and their impact

There is no current international control of adinazolam.

18. Current and past national controls

Adinazolam is classified as a schedule IV substance under Canadian law and is regulated under psychoactive drug control regulations in Germany and the United Kingdom. It does not appear to be controlled under national regulations in other countries.

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

No information was available.

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3.1.3 Bromazolam

1. Substance identification

A. International nonproprietary name

Not assigned

B. Chemical Abstracts Service registry number

71368-80-4

C. Other chemical names

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

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

DE(chloro)-bromo-alprazolam

D. Trade names

Bromazolam is sold under its own name.

E. Street names

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

Novel psychoactive substances belonging to the benzodiazepines class can be purchased mainly on the drug online market under various street names, such as "legal benzodiazepines", "designer benzodiazepines" and "research chemicals" *(2)*.

F. Physical appearance

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

G. WHO review history

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

2. Chemistry

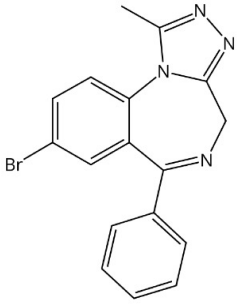
A. Chemical name

IUPAC name:
8-Bromo-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-α][1,4]benzodiazepine

Chemical Abstracts Service index name:
4*H*-[1,2,4]Triazolo[4,3-α][1,4]benzodiazepine, 8-bromo-1-methyl-6-phenyl- (9CI, ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{17}H_{13}BrN_4$
Molecular weight: 353.22 g/mol

C. Stereoisomers

No stereoisomers of bromazolam have been described.

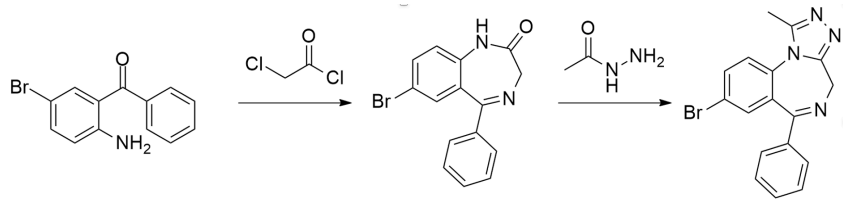
D. Methods and ease of illicit manufacture

Bromazolam is a triazolo-benzodiazepine structurally related to the internationally controlled substance alprazolam in which the chlorine atom is replaced by a bromine atom. Bromazolam is also structurally related to flubromazepam, from which it differs by the lack of a fluorine at the 2-position of the phenyl ring. Bromazolam is also structurally similar to pyrazolam, whereby the pyridinyl group has been replaced by a phenyl group *(3)*.

Bromazolam was first synthesized in the 1970s by Hester et al. *(5)*. A convenient synthesis method has been reported in the patent literature *(3, 6, 7)*. Introduction of a triazole ring into the 1,4-benzodiazepine precursor (8-bromo-1-methyl-6-phenyl-4*H*-s-triazolo[4,3-α][1,4]benzodiazepine) gave bromazolam. The 1,4 benzodiazepine precursor

can be prepared by cyclization of 2-amino-5-bromobenzophenone with chloroacetylchloride (scheme 1) *(8)*.

Scheme 1. Synthesis of bromazolam



2-Amino-5-bromobenzopheone 1,4-Benzodiazepine precursor Bromazolam

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

E. Chemical properties

Melting-point
272.0–275 °C (3, 5)

Boiling-point
No information was found.

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

F. Identification and analysis

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

Analytical methods for identification of bromazolam in seized sample matrices include IR, ^{1}H NMR, gas chromatography–MS and liquid chromatography (LC)–MS *(9, 10)*.

Bromazolam was also analysed in urine in an immunochemical assay *(11)* and in human blood and urine by LC coupled either to high-resolution MS or to triple–quadrupole MS *(9, 10, 12)*.

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

A. Routes of administration and dosage

Seizures by law enforcement personnel indicate that bromazolam is typically formulated in tablets or as a powder *(1)*. Oral use (e.g., tablets, capsules or powder formulations in solutions or mixed in food) has been reported on online forums *(13–16)*. Bromazolam-containing chewable candy products ("gummies") have also been seen *(15)*. While injection is assumed from the presence of a syringe filled with bromazolam-containing solution found next to an overdose victim *(1)*, this route of administration does not appear to be common.

No studies were found of human dosage; however, one informational website has categorized doses according to their intoxicating effects as "light" (0.5–1 mg), "common" (1–2 mg) and "strong" (2–≥ 4 mg) *(17)*. For comparison, the website lists the following doses for diazepam: "light" (2.5–5 mg), "common" (5–15 mg) and "heavy" (15–30 mg) *(18)*. A review of novel psychoactive benzodiazepines listed 1 mg as a "typical recreational dose" *(19)*. The onset of effects is estimated to occur 15–45 min after administration, the duration of action is 5–8 h, and the after-effects last 1–12 h *(17)*. The basis for this information is not clear, and, given its anecdotal nature, caution is suggested in interpreting these data.

B. Pharmacokinetics

In the only study available, the pharmacokinetics of bromazolam was studied in pooled human liver S9 fractions, with further analysis of authentic blood and urine samples from two patients *(20)*. The primary metabolic reactions were hydroxylation, glucuronidation and combinations of the two processes, resulting in eight metabolites. Two prominent monohydroxylated metabolites were formed, tentatively identified as 4-hydroxylated bromazolam and α-hydroxy bromazolam, as well as one dihydroxylated metabolite, α-4-dihydroxy-bromazolam. Glucuronidation resulted in α-hydroxy glucuronide and N-glucuronide as the most abundant phase II metabolites. The parent compound was

detected in the urine of both patients, whereas the monohydroxylated metabolites were detected in only one. Recommended screening targets in urine were α-hydroxy glucuronide and N-glucuronide if conjugate cleavage was performed or the parent compound and the α-hydroxy metabolite if it was not. Isoenzymes involved in phase I metabolism included CYP2B6, CYP2C19, CYP3A4, CYP3A5 and CYP2C9, whereas phase II metabolism involved the isoenzymes UGT1A4 and UGT2B10.

C. Pharmacodynamics

Little information was found on the pharmacodynamics of bromazolam. It has not been evaluated empirically in vivo. Bromazolam was tested in a single in-vitro study of the binding of several compounds (including bromazolam) to α-subunits of the g-aminobutyric acid type A ($GABA_A$) / benzodiazepine receptor complex *(21)*. Affinity for compounds in HEK cell membranes expressing recombinant $GABA_A$/benzodiazepine receptor subtypes (α1β3γ2, α2β3γ2, α3β3γ2, α4β3γ2, α5β3γ2 and α6β3γ2) was measured. Bromazolam was non-selective for the α subunits, with measurable binding affinity at receptors containing α1 (K_i = 2.8 nM), α2 (K_i = 0.69 nM) and α5 (K_i = 0.62 nM) subunits.

5. Toxicology

No studies of the preclinical toxicology of bromazolam were available.

6. Adverse reactions in humans

The presence of measurable concentrations of bromazolam in post-mortem blood samples has been reported in Finland and the USA *(1, 22)*; however, other drugs were also detected in many cases, and the extent to which bromazolam contributed to the deaths was not specified. In Germany, two patients with confirmed bromazolam use were found unconscious or minimally responsive *(20)*. Bromazolam has also been reported in blood samples from impaired drivers in the USA *(22)*. The reports do not provide details of the physical or behavioural effects of bromazolam use.

People who used bromazolam described its effects as "hypnotic" and "sedative" *(13)* and referred to its "muscle relaxing" and "pain relieving" properties *(15)*. Other reported effects include euphoria, increased confidence, and empathy *(23)*. Some people who used bromazolam reported amnesia, while others stated that amnesia was less common with bromazolam than with other benzodiazepines *(16)*. Posts on online

forums describing self-reported experience of use of bromazolam should be considered anecdotal, as no analytical confirmation of sole use was obtained.

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found.

8. Abuse potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found.

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

There are no known therapeutic uses for bromazolam.

10. Listing on the WHO Model Lists of Essential Medicines

Bromazolam is not listed on the 22nd WHO Model List of Essential Medicines or on the 8th WHO Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Bromazolam has no known marketing authorizations.

12. Industrial use

Bromazolam has no known industrial use.

13. Non-medical use, abuse and dependence

Bromazolam appeared on the European recreational drug market in 2016 in Sweden and in the USA in 2019 *(22, 24)*. In addition to intentional use of bromazolam for its benzodiazepine-like psychoactive

effects (see section 6), some people have reported self-medication with bromazolam for indications such as anxiety, to aid sleep and to reduce stimulation caused by another drug such as methamphetamine *(15, 16)*. Bromazolam has been detected in formulations that contain combinations of benzodiazepines in a single preparation (e.g., tablet, capsule, powder), including preparations falsely labelled as legal prescription drugs (e.g., alprazolam, diazepam, zolpidem) *(23, 25)*. The compound has been used in combination with other drugs, including fentanyl and other opioids *(15, 22)*.

The prevalence of chronic use and dependence of bromazolam has not been reported. On online forums, several people have reported difficulty in withdrawing from bromazolam after chronic use, and at least one case of withdrawal-associated psychosis and hallucinations was reported after bromazolam was taken repeatedly in combination with phenibut *(26–28)*. These reports should be considered anecdotal, as no analytical confirmation of bromazolam (or its sole use) was reported.

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

Little information is available on fatal and non-fatal poisonings with analytically confirmed use of bromazolam. In Finland, bromazolam was found in a post-mortem blood sample with other benzodiazepines *(1)*. In Germany, bromazolam was present in biological samples from two patients, one of whom was found unconscious and one of whom was "confused and slow to respond" *(20)*. In the USA, bromazolam has been analytically confirmed in more than 250 cases, with 236 detections in post-mortem blood and 14 in biological samples from impaired drivers *(22)*. While no additional information was available on the clinical course of the cases or on any other drugs present, the average bromazolam blood concentration in post-mortem samples was 65 ng/mL (± 79 standard deviation) *(22)*. In samples from impaired drivers, the average blood concentration was 61 ng/mL (± 47 standard deviation) *(22)*. Between October 2020 and February 2022, 10 cases (seven post-mortem) of analytically confirmed bromazolam were reported by the USA to the Early Warning System Tox-Portal *(29)*. In all cases, bromazolam was designated as contributory (medium) on the causality scale used in the system. Bromazolam was the only substance detected in half of the cases. In 2022, bromazolam was the sole (or one of only a few) substance(s) detected in over 200 samples analysed by Welsh authorities *(23)*. A substantial number of products were falsely labelled as an approved prescription benzodiazepine (e.g., diazepam, alprazolam, zolpidem).

15. Licit production, consumption and international trade

No information was found.

16. Illicit manufacture and traffic and related information

The first documented seizure of bromazolam in Europe was in Sweden in 2016 *(24)*, while reports in the USA first appeared in 2019 *(22)*. In the USA, its detection increased from 1% of samples in the first quarter of 2021 to 13% in the second quarter of 2022 *(22)*. Its detection with fentanyl has increased dramatically, with 75% of bromazolam-positive samples also containing fentanyl in the months before the report was issued in June 2022 *(22)*. Samples containing bromazolam submitted to an anonymous testing site (from 2020 to the present) were received from Austria (n=1), China and other Asian countries (n=5), India (n=1), the United Kingdom (n=1) and the USA (n=27) *(30)*. As submission of samples was voluntary, the distribution of sites of origin may not represent the distribution or trafficking of bromazolam in the world. Other countries in which bromazolam has been detected include Australia *(25)*, Finland *(1)*, Germany *(20)*, Sweden *(24)* and Wales *(23)*.

17. Current international controls and their impact

Bromazolam is not currently under international control.

18. Current and past national controls

Bromazolam is classified as a schedule IV substance under Canadian law and is regulated under psychoactive drug control regulations in Germany and the United Kingdom. It does not appear to be controlled under national regulations in other countries.

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

No information was found.

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3.1.4 Protonitazene

1. Substance identification

A. International nonproprietary name

Not available.

B. Chemical Abstracts Service registry number

95958-84-2 (free base)

119276-01-6 (hydrochloride salt)

C. Other chemical names

Free base:
Benzimidazole, 1-[2-(diethylamino)ethyl]-5-nitro-2-(*p*-propoxybenzyl)-(6CI, 7CI)

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

Protonitazene

Hydrochloride salt:
Benzimidazole, 1-(2-diethylaminoethyl)-5-nitro-2-p-propoxybenzyl-, hydrochloride (6CI)

D. Trade names

Protonitazene is sold as hydrochloride salt under its own name, protonitazene (hydrochloride) *(4)*

E. Street names

Protonitazene is known under its own name or as pronitazene or propoxynitazene (e.g., 5).

F. Physical appearance

Synthetic protonitazene hydrochloride is sold as a standard is a white powder *(6)* or as a crystalline solid *(4)*.

It is described as a "crystallin solid" (no colour specified) by a chemical supply company that sells protonitazene hydrochloride "for research use only, not for human or veterinary use" *(4)*.

A chemical manufacturer based in China *(7)* describes the protonitazene HCl it sells as a yellow or "brown/yellow" powder. The website provides little other information (e.g., no safety data sheet or drug information sheet), which may put into question its legitimacy. Another company based in China *(8)* also offers direct sale of protonitazene HCl, as both a white and a brown powder.

In a health alert issued by the Victoria State Department of Health in June 2022, a "yellow powder" protonitazene was reported as being sold as ketamine in Melbourne *(9)*.

Generally, benzimidazole opioids such as protonitazene lack the bitter taste of other opioid subclasses *(10)*.

G. WHO review history

Protonitazene has not been formally reviewed by WHO and is not currently under international control. Several detections of this drug in the USA in 2021 *(11)* brought this drug to the attention of WHO. As it has no recognized therapeutic use, these detections suggest that protonitazene is manufactured illicitly and poses a risk to public health.

2. Chemistry

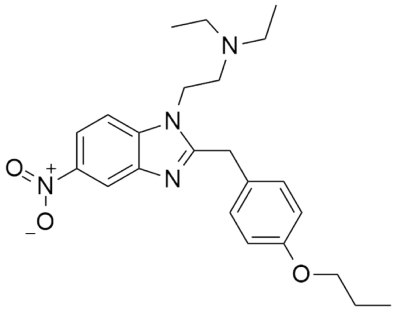
A. Chemical name

IUPAC name:
N,N-Diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]-1*H*-benzimidazole-1-ethanamine

Chemical Abstracts Service index name:
1*H*-Benzimidazole-1-ethanamine, *N,N*-diethyl-5-nitro-2-[(4-propoxyphenyl)methyl]- (ACI)

B. Chemical structure

Free base:



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

Molecular weight: 410.51 g/mol

C. Stereoisomers

No information was found.

D. Methods and ease of illicit manufacture

Protonitazene is a 5-nitro-2-benzylbenzimidazole belonging to the series of 2-benzylbenzimidazole compounds developed in the late 1950s as opioid analgesics *(10)*. It is a metonitazene and etonitazene homologue in which the C4 position of the benzyl moiety is substituted by a methoxy and an ethoxy group, respectively. Protonitazene is an isomer of isotonitazene, as they can be distinguished by the substitution at C4 position of the benzyl moiety with an n-propoxy and an isopropoxy group, respectively.

Synthesis of protonitazene was reported by Hunger et al. *(2)* and more recently by Vandeputte et al. *(12)*. The activated chloro atom of 1-chloro-2,4-dinitrobenzene can easily be substituted by 2-diethylaminoethylamine. Then, a regioselective reduction of the nitro group in the ortho position to the resulting amino function and condensation of the ortho-phenylenediamine species with an *n*-propoxyphenyl imidate (obtained from *n*-propoxyphenylacetonitrile derivative) affords the 5-nitro-substituted product protonitazene.

Protonitazene can also be obtained through synthetic routes reported for the synthesis of its 5-nitro-2-benzylbenzimidazole homologues and isomers (metonitazene, etonitazene and isonitazene) *(12–16)*.

Although no information was found on the actual method and scale of manufacture of protonitazene, the synthetic methods are simple and cost-efficient and do not require regulated precursors *(10)*.

E. Chemical properties

Melting-point
115–116 °C (hydrochloride salt) *(2)*

Boiling-point
No information was found.

Solubility
Protonitazene hydrochloride salt is soluble in dimethylformamide at 25 mg/mL and in dimethyl sulfoxide at 20 mg/mL. It was soluble at 0.5 mg/mL in a 1:1 mixture of dimethylformamide and phosphate-buffered saline (pH 7.2) and at 10 mg/mL in ethanol *(4)*. No definitive data on the solubility of protonitazene free base or its hydrochloride salt were found.

F. Identification and analysis

Synthetic protonitazene was characterized by nuclear magnetic resonance spectroscopy, high-performance liquid chromatography (LC) coupled to diode-array detection, gas chromatography coupled to mass spectrometry and LC coupled to high-resolution mass spectrometry (MS) *(10)*.

Protonitazene hydrochloride is available as a reference material from commercial suppliers for routine analysis in forensic and clinical investigations *(4)*. A method with LC coupled to tandem MS has been published for identification and quantification of protonitazene in biological sample matrices, such as human blood and urine *(17)*.

Analysis of protonitazene and of its isopropoxy isomer isotonitazene is critical, as they have the same molecular weight and similar MS fragmentation patterns. Distinction between the two isomers requires chromatography with analytical reference standards *(18)*.

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

A. Routes of administration and dosage

In seizures, protonitazene has been found in tablet form, presumably for oral use *(19)*.

On an online discussion forum *(20)*, it was reported that protonitazene, although readily soluble in water, could not be vaped through a methamphetamine pipe, as it would "pop and explode around", and a weak effect was observed. Online forums included descriptions of "nodding" and euphoric effects after insufflation of the powder and "skin popping" (i.e., subcutaneous [s.c.] injection). Another user reported that "Inhaling [protonitazene] felt like suffocating on sand and sawdust" *(21)*. In another post, non-tolerant users were advised to try 1 mg of protonitazene per 10 mL of water or ethanol *(22)*.

Low heat resistance is consistent with a hydrochloride formulation that cannot be smoked or vaped (as noted by users). A water- or ethanol-soluble powder would, however, lend itself to intranasal, intravenous, intramuscular or s.c. use, which are routes of opioid administration with significant abuse potential *(23–25)*. Although water-solubility has been reported, empirical data suggest low solubility in water (see section 2). Benzimidazole opioids can be synthesized in either salt or base forms *(2, 3, 13, 26)*. Thus, a free-base formulation of protonitazene can be formulated that can be smoked or vaped, although no evidence was found of the existence of a base formulation.

B. Pharmacokinetics

No information was found *(10, 17)*.

C. Pharmacodynamics

Opioid receptor activity

Investigations of the pharmacodynamics of protonitazene have mainly addressed its affinity for the μ-opioid receptor; however, activity has also been characterized at the other opioid receptor subtypes. Table 1 shows the affinity and efficacy of protonitazene for the μ-, δ- and κ- opioid receptor subtypes (MOR, DOR, KOR, respectively) in comparison with the prototypical opiate, morphine, and the potent synthetic opioid, fentanyl *(27)*.

Table 1. In vitro opioid receptor binding assays in rat brain tissue

Opioid	MOR K_i (nM)	DOR K_i (nM)	KOR K_i (nM)	EC_{50} (nM)	Efficacy (% DAMGO)
Protonitazene	21.5	1796	579	0.14	109
Fentanyl	4.8	356	204	0.10	98
Morphine	2.9	294	74	1.21	99

[^{3}H]DAMGO, [^{3}H]DADLE, and [^{3}H]U69,593 were used to label μ-(MOR), δ- (DOR), and κ- opioid receptors (KOR), respectively. Functional potency (EC_{50}) derived from cAMP inhibition.
Source: reference *27*.

DAMGO, D-Ala2, N-MePhe4, Gly5-ol

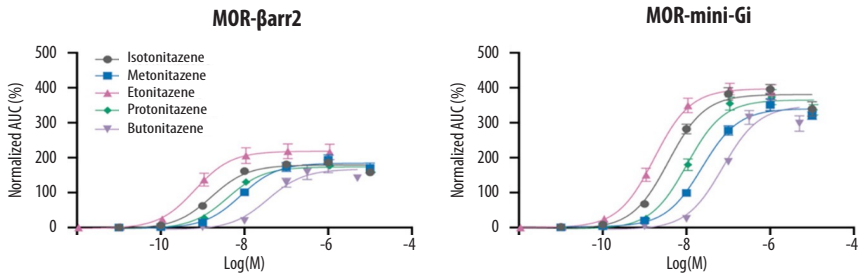
Volz and Moosmann *(28)* characterized the binding affinity (K_i) of six benzimidazoles and 17 non-benzimidazole opiates or opioids at human MOR (n = 3) in a competitive binding assay against 2 nM of [D-Ala2, N-MePhe4, Gly5-ol]-enkephalin, DAMGO). Table 2 shows that the binding affinity of protonitazene is stronger that than those of fentanyl and morphine, but weaker than hydromorphone (a potent opioid analgesic with robust abuse potential) *(29)*.

Table 2. Binding affinity (K_i) of opiates at the human μ-opioid receptor

Opiate	$K_i \pm$ SEM (nM)
Protonitazene	1.09 ± 0.17
Fentanyl	2.17 ± 0.27
Morphine	3.04 ± 0.28
Hydromorphone	0.448 ± 0.048

Vandeputte and colleagues *(12)* characterized the μ-opioid receptor activation profiles of five benzimidazole opioids in in-vitro recruitment assays (MOR-βarr2 and MOR-mini-Gi). Fig. 1 shows the mean receptor activation (± standard error), normalized to the maximum response of hydromorphone.

Fig. 1. Mean receptor activation of MOR-βarr2 and MOR-mini-Gi normalized to that of hydromorphone



Source: Reproduced with permission from reference *12*.

As shown in Table 3, the investigators calculated the potency (EC_{50}) and efficacy (E_{max}) of protonitazene relative to those of fentanyl and hydromorphone. In both assays, protonitazene was highly active in MOR activation, with a potency and efficacy slightly greater than those of fentanyl (107, 129%) and significantly greater than those of hydromorphone (174, 365%).

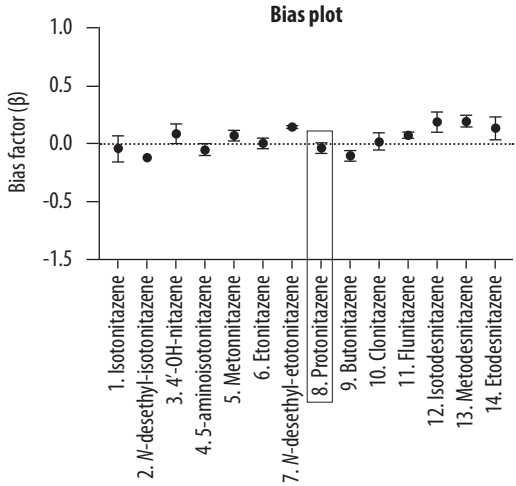
Table 3. Potency (with 95% confidence intervals) of protonitazene in comparison with those of fentanyl and hydromorphone

	MOR-βarr2			MOR-mini-Gi		
	EC_{50}	% Fentanyl (E_{max})	% HM (E_{max})	EC_{50}	% Fentanyl (E_{max})	% HM (E_{max})
Protonitazene	3.95 nM (2.78 ; 5.60)	107 (102 ; 111)	174 (165 ; 182)	10.4 nM (7.79 ; 14.7)	129 (123 ; 136)	365 (347 ; 384)

Source: reference *12*.

The authors *(12)* found no evidence of significantly biased agonism (i.e., a preference for βarr2 or mini-Gi recruitment) in the effects of protonitazene at the μ-opioid receptor, in contrast to hydromorphone (Fig. 2).

Fig. 2. μ-Opioid receptor bias plot for protonitazene and other 2-benzylbenzimidazole opioids



Source: Reproduced with permission from reference *12*.

Analgesia and antinociception

In mice, the relative potency of the antinociceptive activity of protonitazene was estimated to be 200 times that of 5 mg/kg morphine (s.c.) (*1–3*; see reference *10* for a review). In a recent preclinical investigation *(30)*, the analgesic effects of s.c. protonitazene (0.001–0.1 mg/kg) were tested in the rodent tail-withdrawal test with fentanyl (0.0032–0.1 mg/kg) and morphine (1–32 mg/kg). All three opioids dose-dependently increased tail withdrawal latency (i.e., induced antinociception). The calculated ED_{50} values were 0.035 mg/kg for protonitazene, 0.035 mg/kg for fentanyl and 4.9 mg/kg for morphine. These data suggest that the antinociceptive potency of protonitazene is equivalent to that of fentanyl and more than 130 times greater than that of morphine. In an antagonism study, the opioid receptor antagonist naltrexone (0.1 mg/kg) caused a 12-fold rightward shift in the effects of protonitazene and a 7-fold shift for fentanyl.

5. Toxicology

Paronis *(30)* found that protonitazene (0.1 mg/kg) administered to rats, produced notable adverse motor effects in several animals, including righting reflex, twitching and other involuntary motor movements. In studies of antagonism, 7 of the 8 rats that received 1 mg/kg of protonitazene (the dose that fully surmounted the effects of 0.1 mg/kg naltrexone pretreatment) were found dead in their home cage approximately 18 h later. However, in another study (described in detail below), Paronis *(31)* administered protonitazene at 0.0032–0.32 mg/kg s.c. to rats and observed no unusual motor behaviour or mortality.

6. Adverse reactions in humans

The Health Canada Drug Analysis Service has reported detection of protonitazene, but no information was provided on whether the samples were found in cases of fatal drug poisoning *(19, 32)*. Protonitazene was analytically confirmed in nine fatal poisonings or deaths in the USA *(33–35)*. The average blood concentration was 286 (± 556) ng/mL. However, in all cases, the presence of protonitazene was found in combination with several other drugs.

Australia also reported a patient presenting with protonitazene-related toxicity in an emergency department in the state of Victoria *(36)*. Following intranasal use of a drug sold online as protonitazene, the patient lost consciousness and stopped breathing. Upon arrival of paramedics,

the patient was observed to be cyanotic with minimal respiratory effort and a pulse-oximetry oxygen saturation of 50%. Intramuscular naloxone (2 mg) was administered with a positive response. The patient arrived at the emergency department in a normal conscious state, with a heart rate of 95 beats per minute, a blood pressure of 145/102 mm Hg, a respiratory rate was 17 breaths per minute, and an oxygen saturation of 99%. Toxicological analysis detected methylamphetamine, butonitazene and protonitazene.

Although data on humans are limited, a review of original research on benzimidazole opioids noted that, when administered intravenously, all the drugs caused respiratory depression, with a narrow therapeutic ratio between analgesia and respiratory depression *(37)*.

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found. Given its pharmacological profile, however, protonitazene is likely to induce physiological dependence, like other opioids *(12, 38)*.

8. Abuse potential

A. Studies in experimental animals

B. Drug discrimination

Following training during which responding only on one lever was reinforced following injection of 3.2 mg/kg morphine and responding only on the other lever was reinforced following injections of saline. Paronis *(31)* tested the ability of protonitazene (0.0032–0.32 mg/kg s.c.), morphine (0.1–3.2 mg/kg s.c.) and fentanyl (0.001–0.032 mg/kg s.c.) to substitute for morphine in a drug discrimination behavioural paradigm. Like morphine and fentanyl, protonitazene fully substituted for the discriminative stimulus effects of morphine, indicating traditional opioid-like affective properties. The ED_{50} values were 0.008 mg/kg for protonitazene, 0.004 mg/kg for fentanyl and 0.8 mg/kg for morphine.

C. Studies in humans

No information was found. Protonitazene appears to be commonly available online as a hydrochloride salt powder and could thus be administered by routes with faster pharmacokinetics, associated with greater abuse potential, such as insufflation and injection. Anecdotal reports on user forums such as Reddit (see section 4A) support the hypothesis that protonitazene has a robust opioid-like effect, particularly when administered via these routes. Forensic examination of substances found in syringes obtained from a syringe exchange programme in Washington DC (USA) also indicated that protonitazene may be injected *(39)*.

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

Protonitazene has no approved therapeutic application.

10. Listing on the WHO Model Lists of Essential Medicines

Protonitazene is not listed on the 22nd WHO Model List of Essential Medicines or the 8th WHO list of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Protonitazene has no approved therapeutic applications and has never been granted marketing authorization as a medicinal product for human or veterinary use.

12. Industrial use

Protonitazene has no reported industrial uses.

13. Non-medical use, abuse and dependence

No information was found from population surveys; however, data from post-mortem reports suggest that, because of its potency, protonitazene may be used to increase the potency of heroin (similarly to fentanyl) *(37)*. No empirical or anecdotal data on protonitazene's duration of action could be found. Internet forums for people who use drugs suggest interest in protonitazene among people who are experienced with opioid use (queries about, e.g., its potency and subjective pharmacodynamic profile).

Protonitazene has been detected in drug seizures and toxicology samples in Australia, Canada and the USA *(34, 40)*. However, data suggests that

commonly used analytical methods cannot distinguish protonitazene from its isomer isotonitazene *(17, 28, 34)*.

The frequency of protonitazene use could not be estimated from the available data; however, an investigation of online surveillance of novel psychoactive substances as a predictor of their use found no mention of protonitazene *(41)*. Similarly, a recent systematic review on acute intoxications and fatalities associated with benzimidazole opioids did not mention reports related to protonitazene *(35)*.

Fewer detections of protonitazene were made than for other synthetic opioids such as fentanyl and other benzimidazole opioids such as isotonitazene and etonitazene. Data for 2020–2022, however, indicate an increasing presence on the illicit opioid market *(34, 35)*. In Canada, there were no detections in 2019, one in 2020, 63 in 2021 and 64 in 2022 *(19)*.

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

Protonitazene is offered for sale by numerous Internet retailers. As people who use drugs are likely to obtain protonitazene from unregulated sources, its purity and quantity are not assured, posing an additional risk of adverse reactions. Currently, protonitazene has a small impact on public health, as its presence on the drug market is minimal; however, given its pharmacodynamics, protonitazene has a high risk for recreational use, physiological dependence, adverse side-effects and overdose *(10)*.

15. Licit production, consumption and international trade

Protonitazene is available for sale from pharmaceutical retailers for research and forensic applications only.

16. Illicit manufacture and traffic and related information

Protonitazene is offered for sale on numerous Internet sites that do not appear to be reputable pharmaceutical retailers. Some are reported to be based in China and openly advertise sale of protonitazene to other countries.

17. Current international controls and their impact

Protonitazene is not currently under international control.

18. Current and past national controls

Protonitazene does not appear to be subject to restrictive measures in the Member States of the European Union *(18)*. In the USA, protonitazene has been placed under the most restrictive controls (i.e., Schedule 1) *(42)*.

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

No other matters were identified.

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3.1.5 Etazene

1. Substance identification

A. International nonproprietary name

Not available

B. Chemical Abstracts Service (CAS) Registry number

14030-76-3 (free base)

1071546-16-1 ((1:1) hydrochloride salt)

2598176-60-2 ((1:2) hydrochloride salt)

100154-69-6 (hydrochloride salt)

C. Other chemical names

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

Benzimidazole, 1-[2-(diethylamino)ethyl]-2-(*p*-ethoxybenzyl)- (6CI, 7CI, 8CI)

N,*N*-Diethyl-2-{[(4-ethoxyphenyl)methyl]-1*H*-benzimidazol-1-yl}-ethan-1-amine

2-[(4-Ethoxyphenyl)methyl]-*N*,*N*-diethyl-1*H*-benzimidazole-1-ethanamine

2-[2-[(4-Ethoxyphenyl)methyl]benzimidazol-1-yl]-*N*,*N*-diethylethanamine

N,*N*-Diethyl-2-(2-{[4-(ethyloxy)phenyl]methyl}-1*H*-benzimidazol-1-yl) ethanamine

Etodesnitazene

Etazene

Etazone

Etazen

Desnitroetonitazene

D. Trade names

Etazene is sold as citrate salt under the name "Etodesnitazene (citrate)" *(1)* or as a hydrochloride salt under the name "Etazene hydrochloride" *(2)*. Etazene is sold as a free base under the name 1*H*-benzimidazole-1-ethanamine, 2-[(4-ethoxyphenyl)methyl]-*N*,*N*-diethyl- *(3)*.

E. Street names

Etazene has been identified in m30 pills, as noted on online user forums *(4)*.

F. Physical appearance

Etazene dihydrochloride in seized material has been reported as a grey crystalline powder *(5)* or a light-yellow powder *(6)*. Etazene citrate sold as a reference material has been described as a crystalline solid *(1)*.

Law enforcement agencies have found etazene in several solid forms (e.g., white-to-beige powders and rock) and in liquid forms, typically of unknown purity or concentration *(7)*.

G. WHO review history

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

2. Chemistry

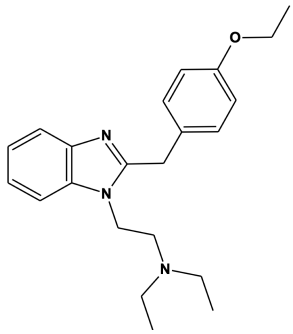
A. Chemical name

IUPAC name:
2-[(4-Ethoxyphenyl)methyl]-*N*,*N*-diethyl-1*H*-benzimidazole-1-ethanamine

Chemical Abstracts Service index name:
1*H*-Benzimidazole-1-ethanamine, 2-[(4-ethoxyphenyl)methyl]-*N*,*N*-diethyl- (ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{22}H_{29}N_{30}$
Molecular weight: 351.494 g/mol

C. Stereoisomers

No information was found.

D. Methods and ease of illicit manufacture

Etazene is the *desnitro* analogue of etonitazene (etodesnitazene) and is thus unsubstituted at C5 of the benzimidazole ring. It is one of a series of 2-benzylbenzimidazole compounds developed in the late 1950s as opioid analgesics *(8)*. The synthesis of etazene was described by Hunger et al. *(9)* and recently by Vandeputte et al. *(10)*. In the synthesis of protonitazene, the activated chloro atom of 2-nitrochlorobenzene is readily substituted by 2-diethylaminoethylamine. Then, reduction of the nitro group to the resulting amino function and condensation of the *ortho*-phenylenediamine species with ethoxyphenylacetic acid in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline affords etazene. Hydrochloric acid can be used to convert etazene into its corresponding salt forms *(6)*.

Etazene can also be obtained by routes reported for the synthesis of its 5-nitro-2-benzylbenzimidazole analogues, such as etonitazene *(10–14)*.

Although no information was found on the actual method and scale of manufacture of etazene, the synthetic methods are simple and cost–efficient and do not require the use of regulated precursors *(8)*.

E. Chemical properties

Melting-point:
65–66 °C (free base) *(15)*
118–120 °C (hydrochloride salt) *(15)*

Boiling-point:
No information was found.

Solubility
Etazene hydrochloride salt is reported to be soluble in water and methanol and partially soluble in dichloromethane *(16)*.

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

F. Identification and analysis

Synthetic etazene has been characterized by proton nuclear magnetic resonance spectroscopy (^{1}H-NMR), high-performance liquid chromatography coupled to diode-array detection, gas chromatography with mass spectrometry (GC-MS) and liquid chromatography (LC) coupled to high-resolution mass spectrometry *(8)*.

Etazene citrate is available as reference material from commercial suppliers and used for routine methods of analysis associated with forensic and clinical investigations.

Analytical methods for identification of etazene in seized sample matrices include X-ray crystallography, infrared spectroscopy, ^{1}H-NMR, GC-MS and LC-MS *(5, 16)*. LC coupled with tandem MS was recently reported for identification but not quantification of etazene in biological sample matrices such as human blood and urine *(17)*.

Metabolites of etazene were tentatively identified in the urine and serum of rats by GC–MS and LC-high-resolution MS *(6)*.

3. Ease of conversion into controlled substances

At the time of the writing, no information was available on the conversion of etazene into other controlled substances.

4. General pharmacology

Routes of administration and dosage

People posting on online forums report mainly intranasal administration as the route of administration of various doses. Participants in forums such as Erowid, Bluelight and Drugs Forum reported using doses of 30–100 mg,

dissolved in water or propylene glycol (to avoid burning the nose and throat).

One user reported taking one "m30" pill tested as etazene daily *(4)*.

B. Pharmacokinetics

In silico profiling of the absorption, distribution, metabolism and excretion of etazene showed that it is three times more lipophilic than morphine. The analysis also predicted that, like morphine, etazene has high gastrointestinal absorption and can permeate the blood–brain barrier. Unlike morphine, etazene does not appear to be a substrate for *p*-glycoprotein. Metabolite profiling showed that etazene inhibits CYP1A2, CYP2C19, CYP2D6 and CYP3A4. Etazene, like morphine, had a bioavailability score of 0.55, indicating that it is active in humans when taken orally *(18)*.

The same authors analysed the metabolites of etazene after a 24-h exposure at 28 °C of *Danio rerio* larvae to 75 μM. The results were compared with those for larvae not exposed to etazene and with those exposed to a control medium sample containing only the drug to detect compound degradation during the incubation step. Metabolites were detected in a high-performance LC–electrospray ionization-quadropole time-of-flight-MS system and were identified by comparing their precursor mass, the calculated molecular formulae and the fragmentation patterns with those of the parent compound and of known metabolites of etazene homologues. Fragmentation patterns revealed an imine fragment at m/z 72 and a diethylamine fragment at m/z 100. Further fragmentation of this metabolite resulted in an *N*-ethylethanamine fragment at m/z 253. Further fragments of the etazene metabolite (not identified) were found at m/z 107, 195 and 224 *(18)*.

C. Pharmacodynamics

Preclinical pharmacology studies showed that the pharmacological profile of etazene is similar to those of the potent Schedule I (under the 1961 United Nations Conventions) synthetic opioids etonitazene and isotonitazene and other μ-opioid receptor agonists *(7)*. Because of these pharmacological similarities to etonitazene and isotonitazene, use of etazene may present a high risk of abuse and may negatively affect people who use drugs and their communities, as it is well established that substances that act as μ-opioid receptor agonists have a high potential for nonmedical use and addiction and can induce dose-dependent respiratory depression.

Data from preclinical studies provided by the US Drug Enforcement Administration *(7)* on etazene binding and agonism at the three main opioid receptors (δ, κ, and μ) showed that etazene has slightly higher binding affinity to μ-opioid receptors than fentanyl and morphine. The affinities of etazene to δ and κ-opioid receptors were lower than those of fentanyl and morphine. Etazene was more potent at μ-opioid receptors than at δ and κ-opioid receptors and showed similar agonism to μ-opioid receptors but lower agonism to δ and κ-opioid receptors than fentanyl and morphine. Further details of the binding and agonism of etazene at opioid receptors are presented in Annex 3.

In the warm-water tail-flick assay with cumulative dosing followed by a time-course of the peak effect of etazene, this opioid had analgesic effects. Etazene increased tail-flick latency to a maximum effect of 100% after administration of 0.32 mg/kg in a dose-dependent manner. Potency ratios (ED_{50} test compound/ED_{50} reference compound) indicated that etazene was more potent than morphine but less potent than fentanyl. Etazene was considered to be as efficacious as morphine and fentanyl. The peak analgesic effects of etazene lasted 15 min.

Subcutaneous injection of naltrexone before administration of 0.32 mg/kg etazene blocked the analgesic effect of etazene, supporting involvement of opioid receptors in the action of etazene *(19)*. Further details of the analgesic effects of etazene are presented in Annex 3.

5. Toxicology

No reports were found on toxic doses of etazene for humans.

A recent study showed that etazene dose-dependently (doses of 10–300 μM) caused developmental toxicity in *Danio rerio* larvae by increasing their mortality, developmental malformations and cardiotoxic effects to a greater extent than morphine (doses of 1–50 mM) *(18)*.

In three post-mortem cases in which etazene was analytically confirmed, the blood concentrations were 1.8, 39 and 60 ng/mL *(20)*.

The UNODC Early Warning Advisory Tox-Portal of the United Nations Office on Drugs and Crome *(21)* included three reports in which etazene was identified. In Australia in 2021, etazene was detected in the femoral blood of a deceased 41-year-old male, but no data were provided on the probable contribution of etazene to the death. Etazene was identified in

the urine of a 38-year-old male the USA in 2021 in a case of driving under the influence of drugs, in combination with methadone and bupropion. It was considered that there was a strong probability that etazene contributed to the clinical status of the individual. In another case in the USA in 2021, etazene was found in the peripheral blood of a deceased 21-year-old male, in combination with 26 ng/mL fentanyl. The possibility that etazene contributed to the death was considered to be medium. No data on the doses of etazene were available in any of the cases.

6. Adverse reactions in humans

Most adverse reactions after etazene use have been reported on unverified online forums. For example, one person described itchiness and a "nice euphoric glow", in addition to pain relief and a sense of well-being, after taking 1 mg of etazene *(22)*. Another user reported a feeling of euphoria similar to that induced by isotonitazene *(23)*. Most of the effects induced by etazene appear to occur almost immediately after administration *(22)*.

Data collected between May 2020 and July 2021 confirmed the presence of etazene in 10 post-mortem specimens of blood and/or urine associated with death investigations *(9)* or clinical intoxications *(1)* in Canada and the USA.

In the US Center for Disease Control State Unintentional Drug Overdose Reporting System, which contains data from death certificates, post-mortem toxicology testing and death scene and witness findings from medical examiner or coroner reports on deaths related to unintentional drug overdoses and those of undetermined intent in 48 US jurisdictions, etazene was listed as the cause of death in one case from all states for which there were usable data (i.e., no trend in causes of death) between July and December 2020 and one case between January and June 2021. In no cases was etazene listed as the cause of death in states for which data were available in each period (6–10 for January 2019–June 2021). It should be noted that data on trends and non-trends in causes of death do not necessarily imply confirmation of etazene as the cause of death in a toxicological report. In cases from toxicological reports (i.e., detected non-trend) from all states with usable data, etazene was detected in one case between July and December 2020 and in two cases between January and June 2021. Etazene was not detected in any post-mortem case in an analysis limited to states with data for each period (6–10 in January 2019–June 2021) *(24)*.

7. Dependence potential

A. Studies in experimental animals

No studies were identified.

B. Studies in humans

No studies were identified.

8. Abuse potential

A. Studies in experimental animals

In drug discrimination studies (two-lever choice method), etazene fully substituted for the discriminative stimulus effects of 3.2 mg/kg morphine after subcutaneous administration to 10 Sprague-Dawley rats at doses of 0.01–0.32 mg/kg. Assessment of the potency ratio (ED_{50} test compound:ED_{50} reference compound) showed that etazene was more potent than morphine but less potent than fentanyl; etazene was considered to be as efficacious as morphine and fentanyl.

Subcutaneous injection to rats of naltrexone before administration of 0.32 mg/kg etazene blocked the morphine-like discriminative stimulus effects of etazene, indicating involvement of opioid receptors in the discriminative stimulus effects of etazine *(25)*. Details of the discriminative stimulus effects of etazene are presented in Annex 3.

B. Studies in humans

No studies were identified. Potential nonmedical use of etazene is described in online forums.

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

In the late 1950s, the Swiss pharmaceutical company CIBA Aktiengesellschaft synthesized a group of benzimidazole derivatives with analgesic properties *(9)*. These derivatives included Schedule I (under the 1961 United Nations Conventions) synthetic opioids such as clonitazene, etonitazene and isotonitazene. None of the derivatives was medically approved.

Etazene is not known to have any medical use.

10. Listing on the WHO Model Lists of Essential Medicines

Etazene is not listed on the 22nd WHO List of Essential Medicines or the 8th WHO list of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Etazene is not known to be authorized for marketing.

12. Industrial use

Etazene is not known to have any industrial use.

13. Non-medical use, abuse and dependence

No information was found. There are only a few self-reports of intentional etazene use on online forums (e.g., Erowid, Bluelight).

Although no studies on the abuse potential of etazene in humans were identified, its structural similarities to other Schedule I (under the 1961 United Nations Conventions) synthetic μ-opioid receptor agonists (e.g., etonitazene, isotonitazene), which have high potential for abuse, suggest that etazene has a similar potential for abuse in humans. This is supported by online reports by people who used this substance.

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

No information was found. Adverse effects experienced by people who have taken etazene are described in section 6.

Reports on online forums suggest the development of tolerance to etazene. For example, one person reported a "strong desire to redose" *(22)*. This 16-year-old male, weighing 85 kg, started by taking 500 μg of etazene and 10 min later took 1 mg more; 15 min after the last dose, he took 1.5 mg and repeated this dose every half hour until he went to sleep about 6 h after the first dose. All the doses were taken intranasally. He used etazene every day (about 5–10 doses a day) for the following 2 weeks. Another user reported experiencing cravings and the desire to frequently re-dose, consuming an average of one pressed "m30" pill (tested for etazene) per day for 11 days *(4)*. Another individual reported having to take 150–180 mg of oxycodone-equivalent single dose to "get high" *(4)*.

Detection of etazene in post-mortem cases, toxicology reports and evidence of its illicit distribution on the drug market suggest that etazene use could cause serious harm and represents a public health concern.

15. Licit production, consumption and international trade

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

16. Illicit manufacture and traffic and related information

Etazene was first detected in Canada in 2020, and 333 identifications of this substance by GC-MS plus Fourier transform IR were reported in 2021–2022 by Health Canada's Drug Analysis Service *(26)*.

According to the European Monitoring Center for Drugs and Drug Addiction, etazene has been identified in some European countries either in seizures or test purchases from online suppliers. For example, on 30 March 2020, a grey powder identified as etazene was seized in Poland, and in June 2020 a liquid form (nasal spray) of etazene was seized by customs police in Finland. The origin of the packages in both cases was Poland, and the destination was an individual in Finland *(7, 27)*. Etazene was also detected in 2020 in Austria, Czechia, Estonia and Sweden *(21)*.

Reports from the US National Forensic Laboratory Information System indicate that etazene was first detected in the USA on 1 October 2020, in Ohio, with 12 reports in 2021 from Florida *(1)*, Missouri *(1)*, Ohio (9) and Pennsylvania *(1)*. Weights were reported in only 9 cases, totaling 3.35 g *(7)*.

17. Current international controls and their impact

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

18. Current and past national controls

Etazene is a schedule I controlled substance in Canada. It has also been placed temporarily in Schedule I in the USA, effective from 12 April 2022 to 12 April 2024 *(28)*.

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

The absence of medical approval for etazene, abuse and identification of this opioid in toxicology case work, its presence on the illicit market and

reports from law enforcement agencies suggest that etazene poses a threat to public health. Moreover, people who use etazene are likely to obtain it from unregulated sources; therefore, the identity, purity and doses of these substances are uncertain and likely to be inconsistent, posing serious adverse health risks to the end user *(7)*.

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3.1.6 Etonitazepyne

1. Substance identification

A. International nonproprietary name

Not available

B. Chemical Abstracts Service registry number

2785346-75-8

C. Other chemical names

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

2-(4-Ethoxybenzyl)-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole

2-[(4-Ethyloxy)phenyl]methyl}-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzimidazole

N-Pyrrolidino etonitazene

D. Trade names

Etonitazepyne is sold as the hydrochloride salt under the name "*N*-pyrrolidino etonitazene" *(1)*.

E. Street names

Etonitazepyne is indicated under its own name or as *N*-pyrrolidino etonitazene.

F. Physical appearance

Etonitazepyne dihydrochloride purchased from online suppliers as a test material has been reported to be a homogeneous yellow powder *(2)*. Etonitazepyne purchased as reference material has been described as a crystalline solid *(1)*.

Reports from the Welsh Emerging Drugs and Identification of Novel Substances project *(3)* indicated the presence of etonitazepyne in "M30" blue tablets, sold as oxycodone.

G. WHO review history

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

2. Chemistry

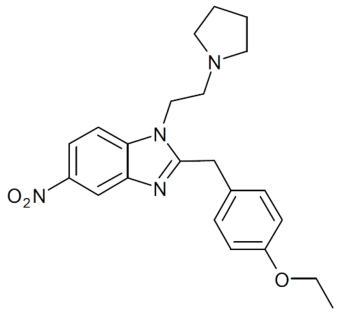
A. Chemical Name

IUPAC name:
2-[(4-Ethoxyphenyl)methyl]-5-nitro-1-(2-pyrrolidin-1-ylethyl)-1*H*-benzoimidazole

Chemical Abstracts Service index name:
1*H*-Benzimidazole, 2-[(4-ethoxyphenyl)methyl]-5-nitro-1-[2-(1-pyrrolidinyl)ethyl]- (ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{22}H_{26}N_4O_3$
Molecular weight: 394.47 g/mol

C. Stereoisomers

No information was available.

D. Methods and ease of illicit manufacture

Etonitazepyne is an opioid 2-benzylbenzimidazole, or "nitazene", which are compounds developed in the late-1950s as opioid analgesics *(4)*. Unlike its analogues, such as etonitazene, isotonitazene and protonitazene, etonitazepyne has not been reported in the scientific or patent literature *(5)*. An analogue bearing the *N*-pyrrolidino group but lacking the nitro group at the 5-position of the benzimidazole ring (*N*-pyrrolidino etodesnitazene) has been described (6). Related nitazene analogue containing a piperidine substitution, named "etonitazepipne", was reported recently *(7)*.

Etonitazepyne is a close analogue of etonitazene, carrying a pyrrolidino ring rather than a diethylaminoethyl moiety at the 1-position of the benzimidazole ring.

Synthesis of etonitazepyne has not been reported in the literature. It can be obtained through synthetic routes reported for synthesis of its 5-nitro-2-benzylbenzimidazole analogues, such as etonitazene, by appropriate replacement of reagents *(8–12)*.

Although no information was found on the method and scale of manufacture of etonitazepyne that was recently detected, use of the synthetic methods for its nitazenes analogues should be simple and cost–efficient and does not require regulated precursors.

E. Chemical properties

Melting-point:
No information was identified.

Boiling-point:
No information was identified.

Solubility:
Etonitazepyne has been reported to be soluble in methanol and partially soluble in water; it is not soluble in dichloromethane *(13)*.

Etonitazepyne is soluble in dimethylformamide at 30 mg/mL and in dimethyl sulfoxide at 1 mg/mL. It is soluble at 10 mg/mL in acetonitrile and methanol and at 5 mg/mL in ethanol *(1)*.

F. Identification and analysis

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

Analytical methods for the identification of etonitazepyne in seized samples include infrared spectroscopy, proton nuclear magnetic resonance, gas chromatography–mass spectrometry and liquid chromatography–high resolution mass spectrometry *(2, 13)*.

Liquid chromatography coupled with mass spectrometry has been used for identification and quantification of etonitazepyne in biological samples such as human blood and urine *(14)*.

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

A. Routes of administration and dosage

Reports from the Welsh Emerging Drugs and Identification of Novel Substances project *(3)* indicate that snorting or sniffing is the preferred route of administration of etonitazepyne. In one case, the substance was taken orally.

B. Pharmacokinetics

No information was found.

C. Pharmacodynamics

In preclinical studies, the pharmacological profile of etonitazepyne was similar to those of potent Schedule I (under the 1961 United Nations Conventions) synthetic μ-opioid receptor agonists such as etonitazene and isotonitazene *(15)*. Because of these pharmacological similarities, use of etonitazepyne may pose a high risk for abuse and may negatively affect people who use it and their communities.

Data from preclinical studies provided by the US Drug Enforcement Administration *(15)* on etonitazepyne binding and agonism at the three main opioid receptors (δ, κ, and μ) showed that it had greater binding affinity to μ- and δ-opioid receptors but lower binding affinity to κ-opioid receptors than fentanyl and morphine. Further details on the binding and agonism of etonitazepyne at opioid receptors are presented in Annex 3.

In-vitro radioligand binding assays performed in human embryonic kidney (HEK) 293 cells showed greater affinity of etonitazepyne for μ-opioid receptors ($K_i = 4.09 \pm 0.63$) than for - ($K_i = 959 \pm 193$) and κ-opioid receptors ($K_i = 980 \pm 213$) (5), as shown in Table 1.

Table 1. Binding affinities to opioid receptors of etonitazepyne, fentanyl and morphine in three independent experiments

	δ-OR [^{3}H]DADLE	κ-OR [^{3}H]U69,593	μ-OR [^{3}H]DAMGO
Drug name	$K_i \pm$ SD	$K_i \pm$ SD	$K_i \pm$ SD
Etonitazepyne	959 ± 193	980 ± 213	4.09 ± 0.63
Fentanyl	479 ± 76	224 ± 33	6.17 ± 0.82
Morphine	220 ± 41	74.4 ± 11.8	3.99 ± 0.40

Source: adapted from reference *5*.

In data provided by the US Drug Enforcement Administration *(15)*, etonitazepyne showed much greater agonism to μ--opioid receptors than fentanyl (about 31 times) and morphine (about 42 times). Its agonism to δ-opioid receptors was similar to that of fentanyl and morphine but lower to κ-opioid receptors (Annex 3).

Etonitazepyne also showed high potency [EC_{50} = 0.348 nM (0.137–0.876)] in a μ-opioid receptor-β-arrestin 2 activation assay. These values exceeded the potencies of both fentanyl [EC_{50} = 14.9 nM (10.6–21.0)] and morphine [EC_{50} = 290 nM (132–668)] *(5)*.

The analgesic properties of etonitazepyne were assessed in the hot-plate test after subcutaneous administration to male Sprague-Dawley rats. Treated rats showed dose-dependent latency of withdrawal, with a potency (ED_{50} = 0.0017 mg/kg) 10 and 2000 times those of fentanyl (ED_{50} = 0.0209 mg/kg) and morphine (ED_{50} = 3.940 mg/kg). The ED_{50} for catalepsy induction (scored on three overt symptoms: immobility, flattened body posture and splayed limbs) was 0.00354 mg/kg (about twice as weak as the antinociceptive potency). The 0.001 and 0.003 mg/kg doses of etonitazepyne slightly but significantly increased the rats' body temperature 60 min after injection, whereas a pronounced, sustained drop in body temperature was noted after injection of the highest dose (0.01 mg/kg). The effects of etonitazepyne on hot-plate latency, catalepsy and body temperature were similar to those of fentanyl and morphine *(5)*.

Etonitazepyne was also tested for its ability to induce analgesic effects in the warm-water tail-flick assay in Swiss-Webster mice with a cumulative dosing procedure (from 0.0001 to 0.01 mg/kg) followed by a time-course of the peak effect of etonitazepyne. Etonitazepyne increased tail-flick latency in a dose-dependent manner. In terms of potency ratios (ED_{50}

test compound:ED_{50} reference compound), etonitazepyne was more potent than morphine and fentanyl. In terms of relative efficacy (E_{max} test compound:E_{max} reference compound ´ 100), etonitazepyne was considered equally efficacious as morphine and fentanyl. The peak analgesic effect of etonitazepyne lasted 30 min.

Subcutaneous injection of naltrexone before administration of 0.01 mg/kg etonitazepyne blocked its analgesic effect, supporting the involvement of opioid receptors on the action of etonitazepyne *(16)*.

5. Toxicology

The peripheral blood concentrations in two post-mortem cases in which etonitazepyne was analytically confirmed were 2.4, and 8.3 ng/mL (17). As the in vivo potency of etonitazepyne is 20 times higher than that of fentanyl in humans, it is reasonable to conclude that these are lethal concentrations *(18)*.

Between January and October 2021, etonitazepyne was analytically confirmed in 21 blood samples and one urine sample from 21 post-mortem cases in North America: 17 in the USA, in West Virginia (8), Florida (2), Colorado (1), Kentucky (1), Minnesota (1), New Jersey (1), New York (1), Pennsylvania (1) and Tennessee (1); and 4 in Canada, in British Columbia. Seventeen of the decedents were male, and three were female; gender was not reported in one case. The ages ranged from 16 to 61 years. Etonitazepyne was detected with fentanyl in 12 cases, with methamphetamine in 12 and with benzodiazepines such as flualprazolam, etizolam, flubromazepam, clonazolam and desalkylflurazepam in 11 cases. Etonitazepyne was the sole substance detected in seven cases *(5)*.

The US State Unintentional Drug Overdose Reporting System reports data from death certificates, post-mortem testing and death scene and witness findings from medical examiner or coroner reports on deaths related to unintentional drug overdose and those of undetermined intent in 48 US jurisdictions. Etonitazepyne was detected in three cases in all states with usable toxicological reports (i.e., detected non-trend) and in three cases in an analysis limited to states for which data were available for each period and restricted to cases in toxicological reports (i.e., detected trend) between January and June 2021. Etonitazepyne was confirmed as the cause of death in three cases in all states with usable data (i.e., cause-of-death non-trend) and three cases in states with data for each period (cause-of-death trend) between January and June 2021 *(19)*.

A case in the United Kingdom in which etonitazepyne was detected in combination with other substances and caused life-threatening clinical toxicity was published recently *(20)*.

6. Adverse reactions in humans

A self-report on an online forum indicated that the first 30 min after use of etonitazepyne were pleasant, followed by drowsiness. Sweating and shaking were reported to have started 7 h and acid reflux after 9 h after taking one "M30" pill. The same individual reported having woken one night with difficulty in breathing, waking up early and having to dose to avoid withdrawal *(21)*.

Etonitazepyne was analytically confirmed in blood (1.15 h after admission) and urine (5.5 h after admission) in a patient admitted for acute intoxication in the United Kingdom in July 2021 *(18)*. The patient presented with reduced consciousness, miosis, respiratory depression and rhabdomyolysis. Methadone and benzodiazepines were also detected, which possibly contributed to the observed effects.

A "high alert" public notice issued by the New Zealand National Drug Intelligence Bureau for etonitazepyne strongly urged people not to take the substance *(22)*. It described euphoria; drowsiness and wakefulness; temporary relief of pain, stress or low mood; itchiness; severe nausea and/or vomiting; severe sweating or fever; slow and/or difficulty in breathing; blue lips or fingertips; cold, clammy skin; tiny pupils; unresponsiveness and/or loss of consciousness. These reports were not verified, and no further details (e.g., doses taken, use of other substances) was identified.

Self-reports of adverse effects include euphoria (9), relaxation (8), increased confidence (5), increased empathy (2), nausea (2), memory loss (2), loss of consciousness (2), enhanced senses (1), increased libido (1), vomiting (1), tiredness (1) and increased energy (1) *(3)*.

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found.

8. Abuse potential

A. Studies in experimental animals

In drug discrimination studies (two-lever choice method), etonitazepyne fully substituted for the discriminative stimulus effects of 3.2 mg/kg morphine after subcutaneous administration of etonitazepyne to nine Sprague-Dawley rats at doses of 0.00032–0.0032 mg/kg.

Assessment of potency ratios (ED_{50} test compound:ED_{50} reference compound) showed that etonitazepyne was more potent than morphine or fentanyl and was considered equally efficacious. The results for the first reinforcer measure were similar to those for the total session.

Subcutaneous injection of rats with 1 mg/kg naltrexone before administration of 0.0032 mg/kg etonitazepyne blocked its morphine-like discriminative stimulus, indicating the involvement of opioid receptors in its discriminative stimulus *(23)*. Further details of the discriminative stimulus effects of etonitazepyne are presented in Annex 3.

B. Studies in humans

No information was found. Law enforcement data, toxicology case work and reports on online forums and websites suggest potential nonmedical use of etonitazepyne *(3, 15, 22)*.

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

In the late 1950s, the Swiss chemical company CIBA Aktiengesellschaft synthesized a group of benzimidazole derivatives with analgesic properties, which included Schedule I substances such as the synthetic opioids clonitazene, etonitazene and isotonitazene. An analogue of etonitazepyne without the nitro group at the 5-position of the benzimidazole ring (*N*-pyrrolidino etodesnitazene) was described, but no reference was made to etonitazepyne *(6)*. Notably, the research did not result in any medically approved analgesic products

Etonitazepyne is not known to have any medical use.

10. Listing on the WHO Model Lists of Essential Medicines

Etonitazepyne is not listed on the 22nd WHO List of Essential Medicines or the 8th WHO List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Etonitazepyne is not known to have any marketing authorizations.

12. Industrial use

Etonitazepyne is not known to have any industrial use.

13. Non-medical use, abuse and dependence

No studies were found of the abuse and dependence potential of etonitazepyne in humans. A few self-reports of intentional etonitazepyne use are found on online user forums (e.g., 3).

Although no studies of the abuse potential of etonitazepyne in humans were found, its structural similarities to other Schedule I (under the 1961 United Nations Conventions) synthetic m-opioid receptor agonists (e.g., etonitazene), which have high potential for abuse, suggest that etonitazepyne has potential for abuse in humans.

One person on an online forum reported rapidly escalating tolerance and described taking half to one pill every 7 h to avoid withdrawal. He stated that switching to large doses of oxycodone was insufficient to prevent or reduce withdrawal symptoms. The individual described withdrawal (including sweating and leg restlessness) that was so severe that he was unable to go to work *(21)*.

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

No information was found on the nature or magnitude of public health problems associated with etonitazepyne use. Adverse effects experienced by people who have taken etonitazepyne are described in section 6.

Detection of etonitazepyne in post-mortem cases and toxicology reports and evidence of its illicit distribution on the drug market suggest that etonitazepyne use may cause serious harm and represents a public health concern.

15. Licit production, consumption and international trade

Etonitazepyne is used as a reference material in scientific research and forensic applications *(1)*.

16. Illicit manufacture and traffic and related information

The European Monitoring Centre for Drugs and Drug Addiction reported identification of etonitazepyne in some European countries in either seizures or test purchases from online suppliers *(24)*.

The Early Warning System Tox-Portal of the United Nations Office on Drugs and Crime reported the presence of etonitazepyne in Belgium, the United Kingdom (both in 2021), the USA (2021), Canada (2021 and 2022) and New Zealand (2022) *(25)*. In February 2021, the presence of etonitazepyne was confirmed by forensic testing in a 1-g test purchase from China, which was communicated to the Belgian focal point within the SCANNER Project *(26)*. In March 2022, the New Zealand National Drug Intelligence Bureau issued a public notice confirming the presence of etonitazepyne in a tablet sold as oxycodone *(21)*; the source of the tablet was not identified. In November 2021, an NPS Early Warning System public notice from Slovenia identified etonitazepyne in a falsified "Percocet" (sold as oxycodone) blue tablet (purchased on the Darknet) in Maribor *(27)*.

In March 2021, the Scanning Novel Opioids on Online Platforms (SNOOP) of the International Narcotics Control Board detected vendors of a substance purported to be etonitazepyne on e-commerce platforms. As of April 2022, six platforms in South, East, and South-East Asia had identified eight vendors offering the substance as powders in bulk via SNOOP. One of the vendors advertised a wholesale price per kilogram of US$ 60–80 for a minimum 1-kg purchase *(26)*.

Data from law enforcement agencies indicate that etonitazepyne appeared on the illicit drug market in the USA in 2021 *(15)*. A public alert issued in June 2021 by the Center for Forensic Science Research and Education New Psychoactive Discovery programme reported that the substance had been associated with eight overdose deaths in the USA *(17)*. Health Canada's Drug Analysis Service first detected etonitazepyne in four overdose deaths due to several substances in British Columbia during the third quarter of 2021. The number of detections in 2021–2022 in Canada subsequently increased to 128 *(28)*.

17. Current international controls and their impact

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

18. Current and past national controls

Etonitazepyne is a schedule I controlled substance in Canada. It has been temporarily placed in Schedule I in the USA, effective 12 April 2022 until 12 April 2024 *(29)*.

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

As etonitazepyne has been identified in products sold as oxycodone *(3, 21)*, it is reasonable to expect that the prevalence of intoxications due to etonitazepyne and related to etonitazepyne may be under-reported.

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3.1.7 2-Methyl-AP-237

1. Substance identification

A. International nonproprietary name

No information was found.

B. Chemical Abstracts Service registry number

98608-61-8 (base)

98608-59-4 (HCl)

Not yet assigned (2-methyl AP-237-d_7 hydrochloride)

C. Other chemical names

2-Methyl-1-(1-oxobutyl)-4-(3-phenyl-2-propenyl)-piperazine

1-{2-Methyl-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazin-1-yl}-1-butanone

1-[2-Methyl-4-[(*E*)-3-phenylprop-2-enyl]piperazin-1-yl]butan-1-one

1-{2-Methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl}-1-butanone

1-{2-Methyl-4-[3-phenylprop-2-enyl]piperazin-1-yl}butan-1-one

2-Methyl-BCP

2-Methyl bucinazine

N-Butyryl-*N*'-cinnamyl-2-methyl-piperazine

1-(4-Cinnamyl-2-methylpiperazin-1-yl)butan-1-one

Methyl-AP-237

1-Butyryl-2-methyl-4-cinnamylpiperazine

D. Trade names

2-Methyl AP-237

E. Street names

2-Methyl AP-237 appears to be most commonly used but other names are also encountered in Internet forums, including 2map, 2MAP, MAP, 2MAP237, 2m-AP237, 2-MAP, 2methylap237 and 2-M-AP-237.

F. Physical appearance

In its pure form, 2-methyl Ap-237 hydrochloride is expected to be odourless and white, like many other synthetic opioids. It has been described as a white crystalline powder *(1, 2)* and as a crystalline solid *(3)*. Seized material identified as 2-methyl AP-237 was also described as a white solid *(4)*.

G. WHO review history

2-Methyl Ap-237 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.

2. Chemistry

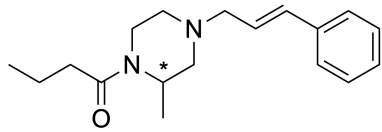
A. Chemical Name

IUPAC name:
1-{2-Methyl-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazin-1-yl}butan-1-one

Chemical Abstracts Service index name:
1-Butanone, 1-[2-methyl-4-(3-phenyl-2-propen-1-yl)-1-piperazinyl]-

B. Chemical structure

Free base:



Molecular formula: $C_{18}H_{26}N_{20}$
Molecular weight: 286.41 g/mol
Note: Asterisk (*) refers to a chiral centre

C. Stereoisomers

The presence of a chiral centre at the 2-position of the piperazine ring gives rise to the enantiomeric pair of (*S*)-2-methyl AP-237 and (*R*)-2-methyl AP-237. 2-Methyl AP-237 is most likely to be available as the racemic mixture, although the occurrence of individual stereoisomers cannot be excluded. The presence of the double bond in the *N*'-cinnamyl

group reflects a stereoisomeric olefin that could give rise to an (*E*)- and a (*Z*)-isomer.

D. Methods and ease of illicit manufacture

No specific information on routes of synthesis used for 2-methyl AP-237 products circulating on the market was found. The chemistry of producing 2-methyl AP-237 and related substances is straightforward and lends itself easily to small and large-scale manufacture. One method published in the literature involves use of racemic 2-methylpiperazine to which cinnamyl chloride is added to give the cinnamyl-piperazine intermediate. This intermediate is then acylated with butanoyl chloride *(1, 2)* to give 2-methyl AP-237. Other routes are also possible, such as use of variations used for the synthesis of the demethyl analogue AP-237 bucinazine (e.g., *5, 6*).

E. Chemical properties

Melting-point:
211–213 °C (hydrochloride salt) (1, 2)

Boiling-point:
No information was found.

Solubility:
2-Methyl AP-237 hydrochloride was reported to be soluble in dimethylformamide (10 mg/mL), dimethyl sulfoxide (15 mg/mL), ethanol (30 mg/mL) and phosphate-buffered saline (pH 7.2; 10 mg/mL) *(7)*. A collected sample of 2-methyl AP-237 hydrochloride was reported to be soluble in dichloromethane, methanol and water *(8)*.

F. Identification and analysis

Identification of 2-methyl AP-237, especially when it is available in larger quantities than are usually available for forensic toxicological work, is straightforward. Analysis of biological samples requires adequate separation techniques and sensitive analytical methods, such as gas or liquid chromatography coupled to (tandem) high- and low-resolution mass spectrometry. 2-Methyl AP-237 is available as a certified reference material, and some analytical data have been reported in the scientific (and patent) literature, including melting-point and elemental analysis, infrared spectroscopy, chromatography and mass spectrometry *(1, 2, 9–11)*. In synthetic blood samples spiked with a mixed standard containing *para*-fluorofuranylfentanyl, U-48800, isotonitazene, etonitazene,

metonitazene, phenylfentanyl, tianeptine, 2-methyl AP-237 and *para*-methylacetylfentanyl, cross-reactivity was observed on common enzyme-linked immunosorbent assay testing kits (Immunalysis Opiates, Oxycodone/Oxymorphone, Fentanyl and Buprenorphine Direct ELISA kits) *(12)*. Some analytical information, including chromatographic, mass spectral, spectroscopic and presumptive spot test data, is available in the public domain *(4, 8, 13–16)*. No information was found on differentiation of the two enantiomers, and not all laboratories might able to do so routinely. As the two olefinic protons on the *N*'-cinnamyl group are most likely to be in the (*E*)-configuration, the (*Z*)-form would constitute another isomer; however, no information was found about this isomer.

3. Ease of conversion into controlled substances

2-Methyl AP-237 cannot be converted into other substances under international control.

4. General pharmacology

A. Routes of administration and dosage

Descriptions on online forums suggest that 2-methyl AP-237 is typically administered orally (e.g., *17, 18*) and by nasal insufflation (snorting) (e.g., *19, 20*), although smoking (e.g., *20, 21*), sublingual *(22)* and rectal administrations (e.g., *23*) have also been described. In a case of non-fatal intoxication, 2-methyl AP-237 was administered with a nasal spray containing the drug dissolved in water *(9, 24)* (section 6). The "caustic" properties (e.g., "caustic burn") of 2-methyl AP-237 are mentioned frequently, indicating unpleasant sensations associated with certain routes of administration (e.g., gastric problems after oral ingestion or burning sensations after snorting).

"Typical" dosages depend on factors such as the route of administration, the tolerance of users, use of other drugs and the desired effects. Given the difficulty of collecting such data, the doses cited below should be viewed with caution. For example, the following dosage ranges have been described for smoked 2-methyl AP-237: low (5–15 mg), common (15–30 mg), strong (30–50 mg), heavy (> 50–60 mg) and overdose threshold (~80 mg) *(20)*. Oral doses of 7–50 mg have been reported, but several administrations and higher oral doses have also been described (e.g., *18, 25*).

B. Pharmacokinetics

No clinical studies were identified. Incubation of 2-methyl Ap-237 with human liver microsomes resulted in the detection of four monohydroxylated phase-I metabolites *(15, 16)*.

Some people believed to have taken 2-methyl AP-237 considered that the effects were relatively short-lived (e.g., *18, 22, 26*).

C. Pharmacodynamics

2-Methyl AP-237 was found to bind to MOR with appreciable affinity (K_i = 12.9 nM) and high selectivity over the δ (K_i = 2910 nM) and κ subtypes (K_i = 5259 nM) *(27)* (Table 1). The binding affinities of DAMGO, fentanyl and morphine were 42, 21 and 18 times higher, with Ki values < 1 nM.

Table 1. Receptor binding and functional activity of 2-methyl AP-237

MOR	**2-Methyl-AP-237**	**DAMGO**	**Fentanyl**	**Morphine**	**Naltrexone**
[^{3}H]DAMGO binding					
K_i (nM)	12.9 ± 2.7	0.304 ± 0.034	0.620 ± 0.033	0.730 ± 0.090	0.156 ± 0.012
IC_{50} (nM)	82 ± 19	–	–	–	–
[^{35}S]GTPγS binding					
Stimulation EC_{50} (nM)	620 ± 180	25.2 ± 2.3	27.9 ± 4.2	41 ± 10	–
Maximal stimulation (%)	46.7 ± 5.3	100	92.1 ± 2.0	77.0 ± 4.3	–
DOR	**2-Methyl-AP-237**	**DPDPE-OH**	**Fentanyl**	**Morphine**	**Naltrexone**
[^{3}H]DPDPE binding					
Ki (nM)	2910 ± 390	3.18 ± 0.68	292 ± 40	222 ± 30	19.3 ± 4.3
IC_{50} (nM)	5020 ± 710	–	–	–	–
[^{35}S]GTPγS binding					
Stimulation EC_{50} (nM)	> 10 000	7.1 ± 1.1	1330 ± 270	970 ± 280	–
Maximal stimulation (%)	18.40 ± 0.50	102.7 ± 2.7	69.1 ± 7.6	80.0 ± 1.3	–
KOR	**2-Methyl-AP-237**	**U50,488H**	**Fentanyl**	**Morphine**	**Nor-BNI**
[^{3}H]U-69,593 binding					
K_i (nM)	5259 ± 90	0.320 ± 0.054	187 ± 21	43.1 ± 9.7	0.169 ± 0.055
IC_{50} (nM)	8490 ± 610	–	–	–	–
[^{35}S]GTPγS binding					
Stimulation EC_{50} (nM)	1750 ± 590	0.53 ± 0.19	379 ± 97	78 ± 18	–
Maximal stimulation (%)	36.5 ± 5.4	99.7 ± 1.4	86.4 ± 4.7	91.5 ± 3.4	–

DOR, δ opioid receptor; KOR: κ opioid receptor; MOR: μ opioid receptor.

Transfected Chinese hamster ovary (CHO) cells expressing human δ- and κ-opioid receptors and rat μ-opioid receptors were used in receptor binding experiments. The standard compounds were the agonists DPDPE (δ), U50,488H (κ), DAMGO (μ), morphine and fentanyl, and the antagonists were naltrexone (δ and μ) and nor-BNI (κ). The results include the standard error of the mean. [^{35}S]GTPγS binding: maximal stimulation by test compound normalized to the maximal stimulation by DPDPE (δ), U50,488H (κ) or DAMGO (μ) above basal.

Source: adapted from reference *27*.

In an in-vitro GTPγS binding assay, 2-methyl AP-237 activated MOR with low efficacy (E_{max} = 46.7% when compared with DAMGO) and potency (EC_{50} = 620 nM). DAMGO, fentanyl and morphine were 25, 22 and 15 times more potent. When compared with DAMGO, fentanyl and morphine activated MOR with an efficacy of 91.1 and 77.0% (27) (Table 1). Relatively low potency was also observed in MOR activation assays with β-arrestin 2 or mini-Gi signalling (Table 2).

Table 2. Results for β-arrestin 2 and mini-Gi-meditated signalling

Compound	β-arrestin 2 (EC_{50} / nM)	E_{max} (%)	Mini-G_i (EC_{50} / nM)	E_{max} (%)	Reference no.
2-Methyl AP-237	2229	109	2229	142	*28*
	749	125	–	–	*9*
Hydromorphone	51.0	100	44	100	*28*
	26.9	98.6	–	–	*9*
Fentanyl	14.3	163	32.7	284	*28*
	23.1	187	–	–	*9*

For 2-methyl AP-237, an EC_{50} value of 568 nM was reported in an AequoScreen® assay (Perkin Elmer) with recombinant CHO-K1 cells expressing human MOR.

Source: adapted from reference *28*.

The analgesic effects of 2-methyl AP-237 have been studied in mice, and it was found to have antinociceptive properties when tested for peripheral and central effects (Tables 3 and 4). In the writhing test (Table 3), 2-methyl AP-237 was active at all doses in some of the tested animals. The activity of 2-methyl AP-237 was considered slightly greater than that of acetylsalicylic acid and phenylbutazone but slightly lower than that of dextropropoxyphene at an s.c. dose of 20 mg/kg.

Table 3. Analgesic properties of 2-methyl AP-237 in the para-phenylbenzoquinone test ("abdominal constriction response" and "writhing test")

Compound	Dose (mg/kg)	No. of animals exhibiting contortions	Mean no. of contortions
Control	–	18/18	21.8 ± 2.6
2-Methyl AP-237	100 oral	2/6	5.5 ± 1.4
	50 oral	3/6	3.3 ± 0.6
	25 oral	4/6	11.5 ± 7.0
Acetylsalicylic acid	100 oral	4/6	13.5 ± 11.1
Phenylbutazone	100 oral	3/6	2.7 ± 1.5
	50 oral	5/6	11.4 ± 11.0
Dextropropoxyphene	20 s.c.	2/6	2.5 ± 2.1

Groups of six male CD-1 albino mice weighing 25–30 were given *para*-phenylbenzoquinone (0.2 mg/mL) intraperitoneally 30 min after oral administration of the test drug. Contortions observed in the next 20 min were counted.

Source: references *1* and *2*.

In the hotplate test, 2-methyl AP-237 increased response latency before nocifensive behaviour at all tested doses (Table 4).

Table 4. Analgesic properties of 2-methyl AP-237 in the hot plate test

Compound	Dose (mg/kg)	Reaction times (s)		
		Basic (s)	After 30 min	After 60 min
2-Methyl AP-237	100 oral	9.3	> 42	34
	50 s.c.	9.7	> 60	> 58
	25 s.c.	6.0	34.3	25.7
	10 s.c.	10.3	19.7	5.3
Dextropropoxyphene	20 s.c.	6.9 ± 7.0	13.8 ± 1.2	–
	10 s.c.	7.5 ± 0.7	14.4 ± 2.5	–

Female CD-1 albino mice (20–25 g); plate temperature kept at 54.5 °C. Reaction time (s) measured when an animal showed obvious symptoms of pain in its rear paws (paws trembled and withdrawn backwards or licked). The reaction time for a normal mouse was 5–13 s. Basic reaction time measured twice for each animal at an interval of 15 min; test drug administered after a further 15 min; reaction time again measured 30 min and 60 min after treatment.

Source: references *1* and *2*.

In a separate study, 2-methyl AP-237 was tested in the warm water tail-flick assay in 10 Swiss-Webster mice to evaluate its analgesic effects *(29)*. A cumulative dosing procedure was used, followed by a time-course study of the peak effect. Mice were tested for baseline tail withdrawal latency in 50 °C water, followed immediately by s.c. injection of the vehicle (0.9% saline). After 15 min, tail-withdrawal latency was re-determined in each mouse, followed immediately by injection of the lowest dose of 2-methyl

AP-237. Testing continued with increasing cumulative doses until the mouse failed to remove its tail from the water before the 10-s cut-off time (maximum antinociception) or until toxic effects (e.g., respiratory depression, convulsions) were observed. Tail-withdrawal latencies were transformed into percentages of the maximal possible effect (% MPE).

2-Methyl-AP-237 (ED_{50} = 0.078 mg/kg), dose-dependently increased tail-flick latencies to a maximum of 99 ± 1% MPE. The ED50 for the morphine standard was 0.38 mg/kg. The maximum peak effect of morphine (E_{max}) was 100% MPE. The ED_{50} for the fentanyl standard was 0.063 mg/kg, and the maximum peak effect of fentanyl (E_{max}) was 98% MPE. The peak analgesic effects of 2-Me-AP-237 lasted 45 min and returned to baseline within 135 min. Naltrexone (1 mg/kg) blocked the analgesic effects of 2-Me-AP-237, which was reflected in the reduction of the tail-flick latency to 30 ± 4 % MPE *(29)*. These results suggest that 2-methyl AP-237 is as potent as fentanyl and more potent than morphine in this assay.

5. Toxicology

No toxicology studies in humans were identified. In male and female CD-1 mice (25–40 g), acute toxicity was tested after intravenous, oral and s.c. administration. The reported LD_{50} values were 55 mg/kg (intravenous), 350 mg/kg (oral) and 550 mg/kg (s.c.) *(1, 2)*.

Furlan *(1, 2)* reported the following observations after intravenous administration: "at 70 mg/kg and in those animals that died at 60 mg/kg, immediate tonic convulsions with stiffening of the tail, increase in body tone, gasping, subsequent loss of posture and death due to respiratory blockage under complete muscular relaxation, within a few minutes after treatment: at 50 mg/kg, immediate jumping with tonic convulsions, dyspnea and gasping, stiffening of the body and tail, and an increase in the tone of the limbs. Touching produced brief tonic-clonic convulsions of low intensity, followed by violent jumping and excessive reaction to environmental stimuli, and central analgesia with Straub tail. Exophthalmos was not observed in these animals. At lower doses, immediately after inoculation, jumping and psychomotor excitement, loss of posture, stiffening of the tail and limbs, dyspnea, abnormal walking, stereotypy and strong central analgesia".

Furlan *(1, 2)* reported the following observations after oral and subcutaneous administration: "at 1000 mg/kg (oral and subcutaneous administration), immediately after inoculation animals showed

psychomotor excitement with Straub tail, and contracting of the limbs which determines abnormal walking. Animals remained immobile lying on their back or on their side, with their limbs hypertonic; reacted positively to acoustic stimuli with brief tonic convulsions, and dyspnea; mortality observed between the 6th and 16th hour following treatment. There was an analogous symptomatology at the lower doses, and cyanosis was observed at the tail and ear vessels. For equal doses the effects were much more evident with oral administration. A certain central analgesia persisted up to three hours following treatment".

6. Adverse reactions in humans

Cases of 2-methyl AP-237 Intoxication in humans

The Early Warning Advisory Tox-Portal of the United Nations Office on Drugs and Crime (UNODC) lists two post-mortem cases involving detection of 2-methyl AP-237 *(30)*. One case was reported from Sweden in July 2019, with a concentration of 46 ng/mL in femoral blood. SL-164 (dicloqualone) was also detected but not quantified. No further information was available. The second case, notified by the USA, occurred in May 2021. 2-Methyl AP-237 and bromazolam were detected in blood (vena cava) but were not quantified, and no further information was provided. In both cases, the relative or probable contribution of the drug was listed as "contributory – medium".

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), two countries reported detection of 2-methyl-AP-237 in biological samples related to serious adverse events between 2019 and 2020, with one sample associated with a death and one associated with acute poisoning. No further details were available *(31)*.

The WHO ECDD Secretariat received data from the US Centers for Disease Control and Prevention's State Unintentional Drug Overdose Reporting System from the US Office of National Drug Control Policy. The data are from death certificates, post-mortem toxicology testing and death scene and witness findings from medical examiner or coroner reports on deaths due to unintentional drug overdose and those of undetermined intent in 48 participating jurisdictions, with comprehensive details not available from other data sources. 2-Methyl AP-237 was listed as the cause of death in 11 cases between January 2020 and June 2021. During the same period, 2-methyl AP-237 was detected in 10 fatal cases, but no information was available to assess whether this drug had contributed to the deaths.

The WHO ECDD Secretariat received copies of redacted autopsy reports in which 2-methyl AP-237 and other substances were detected. In one case from San Diego (CA, USA), a 28-year-old man was found dead in a motel, with loose pills and drug paraphernalia. Toxicological analyses revealed 2-methyl AP-237 (1.0 mg/L, peripheral blood), quetiapine (0.4 mg/L), citalopram (0.28 mg/L), propranolol, desmethylcitalopram, etizolam and mitragynine. A blue tablet found at the scene was found to contain etizolam. An orange residue found in a "baggie" contained propranolol, and white powder found in a capsule contained 2-methyl AP-237. The death was ruled as an accidental acute drug intoxication (overdose) due to the combined acute toxic effects of 2-methyl AP-237, etizolam, mitragynine, citalopram and quetiapine. There was no evidence of suicidal intent. This case may be one of those reported by the DEA *(32, 33)*.

In another case, a 26-year-old man was found unresponsive in a restroom at his workplace in Texas (USA). Used syringes and an empty vial of 2-methyl AP-237 were present at the scene. Analyses of blood samples revealed 2-methyl AP-237 (1400 ng/mL) and fluconazole (positive). Synthetic opioid toxicity (2-methyl AP-237) was ruled as the cause of death, and the manner of death was determined to be accidental.

The WHO ECDD Secretariat also received a number of reports of toxicological analyses of biological samples carried out on behalf of the DEA, which included detection of 2-methyl AP-237 and other substances. Further details (e.g., clinical vs post-mortem) were only available in some cases (Table 5); however, some of the cases may have also been reported by the DEA elsewhere *(32–34)*.

Table 5. Substances detected in biological samples analyzed for the US Drug Enforcement Administration, 2020–2021

Date	Sample	Substances detected (ng/mL)
June 2020	Serum	Sample origin: Seattle (WA, USA). 2-Fluoro-deschloroketamine (5.0), 2-fluoromethamphetamine (10.3), 2-methyl AP-237 (13.5), 5-MAPB (109), mitragynine (185), 7-hydroxy-mitragynine (22.9), etizolam (6.8), fentanyl (11.4), norfentanyl (4.5), flualprazolam (9.5), MDMA (181), HMMA (1.7), MDA (74.3), morphine (1.5), promethazine. This fatal case may be one of those reported by the DEA *(32, 33)*. No more information was available.
January 2021	Whole blood	Sample origin: Olathe (KS, USA). 2-Methyl-AP-237 (141), etizolam (4.5), lidocaine, alprazolam, α-hydroxy alprazolam. This may be the case reported by Samano et al. *(35)*, but further confirmation is required. It may also be one of the cases reported by the DEA *(32–34)*. No more information was available.
March 2021	Whole blood	Sample origin: Omaha (NE, USA). 2-Methyl-AP-237 (208.1), cocaine (0.9), benzoylecgonine (86.5), ecgonine methyl ester (23.7), 11-nor-9-carboxy-delta 9-THC (111), methadone (1.1), EDDP (0.8), alprazolam. This fatal case may be one of those reported by the DEA *(32–34)*. No more information was available.
April 2021	Whole blood	Sample origin: Richmond (VA, USA). 2-Methyl AP-237 (141.0), bromazolam (94.7), desalkylfurazepam (65.0), oxycodone (1.6), benzoylecgonine (28.8), diphenhydramine.
June 2021	Whole blood	Sample origin: Bellingham (WA, USA). 2-Methyl AP-237 (313), mitragynine (0.8), citalopram (2.2), fluoxetine (7.5), norfluoxetine (300), naloxone. A previous toxicological analysis by an alternative provider showed the presence in central blood of citalopram/escitalopram (100 ng/mL), norfluoxetine (710 ng/mL), δ-9-THC (4.1 ng/mL) and δ-9-carboxy-THC (48 ng/mL), naloxone (positive). A 22-year-old man was found dead. He had a history of substance use disorder and was reported to have purchased increasing quantities and strengths of narcotics on the Internet. Autopsy revealed acute cardiorespiratory failure with marked pulmonary oedema filling his lungs, airways and endotracheal tubes. Cause of death: mixed drug intoxication with 2-methyl AP-237, mitragynine, citalopram, fluoxetine, norfluoxetine, naloxone. Manner of death was ruled suicide.
August 2021	Plasma	Sample origin: Wilmington (DE, USA). 2-Methyl AP-237 (171), benzoylecgonine (4.7), lorazepam (876), lormetazepam (28.5), clonazolam (1.5), nordiazepam (0.8), naloxone, clonazepam, dextromethorphan, meprobamate.
August 2021	Urine	Same case, different matrix. 2-Methyl AP-237, cocaine (12.7), benzoylecgonine (322), ecgonine methyl ester, lorazepam, lormetazepam (1570), 7-aminoclonazepam, naloxone, dextromethorphan, dextrorphan, gabapentin, phenibut, nordoxepin.
September 2021	Whole blood	Sample origin: Kansas City (KS, USA). 2-Methyl AP-237 (379), d-9-THC (56.8), 11-nor-9-carboxy-δ-9-THC (141), 8-amino clonazolam (4.6), *O*-desmethyl-*cis*-tramadol (10.9), mitragynine (2.7), 7-amino clonazepam, diphenhydramine, fluoxetine, norfluoxetine, trazodone, mCPP, propranolol.

[a] Analyses carried out by the Clinical Toxicology and Environmental Biomonitoring Laboratory at the University of California, San Francisco (CA), USA. Information on whether the cases were clinical or post-mortem cases (or both) was not provided.

According to the DEA *(33)*, two fatal intoxications involving 2-methyl AP-237 were reported in King County (WA, USA). The presence of 2-methyl AP-237 was confirmed in drug samples. A white powder was found near the body at one scene, and the other was associated with what appeared to be counterfeit Xanax bars. No further information was reported. In January 2021, an overdose death attributed to 2-methyl AP-237 was reported in Kansas (USA). Evidence at the scene indicated that the victim encapsulated 2-methyl AP-237 powder into clear capsules prior to death *(33)*.

Trend reports are published by the Center for Forensic Science Research & Education (PA, USA) that provide summaries of drug detections, predominantly in biological samples during toxicological case work. Table 6 summarizes detections published quarterly. No more details on the toxicological cases could be obtained.

Table 6. Positivity rates for 2-methyl AP-237 in samples submitted for analysis to the Center for Forensic Science Research & Education

Year	Quarter	2-Methyl Ap-237		Total number [a]
		No.	%	
2020	Q2	1	0	775
2020	Q3	3	0	626
2020	Q4	5	1	714
2021	Q1	0	0	454
2021	Q2	6	1	584
2021	Q3	10	1	851
2021	Q4	1	0	621
2022	Q1	2	0	710
2022	Q2	2	1	342

[a] The total included other substances, such as fentanyl, methamphetamine, cocaine, MDMA, eutylone, metonitazene, α-PiHP/α-PHP and dimethylpentylone.

Source: Dr Alex J. Krotulski (Center for Forensic Science Research & Education, Fredric Rieders Family Foundation, Willow Grove (PA), USA).

Scientific literature: non-fatal cases

A 20-year-old man was admitted to intensive care after snorting a substance reported as a synthetic opioid, with worsening dyspnoea 48 h after ingestion. Investigations revealed an acute pulmonary syndrome referred to as a "crack-lung", involving diffuse ground-glass opacities

and acute dyspnoea. The investigation showed bilateral parenchymal ground-glass opacity, mainly with bilateral near-hilum distribution and mediastinal widening. The patient received symptomatic treatment for 72 h and was discharged after 10 days. Blood analysis (25 ng/mL) showed the presence only of 2-methyl AP-237 *(36)*.

A 31-year-old man was found unresponsive at home with respiratory depression after using a nasal spray containing 2-methyl AP-237 (1 g/30 mL) 4 h earlier. Administration of naloxone (0.4 mg intravenously, then 0.8 mg) improved his respiratory and mental status. In the emergency department, he was found to be somnolent but arousable and oriented. The patient reported having ingested methadone earlier in the day and reported long-term use of benzodiazepines. The opioid intoxication symptoms resolved approximately 24 h after reported use. Analyses of whole blood showed 2-methyl AP-237 (peaking at 35 ng/mL about 7 h after nasal administration). Other substances detected included clonazolam (63 ng/mL), pyrazolam (4200 ng/mL), mitragynine, O-desmethyltramadol, eutylone and methadone *(24)*. The same case was reported twice elsewhere *(9, 37)*. The patient was reported to have a history of use of 2-methyl AP-237. The blood concentration on admission was reported to be 21 ng/mL. Other substances identified were O-desmethyltramadol, eutylone, naloxone, pyrazolam, methadone, 7-aminoclonazepam, etizolam, caffeine, mitragynine, 7-hydroxymitragynine and clonazepam *(9)*.

In a case report of suspected 2-methyl-AP-237 intoxication, a 24-year-old man was found unresponsive and hypoxic at home. Naloxone was administered, and the patient regained consciousness and was transported to an emergency department. The urine drug screen was negative, and supportive treatment was recommended. No details on the analysis of biological samples confirming the detection of 2-methyl AP-237 were reported *(38)*.

Scientific literature: fatal cases

A 29-year-old man was found unresponsive at home. A white substance, a scale and other paraphernalia were found at the scene. Femoral blood contained alprazolam (41.1 ng/mL) and etizolam (19 ng/mL), and qualitative analyses showed naloxone, caffeine and cotinine. The urine also contained alprazolam and α-hydroxyalprazolam. The white crystalline powder found on the scene was tested and identified as 2-methyl AP-237. An investigation performed by the reference laboratory provided

qualitative identification of 2-methyl AP-237 in femoral blood in two separate aliquots. Autopsy revealed moderate-to-marked pulmonary oedema, constipation and cerebral oedema with uncal herniation. No natural disease was considered to have accounted for death *(35)*. This case was reported from the Johnson County Medical Examiner's Office in Olathe (KS, USA). Confirmation is required of whether this is the same case reported above.

A 54-year-old man was found dead under a tree. A plastic container labelled "2MAP" and a cut straw were found in the decedent's backpack. Field-testing showed that a white powder in the plastic container and the straw were positive for fentanyl. The decedent had a history of depression, shoulder pain and early signs of dementia. His medical history revealed he had been treated for a drug overdose in October 2018. The concentrations of 2-methyl AP-237 in blood and urine were 480 ng/mL and 4200 ng/mL, respectively. Alprazolam was also detected in blood, at 55 ng/mL *(39)*.

A summary was published of four fatal cases with detection of 2-methyl AP-237 and other substances *(9)* (Table 7). The cases were received between February 2020 and April 2021. Post-mortem blood concentrations were reported to range between 820 and 5800 ng/mL.

Table 7. Fatal cases with detection of 2-methyl AP-237 and other substances

Date	Comments
29/M	Decedent discovered unresponsive at a "sober living" facility. 2-Methyl AP-237 concentration in blood: 5800 ng/mL. Caffeine, cotinine, quinine, naloxone, trazodone, phenibut (77 000 ng/mL) were also found. Further details of this case were presented elsewhere *(40)*. The deceased had a history of nonmedical benzodiazepine and gabapentin use, chronic gastrointestinal problems, back pain and depression. The previous evening, the decedent had appeared drowsy, and his roommate had helped him to bed. When the roommate woke in the morning, he saw a bloody purge emanating from the decedent's nose and called the emergency services. Naloxone was administered without improvement, and death was pronounced on the scene. The "sober living" supervisor noted that residents underwent weekly drug testing and the decedent had tested negative 2 days before his death. A white powder collected at the scene was identified as 4-phenyl-2-pyrrolidinone, and pill fragments collected from the small intestine at autopsy revealed 4-phenyl-2-pyrrolidinone, menthol and nicotine. 4-Phenyl-2-pyrrolidinone is an acidic compound and was not detected in a comprehensive in-house panel of blood specimens, which does not include extraction for acidic drugs. Research showed that this compound is the cyclic product of phenibut created at high temperatures. The cause of death was certified as the combined effects of 2-methyl AP-237 and phenibut, and the manner of death was listed as accidental.

Table 7. *continued*

Date	Comments
35/M	The individual was found dead in a car in a ditch. 2-Methyl AP-237 was found (ng/mL) in: blood (1100), urine (5000) and vitreous humor (270). Also detected were caffeine, carisoprodol (840), meprobamate (7300), δ-9-THC (1.1), carboxy-THC (6.1), promethazine (33), amphetamine (8.9), methamphetamine (45), etizolam (22), meclonazepam (26), 2-FDCK and 3-HO-PCP.
29/M	Sample origin: Omaha (NE, USA). 2-Methyl-AP-237 (208.1), cocaine (0.9), benzoylecgonine (86.5), ecgonine methyl ester (23.7), 11-nor-9-carboxy-delta 9-THC (111), methadone (1.1), EDDP (0.8), alprazolam. This fatal case may be one of those reported by the DEA *(32–34)*. No more information was available.
Unknown	Sample origin: Richmond (VA, USA). 2-Methyl AP-237 (141.0), bromazolam (94.7), desalkylfurazepam (65.0), oxycodone (1.6), benzoylecgonine (28.8), diphenhydramine.

Source: reference *9*.

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No clinical studies on withdrawal from or physical dependence on 2-methyl AP-237 were identified. Self-reports by people who reported having used 2-methyl AP-237 suggest that regular consumption is associated with the development of tolerance and withdrawal in some cases (e.g., *22, 26, 41*).

8. Abuse potential

A. Studies in experimental animals

Drug discrimination: In a two-lever discrimination task was given to nine male Sprague-Daley rats that had received a morphine sulfate training dose of 3.2 mg/kg in a fixed-ratio (FR10) schedule of reinforcement, 2-methyl AP-237 (test doses, 0.1–1 mg/kg) fully substituted (ED_{50} = 0.25 mg/kg) for the discriminative stimulus effects of morphine (ED_{50} = 1.08 mg/kg). The ED_{50} for a fentanyl standard was 0.0042 mg/kg. The peak morphine-appropriate response (E_{max}) was 92 ± 5%. The response rate was decreased to 39% that of the vehicle control after 1 mg/kg of 2-methyl AP-237. Naltrexone (1 mg/kg) blocked the morphine-like discriminative stimulus effects of 2-methyl AP-237, reducing the morphine-appropriate response to 12 ± 11% *(42)*.

B. Studies in humans

No Information was found.

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

No information was found.

10. Listing on WHO Model Lists of Essential Medicines

2-Methyl AP-237 is not listed on the 22nd WHO Model List of Essential Medicines or the 8th WHO list of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

No information was found.

12. Industrial use

No information was found.

13. Non-medical use, abuse and dependence

No epidemiological evidence was found in household surveys of use of 2-methyl AP-237. Detection of 2-methyl AP-237 in biological fluids confirms that this substance is used recreationally (intentionally or unintentionally). Information from Internet forums suggests that people who use heroin, prescription opioid analgesics and other synthetic opioids also use this substance. 2-Methyl AP-237 is available in its own right and is advertised for sale by some Internet retailers, including those operating on the "cryptomarket" *(43)*. Current information suggests (sections 4 and 8) that 2-methyl AP-237 shows abuse liability and that this probably extends to dependence-producing properties comparable to those of other non-fentanyl synthetic opioids that are under international control.

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

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

No epidemiological data were found on harm associated with 2-methyl AP-237. The detection of this substance in fatal and non-fatal intoxications (section 6) suggests poly-substance use in most cases; although fatal

intoxications associated with 2-methyl AP-237 alone have also been reported, including those where 2-methyl AP-237 was considered the cause of death. No data were found on the effect of 2-methyl AP-237 on the ability to drive and operate machines. As it is well established that opioid analgesics affect the mental and physical ability required for driving and operating machinery, this is likely to extend to 2-methyl AP-237. People who inject opioids might also use synthetic opioid "research chemicals"; however, they may not be aware of the high potency of some synthetic opioids, which might increase the risk of life-threatening overdoses. The risk of poisoning may be greater with the unintentionally high doses that users may take, especially when combined with other substances, such as other opioid analgesics and other central nervous system depressants that can increase the risk of life-threatening respiratory depression. In a review of all fatal poisonings related to new synthetic opioids in Australia recorded in the National Coronial Information System between 2000 and 2021, 2-methyl AP-237 was identified in one of 31 cases *(44)*. In a count of cases in 2019 (no details), 2-methyl AP-237 was listed among new synthetic opioids observed in case work recorded in Sweden *(45)*. A data-mining exercise involving a retrospective analysis of raw data obtained on post-mortem cases and driving under the influence of drugs included four cases of use of 2-methyl AP-237. It was first detected in the USA in 2019 *(46)*.

The US DEA's Toxicology Testing Program, a surveillance programme for detecting new psychoactive substances in biological samples in the USA, reported two detections of 2-methyl AP-237 in the second quarter of 2021 *(47)*; three detections in the third quarter of 2021 (with concentrations of 13.5 ng/mL in serum, 171 ng/mL in plasma and 141 ng/mL in blood) *(48)*; one detection in the fourth quarter of 2021 (313 ng/mL in whole blood) *(49)* and two detections in the second quarter of 2022 ("313–379" ng/mL in whole blood) *(50)*. It was not clear whether the two detections of 313 ng/mL 2-methyl AP-237, both reported in Washington State *(49, 50)* were the same. It was also unclear whether they were the same cases described in section 6.

In the USA, at least 10 confirmed cases of fatal poisonings and several reports of emergency room visits associated with 2-methyl-AP-237 (possibly including those reported in section 6) have been reported *(51)*.

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

15. Licit production, consumption and international trade

2-Methyl Ap-237 is used as reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic use. Some Internet retailers advertise it for sale as a "research chemical".

16. Illicit manufacture and traffic and related information

2-Methyl AP-237 was formally notified to the European Union Early Warning System Network on behalf of Sweden in April 2019 after a seizure during a house search on 29 January 2019 and a sample purchased on the Internet by the Public Health Agency of Sweden on 26 February 2019 *(31)*. 2-Methyl AP-237 has been available on the drug market in Europe since at least 2019. Since it was formally notified, the EMCDDA has received reports of 31 seizures of 2-methyl AP-237. In seizures, 2-methyl AP-237 was mostly found as a powder (approximately 55% of all cases reported), although liquids (26% of cases) and tablets (13% of cases) were also reported. As of 15 July 2022, approximately 121 g of 2-methyl AP-237 had been seized in total; 109 g were in liquid form and 12 g were powders. All of the liquids were seized in 2019 (109 g in eight seizures), and approximately half of the powder was seized in 2019 (5.1 g in 12 seizures) *(31)*.

The numbers of countries that reported detections of 2-methyl AP-237 to the UNODC Early Warning Advisory on new psychoactive substances database were eight in 2019, three in 2020, two in 2021 and two in 2022. In some instances, multiple entries from the same country were counted for the same year *(52)*.

The National Forensic Laboratory Information System, which collects drug cases submitted by state and local laboratories in the USA, has registered detections of 2-methyl AP-237. The numbers of reports of 2-methyl AP-237 in the public domain were 21 in 2019 (the first time), four in 2020 and two in 2021 (as of June 2021). 2-Methyl-AP-237 was found alone or with other substances *(53)*. The presence of 2-methyl AP-237 was confirmed in 27 samples submitted to the Forensic Laboratory Information System when queried on 27 May 2021 (34). On 21 May 2021, it stated that laboratories that report to the System had received 27 submissions on 2-methyl AP-237 since April 2019 *(33)*. A total of 45 reports were received in 2021 *(51)*.

The US Customs and Border Protection National Targeting Center compiled all known shipments of 2-methyl AP-237 to the USA between

January 2019 and May 2021 *(33)*. The shipments arrived in New York City (NY), Miami (FL) and Memphis (FL) from countries of origin identified as China, Germany, the Netherlands and Switzerland, with the majority from the Netherlands. The data indicate that most shipments were sent from Europe, although it was considered possible that the shipments originated from China or another country and were trans-shipped through Europe. While the report does not align precisely with those of the DEA, it identifies China as the origin of 63.8 g of 2-methyl AP-237 shipped to the USA in April 2020 *(33)*.

In a study of trends in the listing of novel non-fentanyl synthetic opioids on one cryptomarket *(43)*, 2-methyl AP-237 was identified as one of the most widely sold synthetic opioids between 1 June and 18 August 2020. A total of 136 listings were identified with 2592 sales transactions and 163 sales, for a total of 530.5 g sold. The average volume was 163.1 g (minimum, 0.5 g; median, 10 g; maximum, 100 g). The countries of origin were identified as Australia (52.4%), China (40.1%) and the USA (7.5%), and the destinations were Australia (52.4%), the world (40.1%) and the USA (7.5%).

A white powdered material found in a capsule ordered from an Internet retailer in China was found to contain 2-methyl AP-237 *(13)*.

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

17. Current international controls and their impact

2-Methyl AP-237 is currently not controlled under the 1961, 1971 or 1988 United Nations conventions.

18. Current and past national controls

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

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

None.

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3.1.8 α-PiHP

1. Substance identification

A. International nonproprietary name

No information was found.

B. Chemical Abstracts Service registry number

2181620-71-1 (base)

2363169-94-0 (*R*)-enantiomer

2415172-12-0 (*S*)-enantiomer

2705245-60-7 (HCl)

C. Other chemical names

α-Pyrrolidinoisohexanophenone

α-Pyrrolidinoisohexaphenone

α-Pyrrolidinoisohexiophenone

4-Methyl-α-PVP

γ-Methyl-α-PVP

4-Methyl-α-pyrrolidinopentanophenone

4-Methyl-α-pyrrolidinopentiophenone

4-Methyl-α-pyrrolidinovalerophenone

4-Methyl-desmethylpyrovalerone

4-Methyl-βk-prolintane

D. Trade names

α-PHiP

E. Street names

Some of the chemical names listed above are also encountered as street names. Other code names include α-PiHP, α-PHiP, pihp, aphip and phip. In a notification received by the EMCDDA, one European Union Member State reported identification of α-PiHP with 1-(2*H*-1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)hexan-1-one in a branded product named "Insomnia". It should be noted that the composition of such branded products is likely to change over time.

F. Physical appearance

In its pure form, α-PiHP hydrochloride is expected to be odourless and white, like many other ring-substituted synthetic cathinones. It has been reported as an off-white solid or powder *(2, 3)*, a white powder *(4)*, a crystalline solid *(5)* and white powder in "rock" form *(6)*.

G. WHO review history

α-PiHP 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.

2. Chemistry

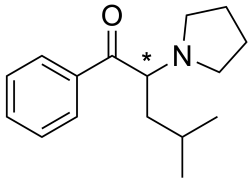
A. Chemical name

IUPAC name:
4-Methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one

Chemical Abstracts Service index name:
4-Methyl-1-phenyl-2-(1-pyrrolidinyl)-1-pentanone

B. Chemical structure

Free base:



Molecular formula: $C_{16}H_{23}NO$
Molecular weight: 245.36 g/mol
Note: Asterisk (*) refers to a chiral centre

C. Stereoisomers

The presence of a chiral centre at the α-carbon of the side chain gives rise to the enantiomeric pair (S)-α-PiHP and (R)-α-PiHP. α-PiHP is most likely to be available as the racemic mixture, although the appearance of individual stereoisomers cannot be excluded.

D. Methods and ease of illicit manufacture

No specific information was found on the routes used to synthesize α-PiHP products circulating on the market; however, the chemical production of synthetic cathinones is well established and straightforward. No currently controlled precursors are required. Although there are several methods, one of the most common is based on so-called α-bromination of a ketone intermediate followed by amination. These types of reactions are easy to perform and lend themselves to both small- and large-scale manufacture. An example of an α-PiHP synthesis has been reported *(3)*. Although α-PiHP was not specifically mentioned, it was also included in a patent application on a range of synthetic cathinones, including pyrovalerone-based (i.e., α-pyrrolidino-type) compounds. The chemical method used was essentially similar *(7)*.

E. Chemical properties

Melting-point:
No information was found on certified reference material; however, the melting-point of seized material identified as α-PiHP has been reported as 76 °C *(8)*.

Boiling-point:
No information was found.

Solubility:
α-PiHP hydrochloride was reported to be soluble in dimethylformamide (3 mg/mL), dimethyl sulfoxide (5 mg/mL), ethanol (3 mg/mL), methanol (1 mg/mL) and phosphate-buffered saline (pH 7.2; 10 mg/mL) *(9)*. A sample of α-PiHP hydrochloride was reported to be soluble in dichloromethane, methanol and water *(2)*.

F. Identification and analysis

Identification of α-PHP, especially when it is available in larger quantities than are usually available for forensic toxicology, is straightforward. Analytical difficulties may arise, for example in the presence of closely

related isomers such as α-PHP, listed in Schedule II of the United Nation Convention on Psychotropic Substances of 1971 *(1)*) or pyrovalerone (1-(4-methylphenyl)-2-(pyrrolidin-1-yl)pentan-1-one) listed in Schedule IV of the United Nations Convention on Psychotropic Substances of 1971 *(1)*). Adequate separation techniques are required to reduce potential misidentification, especially in samples (e.g., biological) containing only trace quantities. α-PiHP is, however, available as a certified reference material, and analytical data have been reported using various separation techniques and spectroscopic, crystallographic and mass spectrometric methods *(8, 10–18)*. Analysis of biological samples requires sensitive methods, e.g., gas or liquid chromatography coupled to (tandem) mass spectrometry (high and low resolution). Some chromatographic, mass spectral and spectroscopic data are available in the public domain *(2, 4, 19, 20)*. The results of presumptive colour tests as part of drug-checking services have also been reported publicly *(21)*. In a non-fatal case of intoxication in which 4′-fluoro-isobutyrylfentanyl and α-PiHP were identified, a false-positive result for amphetamine was noted, which was attributed to the presence of α-PiHP *(22)*.

3. Ease of conversion into controlled substances

No specific information was found on a conversion of α-PiHP to substances under international control, but this is unlikely to be feasible.

4. General pharmacology

A. Routes of administration and dosage

No clinical studies on α-PiHP were identified, and information from Internet discussion forums appears to be limited. Current information indicates, however, that α-PiHP can be administered by oral, intravenous and rectal routes, nasal insufflation and inhalation (vaping). Inhalation from the heating of foil has also been described *(23–26)*.

Some information on doses received after different routes of administration is in the public domain (Table 1). Reports by people believed to have taken α-PiHP suggest a tendency to re-dose, so that the doses taken may exceed those reported in Table 1 *(23–25)*.

Table 1. Reported doses of α-PiHP by different routes of administration

Dose	Oral	Insufflated	Vaporized
Threshold	3–5 mg	1–3 mg	1–2 mg
Light	5–15 mg	3–10 mg	2–10 mg
Common	15–30 mg	10–25 mg	10–20 mg
Strong	30–50 mg	25–40 mg	20–30 mg

Source: reference *5*.

Assessment of such reports is difficult, not least because people who use these substances might be unable to confirm the actual substance or the amount used. Given the difficulties of collecting accurate self-reported data, these reports should be interpreted with caution.

B. Pharmacokinetics

No clinical studies were identified. Some estimates of the duration of effects are in the public domain (Table 2). Reports from some people believed to have consumed α-PiHP suggest that the duration varies among individuals, including shorter durations than those listed in Table 2 *(25)*. Reports from Internet forums in languages other than English indicate that the effects of α-PiHP were of shorter duration than those of α-PVP *(11)*.

Table 2. Reported duration of effects of α-PiHP

	Oral	Insufflated	Vaporized
Onset	30–60 min	1–2 min	1 min
Duration	2–5 h	2–4 h	1–3 h
After-effects	6–12 h	6–12 h	6–12 h
Strong	30–50 mg	25–40 mg	20–30 mg

Source: reference *5*.

No information was found on the metabolism of α-PiHP; however, it is expected to be similar to that of closely related cathinones such as the isomeric α-PHP, in which metabolic transformations include reduction of the keto group, various oxidations and *N*-dealkylation *(27–30)*.

C. Pharmacodynamics

The results of in-vitro assays involving binding to monoamine transporters and inhibition of uptake are summarized in Table 3. These show higher selectivity for the dopamine (DAT) and norepinephrine (NET) transporters than for the serotonin transporter (SERT) *(31)*. The binding

affinities determined for α-PiHP in HEK293 cells expressing human recombinant DAT and NET were 35.7 and 340 nM, respectively, whereas the binding affinity for SERT was > 7500 nM. Cocaine, methamphetamine and methcathinone were tested for comparison. At DAT, the binding affinity of α-PiHP was ~16 times higher than that of cocaine and ~115 and ~132 times higher than those of methamphetamine and methcathinone. Only cocaine showed some affinity below 1000 nM. α-PiHP also showed appreciable binding affinity to NET (K_i = 340; cocaine: K_i = 1600; methamphetamine: K_i = 2470; and methcathinone: K_i = 5800 nM).

Table 3 Binding and effects of α-PiHP on uptake in HEK-hDAT, HEK-hSERT and HEK-hNET cells

HEK-hDAT	α-PiHP	Cocaine	Methamphetamine	Methcathinone
[^{125}I]RTI-55 binding; IC_{50} (nM)	36.5	–	–	–
[^{125}I]RTI-55 binding; K_i (nM)	35.7	560	4100	4700
[^{3}H]DA uptake; IC_{50} (nM)	16.5	202	107	247
HEK-hSERT	**α-PiHP**	**Cocaine**	**Methamphetamine**	**Methcathinone**
[^{125}I]RTI-55 binding; IC_{50} (nM)	> 7 700	–	–	–
[^{125}I]RTI-55 binding; K_i (nM)	> 7 500	900	174 000	268 000
[^{3}H]5-HT uptake; IC_{50} (nM)	> 10 000	303	4 800	33 600
HEK-hNET	**α-PiHP**	**Cocaine**	**Methamphetamine**	**Methcathinone**
[^{125}I]RTI-55 binding; IC_{50} (nM)	341	–	–	–
[^{125}I]RTI-55 binding; K_i (nM)	340	1600	2470	5800
[^{3}H]NE uptake; IC_{50} (nM)	41.4	222	11.0	26.2

DA, dopamine; 5-HT, serotonin; NE, norepinephrine.

Source: modified from reference *31*.

With radiolabelled neurotransmitters, α-PiHP was also found to function as a monoamine transporter blocker, with pronounced selectivity for DAT (IC_{50} = 16.5 nM) and NET (IC_{50} = 41.4 nM) as compared with SERT (IC_{50} >10 000 nM). In comparison with cocaine (IC_{50} = 202 nM), methamphetamine (IC_{50}= 107 nM) and methcathinone (IC_{50} = 247 nM), α-PiHP was the most potent DAT inhibitor under the conditions tested. At NET, α-PiHP was about five times more potent than cocaine but slightly less potent than methamphetamine and methcathinone (Table 3). From a mechanistic perspective, cocaine is a well-established transporter inhibitor, whereas methamphetamine and methcathinone are substrate-type releasers. In rat brain synaptosomes, the positional isomer α-PHP has been established as a monoamine transporter inhibitor, similar to other cathinones, with elongated α-carbon chain length *(32)*. This is likely to extend to α-PiHP, but further studies should be conducted.

In reports from Internet forums in languages other than English, the effects of α-PiHP were reported to be predominantly mood improvement (euphoria) and gentle stimulation. The effects of α-PiHP were considered to be similar to those reported for α-PVP. Adverse effects of this cathinone were reported to include tachycardia, vasoconstriction and paranoia *(11)*.

5. Toxicology

No acute or chronic preclinical toxicology studies with α-PiHP were found.

6. Adverse reactions in humans

Cases of α-PiHP intoxication in humans

The UNODC Early Warning Advisory Portal lists seven cases in Sweden in which α-PiHP was detected in either blood or urine samples. No details on the type of event (e.g., clinical admission or post-mortem) were available. The cases were reported between August and October 2019 and involved five men and two women aged 25–44 years (four cases) and 45–64 years (three cases) *(33)*.

Between 2017 and 2019, one country in the European Union Early Warning System Network reported four deaths to the EMCDDA by event-based reporting, in which exposure to α-PiHP was analytically confirmed in a biological sample. In addition, between 2017 and 2021, four countries reported by aggregated reporting the detection of α-PiHP in biological samples that were linked to serious adverse events, including 20 samples associated with deaths and 4 samples associated with acute poisoning. As more than one biological sample may have been taken during the same event, the actual number of events cannot be ascertained. Serious adverse events reported in aggregated datasets may overlap with the event-based events presented in the previous paragraph *(34)*.

The WHO ECDD Secretariat received information from the US Centers for Disease Control and Prevention's State Unintentional Drug Overdose Reporting System via the US Office of National Drug Control Policy. The data were from death certificates, post-mortem toxicological testing and death scene and witness findings in medical examiner and coroner reports on unintentional drug overdose deaths and those of undetermined intent in 48 participating jurisdictions, providing comprehensive details about deaths due to drug overdose that are not available from other sources. According to the Reporting System, α-PiHP was listed as the cause of death in 18 cases between January 2020 and June 2021. During the same

period, α-PiHP was detected in 13 fatal cases, but no information was available to determine whether the drug contributed to the deaths.

Information was received from the National Institute for Health and Welfare in Helsinki (Finland) that α-PiHP was detected in seven post-mortem cases between May 2021 and June 2022 (Table 4). The six men and one woman were aged 26–50 years (median, 34 years). For comparison during the same period, α-PHP was detected in 16 post-mortem cases and α-PVP in eight cases. Of the approximately 6500 post-mortem cases received per year, about 500 involved controlled substances or abuse of prescription drugs (Dr Pirkko Kriikku, National Institute for Health and Welfare, personal communication).

Table 4. Detection of α-PiHP post mortem by the National Institute for Health and Welfare in Helsinki (Finland)

Matrix	Concentration (mg/L)	Role of α-PiHP in the cause of death	Manner of death
Femoral blood	0.13	Fatal poisoning by methadone, alcohol, α-PiHP and propranolol	Undetermined
Femoral blood Urine	< 0.02 0.04	Motorcycle accident Use of specified drugs (including α-PiHP) as contributing cause of death	Accident
Urine	0.04	Fatal poisoning by buprenorphine, methamphetamine, amphetamine, α-PiHP and gabapentin	Accident
Femoral blood Urine	0.08 0.5	Use of buprenorphine, amphetamine, α-PiHP and cannabis	Disease*
Urine		Fatal poisoning by α-PiHP, methadone, THC, amitriptyline, levomepromazine and olanzapine	Accident
Femoral blood Urine	0.04 0.03	Information not yet available	Information not yet available
Urine	0.03	Information not yet available	Information not yet available

* Possible mislabelling of poisoning as disease.
Source: Dr Pirkko Kriikku.

A series of trend reports *(35)* is published by the Center for Forensic Science Research and Education (Pennsylvania, USA) that summarizes drug detections predominantly in biological samples during toxicological case work. Table 5 summarizes detections published quarterly. No detailed information was available about the nature of the toxicological cases, and differentiation between α-PiHP and its isomer α-PHP was not reported, precluding the exact number of α-PiHP detections from being determined.

Table 5. Summary of positivity rates (trend reports) for new psychoactive stimulants, hallucinogens and some new psychoactive dissociatives submitted for analysis to the Center for Forensic Science Research and Education

Year	Quarter	α-PiHP /α-PHP [a]		Total number [b]
		No.	%	
2018	Q1	2	0	616
2018	Q2	8	1	1460
2018	Q3	1	0	739
2018	Q4	1	0	473
2019	Q1	0	0	148
2019	Q2	2	2	107
2019	Q3	0	0	264
2019	Q4	1	0	321
2020 [c]	Q1	4	1	384
2020	Q2	4	1	775
2020	Q3	5	1	626
2020	Q4	1	0	714
2021	Q1	0	0	454
2021	Q2	3	1	584
2021	Q3	1	0	851
2021	Q4	3	0	621
2022	Q1	4	1	710
2022	Q2	3	1	342

[a] The specific isomer was not differentiated; samples were of biological origin.
[b] The total number of substances included other substances, such as fentanyl, methamphetamine, cocaine and 3,4-methylenedioxymethamphetamine.
[c] In Q1 2020, one additional detection of α-PiHP/α-PHP was reported in a seized sample *(36)*.

Source: Dr Alex J. Krotulski (CFSRE, Fredric Rieders Family Foundation, Willow Grove, Pennsylvania, USA).

Scientific literature: non-fatal cases

In Poland, an unconscious 29-year-old man was found with symmetrical, highly constricted pupils unresponsive to light. The patient showed abnormal kidney function and was treated with naloxone (0.2 mg every hour for 15 h; total dose, 3 mg), omeprazole (40 mg, per os), acetaminophen (1 g, 100 mL, intravenous injection) and mannitol (15%, 100 mL, intravenous injection). Fluid replacement and oxygen therapy were administered. The patient was discharged after 4 days in hospital. The authors attributed an increased creatine phosphokinase level to rhabdomyolysis resulting from muscle tremors induced by α-PiHP intoxication. Analysis of peripheral blood revealed the synthetic opioid

4′-fluoro-isobutyrylfentanyl (87.7 ng/mL) and α-PiHP (5.0 ng/mL). In urine, concentrations of 2291.0 ng/mL and 722.2 ng/mL were detected. The authors suggested that the patient might have smoked a mixture of these two drugs *(22)*.

Scientific literature: fatal cases

In the case reported above *(22)*, the authors also described the case of a young woman who was found dead. 4′-Fluoro-isobutyrylfentanyl was detected in various biological samples: 119.0 ng/mL in blood, 289.0 ng/mL in urine, 101.0 ng/mL in vitreous humour, 112.0 ng/g in brain tissue and 1540.0 ng/g in liver tissue. α-PiHP concentrations were included in the analysis and found to be as follows: 6.1 ng/mL in blood, 31.7 ng/mL in urine, 2.5 ng/mL in vitreous humour, 7.8 ng/g in brain tissue and 246.0 ng/mL in gastric contents. In addition, 4-chloromethcathinone, O-desmethyltramadol, cis-tramadol and N-desmethyltramadol were detected. No further information was provided *(22)*. In a previous publication *(37)*, however, more details were presented about the deceased woman. She was 22 years old, and the death occurred in September 2018. She was believed to have taken recreational drugs in the days preceding her death and analgesics after an accident and lower limb injuries. A white powder (57.8 mg) was found at the scene, and subsequent analysis revealed 4′-fluoro-isobutyrylfentanyl (40.25 mg) and α-PiHP (1.84 mg). The autopsy revealed cerebral tissue oedema, pulmonary emphysema and acute mucositis *(37)*.

Another case in Poland involved an 18-year-old man who was found dead in an apartment *(11)*. He had last been seen alive the previous evening, lying in bed. At night, he was heard to be wheezing. He had a history of regular substance use, including NPS. He was reported to have become agitated after use, hallucinating and talking to himself. When he calmed down, he lay down and slept for 24 h. He had also drunk alcohol (beer). Autopsy revealed no evident lesions considered to be related to his death, although small changes to the heart and blood vessels were found, comprising a little generalized cardiac hypertrophy and slight atherosclerosis of the coronary arteries and aorta. Visible coalworker's pneumoconiosis was found in the lungs, and focal cardiac adiposis was found on microscopic examination. In addition, macro- and microscopic evidence of acute circulatory and respiratory failure were disclosed, with pulmonary and cerebral oedema and congestion of internal organs. The autopsy did not determine the primary cause of death, and it was concluded that the man had died due to acute circulatory and respiratory

failure. Toxicological analysis showed α-PiHP in various tissue samples (Table 6) but also other substances, such as 4-chloromethcathinone (urine: 1477 ng/mL; bile: 41 ng/mL), *N*-ethylhexedrone (urine: 1352 ng/mL; bile 34 ng/mL; lung – bloody fluid: 3 ng/mL; brain – tissue homogenate: 5 ng/g), benzoylecgonine (urine: 30 ng/mL; hair: 0.67 ng/mg) and 3,4-methylenedioxymethamphetamine (hair: 0.34 ng/mg). No other substances (including alcohol) were detected. The authors considered that the other substances had not contributed to death and attributed the fatality to α-PiHP alone.

Table 6. α-PiHP concentrations in tissues of a fatal case in Poland

Sample material	α-PiHP concentration
Blood	69 ng/mL
Urine	2072 ng/mL
Bile	341 ng/mL
Liver (tissue homogenate)	7 ng/g
Liver (bloody fluid)	33 ng/mL
Kidney (tissue homogenate)	78 ng/g
Kidney (bloody fluid)	194 ng/mL
Stomach (tissue homogenate)	478 ng/g
Intestine (tissue homogenate)	115 ng/g
Intestine (bloody fluid)	185 ng/mL
Lung (tissue homogenate)	213 ng/g
Lung (bloody fluid)	448 ng/mL
Brain (tissue homogenate)	230 ng/g

Source: reference *11*.

Another fatal case was reported, in which the cause of death was trauma from a fall. The contribution of the drugs present could not be determined. A bag with white powder related to the case was confirmed to contain the synthetic cannabinoid methyl 3,3-dimethyl-2-{[1-(pent-4-en-1-yl)-1*H*-indazole-3-carbonyl]amino}butanoate. Femoral blood was also positive for flualprazolam and α-PiHP. No more information on this cathinone, including concentrations, was reported *(38)*.

In a report of a series of post-mortem cases involving the synthetic opioid *N*-pyrrolidino etonitazene, detection of either α-PiHP or α-PHP (isomer not differentiated) was also noted, with etizolam, α-hydroxyetizolam,

flubromazepam, desalkylflurazepam and 2-methyl AP-237. No other information was reported. The date of collection of a femoral blood sample, however, was reported to have been 25 May 2021 *(39)*, and it is possible that this case was also captured in the Center for Forensic Science Research and Education trend reports described above.

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found.

8. Abuse potential

A. Studies in experimental animals

Information received by the WHO ECDD Secretariat (unpublished, under embargo) indicates that α-PiHP induced time- and dose-dependent stimulation of locomotor activity in male Swiss-Webster mice. The maximal stimulant effect was comparable to those of cocaine and methamphetamine during the 30-min period in which maximal stimulant effects occurred (0–30 min after injection) *(40)*.

Drug discrimination studies:
Additional data obtained from drug discrimination studies and received by the WHO ECDD Secretariat (unpublished, under embargo) confirmed that α-PiHP fully substituted for the discriminative stimulus effect produced by cocaine (1 mg/kg) and (*S*)-methamphetamine (1 mg/kg) *(41, 42)*.

B. Studies in humans

No information was found.

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

No information was found.

10. Listing on the WHO Model List of Essential Medicines

α-PiHP is not listed on the 22nd WHO Essential Medicines List or on the 8th WHO Essential Medicines List for Children.

11. Marketing authorizations (as a medicinal product)

No information was found.

12. Industrial use

No information was found on recorded industrial use.

13. Non-medical use, abuse and dependence

No epidemiological evidence on use of α-PiHP was found. α-PiHP is available in its own right and is advertised for sale by some Internet retailers. Currently available information (sections 4 and 8) suggests that α-PiHP is likely to show abuse liability and that it displays psychostimulant properties comparable to those of some other synthetic cathinones under international control, such as α-PHP *(43)* and α-PVP *(44)*.

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

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

No epidemiological data on harm associated with α-PiHP was found. The information on post-mortem cases (section 6) suggests poly-substance use in which α-PiHP was detected. No information was found on the involvement of α-PiHP in monitoring of driving under the influence of drugs.

Information from drug testing services in the USA suggests that α-PiHP was detected in products acquired or sold as other substances, including various cathinones (including α-PVP), 3,4-methylenedioxymethamphetamine and 1-(1-benzofuran-6-yl) propan-2-amine *(20)*. According to the EMCDDA *(6)*, two green tablets seized in one Member State in 2017 were found to contain α-PiHP. This suggests that people who use recreational drugs might be exposed to α-PiHP unintentionally, either alone or in combination with other substances that might pose additional risks (e.g., potential exacerbation of a psychostimulant toxidrome).

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

15. Licit production, consumption and international trade

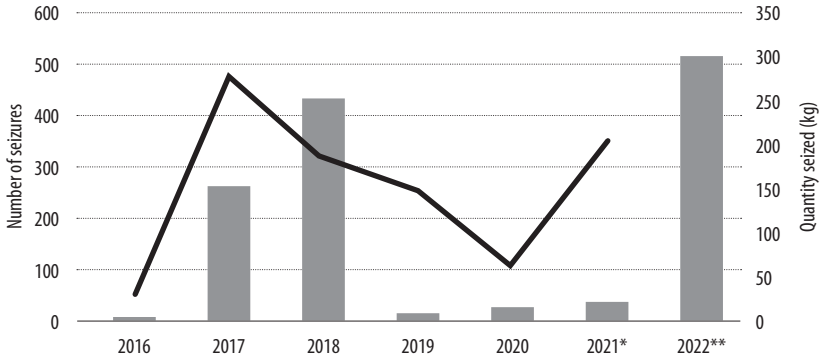
α-PiHP is used as reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic use. Some Internet retailers advertise it for sale as a "research chemical".

16. Illicit manufacture and traffic and related information

According to the EMCDDA *(34)*, α-PiHP has been available on the drug market in Europe since at least 2016. As of 15 June 2022, a total of 18 European Union Member States and Norway had reported physical detection of α-PiHP to the EMCDDA. At the time of writing, the total number of seizures was 1565, with a total quantity of 750.5 kg (all physical forms). The total quantity of powder seized was 748.4 kg. Since it was formally notified, the EMCDDA has received reports of 1565 seizures of α-PiHP. α-PiHP was found mainly as a powder (approximately 88% of all seizures reported), with herbal material occasionally reported (12% of cases).

Overall, approximately 750 kg of α-PiHP have been seized, of which 748 kg were in powder form and 2 kg in herbal material. Most powder was seized in 2018 (250 kg in approximately 275 seizures) and in 2022 (300 kg in a single seizure that originated from India). It should be noted that data for 2022 are incomplete and reflect only events-based data reported to the EMCDDA from the European Database on New Drugs between January and May 2022 (Fig. 1).

Fig. 1. Trends in the number of seizures of α-PiHP in all physical forms and the quantity of powder seized reported to the European Union Early Warning System on new psychoactive substances, European Union and Norway, 2016–2022



Note: *Data on seizures for 2021 are preliminary and may be subject to change. **Data on seizures for 2022 are incomplete and reflect only events-based data reported to the EMCDDA via the European Database on New Drugs between January and May 2022 *(34)*.

Globally, the number of countries that reported α-PiHP detections to the UNODC Early Warning Advisory on new psychoactive substances since its first detection in 2016 were 3 in 2016, 11 in 2017, 10 in 2018, 19 in 2019, 17 in 2020, 8 in 2021 and 2 in 2022. Multiple entries were recorded from the same country for the same year *(45)*.

The US National Forensic Laboratory Information System (NFLIS), which collects cases of drug detection submitted by state and local laboratories in the USA, has registered detections of α-PiHP (Table 7). According to the US Office of National Drug Control Policy (in a communication to the WHO ECDD Secretariat), NFLIS first identified α-PiHP in the USA in 2017. NFLIS midyear and annual reports began to list α-PiHP in 2019, in which it is listed (with other cathinones) in the substance group classified as "phenethylamines".

Table 7. Numbers of reports received and published by NFLIS on detections of α-PiHP in law enforcement operations

Year [a]	α-PiHP	Total [b]	Reference no.
2017 (AR)	Not listed	382 297	*45*
2018(MY)	Not listed	198 587	*46*
2018 (AR)	Not listed	424 493	*47*
2019 (MY)	289	227 566	*48*
2019 (AR)	481	452 075	*49*
2020 (MY)	245	193 917	*50*
2020 (AR)	322	413 310	*51*
2021 (MY)	158	225 801	*52*

[a] MY, mid-year report (January–June); AR, annual report (January–December).
[b] Total number of reports in the substance group classified as "phenethylamines".

According to the US Office of National Drug Control Policy, 316 reports on α-PiHP were identified in the NFLIS Drug information system in 2021 (queried 28 April 2022). The total reported weight of 222 of these was 2.179 kg. It was noted that reports were still pending for 2021 and 2022. The Office of National Drug Control Policy also noted that, at the time of query, the total number of α-PiHP NFLIS reports was 1054.

The NFLIS "snapshot reports" are summarized in Table 8.

Table 8. NFLIS reports on the five most frequent drugs in the category "selected synthetic cathinones"

Period	α-PiHP (%)	Total	Reference no.
January–March 2020	86 (4.64)	1854	*53*
April–June 2020	83 (2.94)	2820	*54*
October–December 2020	32 (0.97)	3309	*55*
January–March 2021	Not listed	2809	*56*
July–September 2021	48 (1.51)	3186	*57*
October–December 2021	61 (2.72)	2244	*58*
January–March 2022	186 (4.83)	3852	*59*

Emerging Trends Reports published by the US Drug Enforcement Administration also reported identification of α-PiHP among other substances. The data for the report were compiled from archived information on seizures and analysis of drug evidence by the Administration's laboratory system (Table 9).

Table 9. Annual emerging threat reports on α-PiHP published by the US Drug Enforcement Administration

Year	α-PiHP (No.)	Total no. of cathinones	Reference no.
2018	11	327	*60*
2019	27	184	*61*
2020	6	200	*62*

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

17. Current international controls and their impact

α-PiHP is not currently controlled under the 1961, 1971 or 1988 United Nations conventions.

18. Current and past national controls

α-PiHP is controlled in some United Nations Member States.

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

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

None.

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3.1.9 3-MMC

1. Substance identification

A. International nonproprietary name

No information was found.

B. Chemical Abstracts Service registry number

1246911-86-3 (base)

2291027-30-8 (*R*)-enantiomer (base)

2107851-15-8 (*S*)-enantiomer (base)

1246816-62-5 (HCl)

1329834-37-8 (*N*-CD_3) (HCl)

1330267-42-9 (*N*-CD_3) (base)

2416463-56-2 (2,2,2-trifluoroacetate (1:1))

C. Other chemical names

1-(3-Methylphenyl)-2-(methylamino)propane-1-one

1-(3-Methylphenyl)-2-(methylamino)-1-propanone

2-(Methylamino)-1-(*m*-tolyl)propan-1-one

3-Methylmethcathinone

3-Methyl-methcathinone

3-Methyl-*N*-methylcathinone

Metaphedrone

3-MMC

3-MeMMC

3-Mephedrone

3-Methylephedrone

Mepedrone

3-Me-M-CAT

3-Methyl MC

D. Trade names

3-MMC

E. Street names

Some of the chemical names listed above are also used as street names, and "3-MMC" and "metaphedrone" appear to be used commonly. The term "sladoled" (ice cream) has been used in Slovenia *(1)*. 3-MMC has also been reported in a product called "MCH", and products labelled "Product Imitation: Red Dirt" and "Ruby Sand Additive, 0.5 Gram – Product Imitation"' were reported to contain 3,4-dimethylmethcathinone and 3-MMC, respectively *(2)*. 3-MMC has been traded as "Synthacaïne" or "Synthacaine", "Charly Sheen" and "Crystal"' *(3)*. It should be noted, however, that the compositions of branded products are likely to change over time. Other names include "Miauw 2.0 "and "The 3".

F. Physical appearance

In its pure form, 3-MMC hydrochloride is expected to be odourless and white, like many other ring-substituted synthetic cathinones. Synthesized 3-MMC hydrochloride has been described as a white powder *(4)*, a white solid *(5)* and a grey solid *(6)*. A sample obtained from a material reference collection was described as a white powder *(7)* and a crystalline solid *(8)*. According to the EMCDDA *(3)*, the majority of seized and collected 3-MMC samples were in powder form. Powders were reported to range from "white rocks" to "white/off-white powders" (mostly pure); in some cases, 3-MMC was yellow and orange (usually with other substances).

G. WHO review history

3-MMC was critically reviewed at the 38th meeting of the WHO ECDD, in November 2016 *(9)*. It was decided to request a further critical review when more information became available and to consider it at a subsequent meeting of the Expert Committee *(10)*.

2. Chemistry

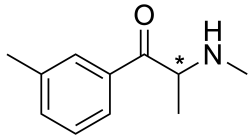
A. Chemical Name

IUPAC name:
2-(Methylamino)-1-(3-methylphenyl)propan-1-one

Chemical Abstracts index name:
2-(Methylamino)-1-(3-methylphenyl)-1-propanone

B. Chemical structure

Free base:



Molecular formula: $C_{11}H_{15}NO$
Molecular weight: 177.25 g/mol
Note: Asterisk (*) refers to a chiral centre

C. Stereoisomers

The presence of a chiral centre at the α-carbon of the side chain gives rise to the enantiomeric pair (*S*)-3-MMC and (*R*)-3-MMC. 3-MMC is most likely to be available as the racemic mixture, although the appearance of individual stereoisomers cannot be excluded.

D. Methods and ease of illicit manufacture

No information was found on the routes of synthesis for 3-MMC products circulating on the market; however, the chemistry of production of ring-substituted synthetic cathinones is well established and straightforward. No precursors that are currently controlled are required. Although several methods are available, one of the most common is based on so-called α-bromination of a ketone intermediate followed by amination. These types of reactions are easy to perform and lend themselves to both small and large-scale manufacture *(4, 11, 12)*. Other synthetic routes could be applied to 3-MMC *(3)*.

According to the EMCDDA *(13)*, at least 2100 kg of α-bromoketone intermediates were seized in Europe, most being 2-bromo-4-chloropropiophenone used in the synthesis of 4-chlorormethcathinone, and 2-bromo-4-methylpropiophenone, used in the synthesis of 4-MMC (mephedrone). Given the practicality of this synthesis procedure, it is likely to have been adopted for large-scale manufacture of 3-MMC.

Of particular note is that the EMCDDA reported seizure of 350 kg *N*-acetyl-3-MMC in one European Union Member State *(3)*. In the context of new psychoactive substances (NPS), such modifications may be referred to as "masked derivatives", "masked precursors" or "designer precursors", which indicate that they can be converted back into 3-MMC in one simple chemical step. These types of protecting group are widely used in synthesis procedures. Another alternative was used in the amination step, whereby *N*-benzyl-*N*-methylamine was reacted with the brominated intermediate, and the resulting intermediate was converted to 3-MMC with 1-chloroethyl chloroformate *(5, 6)*. The *N*-benzyl-3-MMC intermediate could serve as another potential "masked precursor" for 3-MMC, although other types of protection groups can also be used.

E. Chemical properties

Melting-point:

188–190 °C (HCl) *(4)*

206.5 °C (HCl) *(7)*

193.2 °C (HCl) *(14)*

190–192 °C (HCl) *(5)*

193–195 °C (HCl) *(6)*

Boiling-point:

No information was found.

Solubility:

3-MMC hydrochloride was reported to be soluble in phosphate-buffered saline (pH 7.2; ~10 mg/mL), ethanol (~5 mg/mL), dimethyl sulfoxide (~2.5 mg/mL) and dimethylformamide (~1 mg/mL) *(15)*. The hydrochloride salt is also considered to be water-soluble and can be dissolved for oral use and injection *(3)*. The water solubility of the hydrochloride salt was reported to be 2.0 mg/mL *(14)*.

G. Identification and analysis

Identification is straightforward, especially when larger quantities of the substance are available than are usually the case in forensic toxicology. Analytical difficulties may arise, for example, in differentiation of the

2- and 4-methylphenyl regioisomers 2-MMC and 4-MMC (mephedrone, listed in Schedule II, United Nations Convention on Psychotropic Substances, 1971 *(16)*). Adequate separation techniques are required to reduce potential misidentification, especially in samples (e.g., biological) containing only small quantities. 3-MMC and its isomers are, however, available as certified reference materials, and the results of various analytical methods have been described extensively in the scientific literature (Annex 2). Analysis of biological samples requires sensitive methods, e.g., gas or liquid chromatography coupled to (tandem) mass spectrometry approaches (high and low resolution). Some analytical data, including chromatographic, mass spectral and spectroscopic data, are available in the public domain (e.g., *7, 17, 18*).

3. Ease of conversion into controlled substances

No specific information was found on a conversion of 3-MMC to substances under international control, but this is unlikely to be feasible.

4. General pharmacology

A. Routes of administration and dosage

No clinical studies on 3-MMC were found; however, the available information suggests that 3-MMC is typically administered by nasal insufflation (snorting), orally and by intravenous injection. Other routes have been reported occasionally, such as rectal administration and inhalation or smoking *(1, 3, 19, 20, 21)* (sections 6 and 14). Some people who used 3-MMC expressed a preference for nasal insufflation over oral administration *(1)*.

In a study of 3-MMC intoxications in the Netherlands, two distinct patient groups were identified: younger patients who used 3-MMC by ingestion or snorting and older patients who used 3-MMC by injection. The authors found that younger patients were more likely to use 3-MMC in a social, nonsexual context, whereas older patients ("mostly middle-aged men") were more likely to prefer use by injection in the context of sexual activity ("slamsex") *(21)* (see also section 14).

Some information on the doses used by different routes of administration is in the public domain. For oral administration, a "light" dose was suggested to be 25–75 mg; "common", 75–150 mg; and "strong", 150–≥ 300 mg *(22)*, but higher doses have also been reported *(23)*. In cases involving acute intoxication, doses in the range ~0.5–2 g were

reported, and some people reported taking several doses in succession on consecutive days *(19)*.

In a survey of people who used 3-MMC, 26.2% took > 1.5 g of 3-MMC during a single evening (n = 168), and over half of the respondents consumed > 0.5 g of 3-MMC during a single evening *(1)*. Binge use of 3-MMC was identified in a follow-up investigation of interviews with NPS users: when 3-MMC was used for several days, the amount consumed ultimately exceeded the amount originally planned *(24)*. In a retrospective analysis of intoxications involving 3-MMC, the median self-reported dose per session was estimated to be 1000 mg (range, 0.3–6000 mg) *(21)*.

"Typical" dosages depend on factors such as the route of administration, individual tolerance, use of other drugs and the desired effects. Assessment of such reports is difficult, as people who use these substances might not be able to confirm the actual substance or the amount used. Given the difficulty of collecting accurate self-reported data, these reports should be interpreted with caution.

In a patent application for 3-MMC-assisted psychotherapy, four examples were included in which a range of doses was used, depending on the therapeutic context: 1: three sessions with 200 mg given orally (treatment of post-traumatic stress disorder); 2: six sessions with 150 mg (plus 100 mg) over 6 months (couples therapy); 3: three sessions with 300 mg for relationship distress; and 4: twice weekly administration of 200–400 mg 3-MMC on 2 consecutive days for 8 weeks (post-traumatic stress disorder and generalized anxiety disorder) *(25)*.

In another patent application, in which 3-MMC was proposed for treatment of menstrual cycle-induced disorders and symptoms, a number of trials were conducted which typically involved oral administration of 3-MMC at doses of 12.5–50 mg per trial *(26)*.

B. Pharmacokinetics

No clinical studies were identified.

A study was reported in 3-month-old male pigs given a single intravenous dose of 0.33 mg/kg followed by oral administration of 3 mg/kg *(14)*. A short half-life was observed (0.8 h) after both routes. The apparent volume of distribution after injection was 8 L/kg (28–34 kg body weight), while bioavailability after oral administration was only 7%, which may have been

due to an extensive first-pass effect. The maximal concentration after oral administration was detected after 0.08 h, suggesting rapid absorption; rapid elimination was also observed.

The duration of effects depends on factors such as the route and frequency of administration, individual tolerance, use of other drugs and the desired effects. The profile after oral administration has been reported by people who have used the drug as follows: total duration: 4–6 h; onset: 10–30 min; "come up": 30–60 min; peak: 2–3 h; "offset": 1–1.5 h; and "afterglow": 2–4 h. The profile after nasal insufflation was: total duration: 2.5–4.5 h; onset: 5–10 min; "come up": 10–20 min; peak: 1–1.5 h; "offset": 1–2 h; and "afterglow": 1–1.5 h *(27)*. These profiles agree to some extent with other reports (e.g., *23, 28–30*). The effects of 3-MMC were perceived as short-lived by some users *(21)*.

No studies were found of the metabolism of 3-MMC, although some metabolites were identified in biological samples. In a fatal case, 3-MMC was detected with nor-3-MMC, dihydro-3-MMC, nor-dihydro-3-MMC, hydroxytolyl-3-MMC, 3-carboxy-3-MMC and 3-carboxy-dihydro-3-MMC (Rojek et al. cited in *31*). Detections of 3-MMC, dihydro-3-MMC and nor-dihydro-3-MMC were described in pubic hair samples *(32)*, and detection of nor-3-MMC and hydroxylated 3-MMC was reported in femoral blood in an investigation of a fatal case *(20)*, suggesting that the metabolism of 3-MMC may be similar to that of 4-MMC (mephedrone) (e.g., *33*). Nor-3-MMC and dihydro-3-MMC metabolites were tentatively detected in cases of non-fatal intoxication with 3-MMC *(34)*.

C. Pharmacodynamics

In-vitro assays of monoamine uptake mediated by human dopamine (hDAT), norepinephrine (hNET) and serotonin transporters (hSERT), stably expressed in HEK293 cells, showed that 3-MMC inhibited the uptake of radiolabelled neurotransmitters (Table 1). The DAT:SERT ratios calculated from these results were 3.7, 10.4, 53.6 and 31.5, which suggests selectivity for DAT over SERT. It has been suggested that substances with high DAT:SERT ratios have higher abuse liability than those with low ratios *(35)*. Further in-vitro studies confirmed that 3-MMC has some affinity to monoamine transporters and receptors (Table 2). 3-MMC did not activate serotonin subtype receptors at a meaningful concentration, and activation of the mouse trace amine-associated receptor 1 was negligible *(36)* (Table 2).

Table 1. Mean IC_{50} values for inhibition of monoamines at human dopamine (hDAT), norepinephrine (hNET) and serotonin transporters (hSERT), stably expressed in HEK293 cells

hDAT IC_{50} [μM]	hNET IC_{50} [μM]	hSERT IC_{50} [μM]	Reference no.
2.6	0.27	9.5	*37*
0.43	0.08	4.5	*38*
2.5	5.2	134	*39*
4.1 [a]	3.1 [a]	129 [a]	*39*

[a] 3-MMC sample obtained from an Internet retailer.

Table 2. Monoamine transporter and receptor binding affinities

Monoamine transporter	K_i (μM)[a] *(37)*	EC_{50} (μM) *(37)*	K_i (μM)[b] *(38)*
NET	5.6	–	2.85
DAT	3.2	–	6.33
SERT	> 22	–	7.9
D_2	> 12	–	–
α_{1A}	7.9	–	–
α_{1A}	1.1	–	–
5-HT_{1A}	4.8	–	–
5-HT_{2A}	3.4	> 20	–
5-HT_{2B}	–	>	20
5-HT_{2C}	3.6	–	–
$TAAR1_{human}$ [c]	–	>	30
$TAAR1_{rat}$ [c]	5.7	>	10
$TAAR1_{mouse}$ [c]	11	3.8 (E_{max} = 25%)[d]	–

[a] Radioligands used: *N*-methyl-[^{3}H]-nisoxetine and indatraline (NET), [^{3}H]citalopram and indatraline (SERT), [^{3}H]WIN35,428 and indatraline (DAT), [^{3}H]8- hydroxy-2-(di-n-propylamine)tetralin and indatraline (5-HT_{1A}R), [^{3}H]ketanserin and spiperone (5-HT_{2A}R), [^{3}H]mesulgerine and mianserin (5-HT_{2C}R), [^{3}H]prazosin and risperidone (α_1R), [^{3}H]rauwolscine and phentolamine (α_2R), [^{3}H] spiperone and spiperone (D_2R) and [^{3}H]RO5166017 and RO5166017 (TAAR1R)

[b] Radioligand used: [^{125}I]RTI-55

[c] Simmler et al. *(36)*

[d] Reference substances for comparisons of affinity values and functional potency and efficacy: phenethylamine, p-tyramine and tryptamine.

3-MMC was also shown to act as substrate-type releaser, inducing transporter-mediated release of monoamines. In rat brain synaptosomal preparations, the EC_{50} values of DAT- and SERT-mediated release were 70.6 and 292 nM (DAT:SERT = 4.1) *(5)* (NET: 94% induced by 10 μM) and 28 and 268 nM (DAT:SERT = 9.6). The EC_{50} value for NET-mediated release was 27 nM *(6)*. In comparison, the DAT:SERT ratio for 4-MMC

(mephedrone) under the same conditions was 2.4, indicating that 3-MMC was more potent at DAT and less potent at SERT than 4-MMC *(6)*. In HEK293 cells that stably express human DAT, NET and SERT, monoamine release was induced by one high dose of 3-MMC (100 μM); release was observed for all three transporters (DAT: ~160% relative to mazindol; SERT: ~155% relative to citalopram; NET: ~155% relative to nisoxetine) *(37)*.

The results of an in-vitro assay of neuronal activity have been reported *(39)*. Exposure to 3-MMC and a number of other cathinones led to changes in spontaneous neuronal activity in rat primary cortical cultures grown on microelectrode arrays. The test drugs inhibited the mean spike rate, mean burst rate and mean network burst rate after acute exposure. The IC_{50} values obtained for 3-MMC after acute (30 min), prolonged (4.5 h) and recovery (after washout of the exposure 24 h after the start of the 5-h exposure) were 65, 87 and 710 μM (mean spike rate); 79, 109 and > 1000 μM (mean burst rate) and 67, 116 and >1000 μM (mean network burst rate). 4-MMC was less potent. The extent to which such observations indicate neurotoxicity in humans remains to be determined *(39)*. Increased acute inhibition of neuronal activity was also reported at higher temperatures *(40)*.

Some people who use 3-MMC might find its effects less intense than those of 4-MMC (mephedrone) (e.g., *1, 3*), but most of the information currently available suggests that 3-MMC has a typical psychostimulant profile.

In a study of the impact of 3-MMC on weight gain in pigs (one intravenous and five consecutive oral administrations), significant reductions in weight gain and food intake were observed, which confirmed its appetite-suppressant effect. Triglyceride levels were also reduced *(14)*.

Repeated intraperitoneal injections of 3-MMC (3 mg/kg) for 7 days to adult male Sprague-Dawley rats weighing 280–300 g increased the number of c-Fos-labelled neurons in the nucleus accumbens, the ventral tegmental area and the anterior cingulate cortex, which indicates increased expression of c-Fos, comparable to that of methamphetamine at 1 mg/kg intraperitoneally *(41)*. Electrophysiology experiments were conducted in which whole-cell patch-clamp recordings were made from nucleus accumbens slices 24 h after the last exposure to record spontaneous excitatory and inhibitory postsynaptic currents. Both methamphetamine and 3-MMC decreased the amplitude of inhibitory postsynaptic currents,

while the frequency remained unchanged. Neither drug changed the frequency or amplitude of spontaneous excitatory postsynaptic currents, suggesting that chronic exposure to both test drugs inhibited only inhibitory neurotransmission *(41)*.

5. Toxicology

Administration of 3-MMC (intravenously at 0.3 mg/kg and a single daily oral dose of 3 mg/kg to six healthy pigs (Landrace; 28–34 kg, 3 months old) caused no abnormal alterations to clinical chemistry and haematological parameters. Histopathological examination of two treated and two untreated animals showed mild diffuse hepatocellular vacuolation. In two treated animals, the authors observed mild multifocal collapse of alveolar walls and mild multifocal mononuclear infiltration of the alveolar and interlobular septa (interstitium). Mild hyperplasia of bronchiolar-associated tissue was observed in one control pig. No abnormal histopathological changes were observed in any other tissue sample investigated *(14)*.

3-MMC did not induce gene mutations in a *Salmonella* microsomal assay, although it caused single and double-strand breaks of DNA in a human-derived buccal cell line (TR146) when using a single-cell gel electrophoresis assay. Significant induction of micronuclei was noted as a consequence of structural and chromosomal aberrations at 100 and 150 μM. No oxidative damage to DNA was observed *(42)*.

Isolated primary Wistar rat hepatocytes were exposed to 3-MMC for 24 h at 37 °C (31 nM–10 mM) to study various toxicological outcomes, and cytochrome P450 inhibition was studied in CYP2E1, CYP2D6 and CYP3A4 and general CYP inhibition at 1 mM *(43)*. Cell viability was assessed in three assays (leakage of lactic dehydrogenase, neutral red uptake and tetrazolium dye (MTT) reduction) with potencies (EC_{50}) of 3.13, 1.36 and 1.68 mM. The authors stated that when CYP2D6 was inhibited (MTT test), significantly higher 3-MMC concentrations were necessary to induce similar levels of cell death (EC_{50} = 2.08 mM); when cells were pre-treated with metyrapone (CYP2E1 inhibitor), the EC_{50} decreased to 1.40 mM at 3-MMC concentrations up to ~1.20 mM, indicating less metabolic CYP2E1 inhibition at low concentrations. Inhibition of CYP2E1 increased cell death at higher 3-MMC concentrations, whereas inhibition of CYP3A4 did not influence 3-MMC toxicity. General inhibition of CYP450 increased cell death only from ~1.03 mM 3-MMC. Production of oxygen and nitrogen reactive species

increased significantly at concentrations of 10, 100 and 500 μM but not at 1 μM. Mitochondrial membrane potential was not affected by 3-MMC, although cellular ATP levels decreased significantly at concentrations ≥ 100 μM. Pro-apoptotic caspase-3, -8 and -9 activities increased significantly at 10 μM. Evaluation of nuclear morphology suggested induction of apoptosis at 1 μM, the highest late apoptotic levels occurring at 10 μM and 100 μM. At the highest concentrations, necrosis was found to predominate at 500 μM. 3-MMC was also reported to increase acidic vesicular organelles, compatible with autophagy, particularly at 100 μM.

Studies of cytotoxicity in hSERT-, hDAT- and hNET-transfected HEK 293 cells (ToxiLight bioassay kit) after drug treatment for 1 h at room temperature showed no effects on adenylate kinase release as a result of cell membrane integrity loss *(37)*. Tests of the viability of HEK 293 cells and primary rat cortical cultures in the neutral red assay with a 4.5-h exposure to the drug at 1–1000 μM (37 °C) showed no signs of cytotoxicity at concentrations > 1000 μM *(39)*. In a follow-up study to mimic hyperthermic conditions (41 °C), no reduced cell viability was observed in rat cortical cells after prolonged exposure (4.5 h) and washout (recovery; 19 h after exposure, i.e., 24 h after the start of exposure) at concentrations of 1–1000 μM *(40)*.

C2C12 myoblasts were exposed to 3-MMC for 1 or 24 h in various cytotoxicity assays. Incubation with 3-MMC affected cell membrane integrity (24 h exposure, IC_{50} > 2 mM) and ATP content (IC_{50} = 1.08 mM) but not mitochondrial oxygen consumption. Mitochondrial superoxide production increased significantly at 500, 1000 and 2000 μM. Overall, although 3-MMC was found to deplete the cellular ATP pool and impair cell membrane integrity in C2C12 myoblasts, the concentrations reached were considered greater than those that would be expected after ingestion of typical doses *(44)*.

6. Adverse reactions in humans

Cases of 3-MMC intoxication in humans (fatal and non-fatal)

The UNODC Early Warning Advisory Tox-Portal lists 27 cases in which 3-MMC was detected in blood and/or urine samples. Twenty-six cases were submitted from France and one from the United Kingdom. Nineteen cases were in people aged 25–44, four in people aged 45–64 and three in people aged 15–24. Twenty-five cases were in males and two in females. The cases in France occurred between June 2016 and May 2022 (20 since 2020). The case reported from the United Kingdom occurred in March 2018 *(45)*.

Twenty-one cases were clinical admissions, one involved DUID, two were post-mortem investigations, and two were unspecified. No specific information was available on the cases; however, blood concentrations were provided in six cases (6.8–110 μg/L). In one post-mortem case (peripheral blood concentration, 8.1 μg/L), 3-MMC was reported as "present but contributory (low)". In the other post-mortem result, reported from the United Kingdom, 3-MMC was reported as detected (no concentration) with another cathinone, 4-methyl-N-ethylpentedrone ((2-(ethylamino)-1-(4-methylphenyl)pentan-1-one)). The femoral blood concentration was reported to be 0.93 mg/L. No more details were available, and a causal relationship "could not be established". Seven cases involved detection of additional substances *(45)*.

The EMCDDA risk assessment of 3-MMC included a total of 14 acute poisonings with confirmed exposure to 3-MMC (most considered to be non-fatal) reported from France (6), the Netherlands (6), Germany (1) and Spain (1). Exposure to other substances was reported in seven cases, including central nervous system depressants and central nervous system stimulants. It was not known whether the remaining seven cases represented mono-intoxications. It was reported that four of the cases were considered life-threatening (required admission to intensive care or involved a life-threatening condition such as respiratory arrest or coma). The EMCDDA also received reports on 192 cases of suspected exposure to 3-MMC from five Member States, although no analytical confirmation was available at the time *(3)*.

Twenty-seven deaths with confirmed exposure to 3-MMC were reported from Sweden (nine), the Netherlands (eight), France (six), Spain (three) and Slovenia (one). The information indicated that 21 of these cases occurred between 2013 and 2021: seven in 2013, three in 2016, five in 2019, five in 2020 and one in 2021. In the 13 cases in which information was available, 12 were in males and 1 in a female. Age was reported for seven men aged 22–46 (mean, 29; median, 27). In at least eight cases, 3-MMC was reported to be the cause of or to have contributed to the death. Eighteen of the cases were reported as either mixed poisonings or with other substances identified in biological samples; no information on the remaining nine cases was available. Other substances were identified in biological samples (seven cases), and other substances were involved in six cases. Mixed intoxications with no information on substances were reported for the five remaining cases. Individuals were found dead in three cases, and the deaths were related to sexual practices (chemsex, intentional sex under the influence of psychoactive drugs, mostly among men who

have sex with men) *(3)*. Some of these cases have also been published in the scientific literature (see below).

Scientific literature: non-fatal cases

Over 400 detections of 3-MMC (including DUID and non-fatal intoxications) have been described in the scientific literature since 2013. In the majority of cases, other substances have been detected, and some cases were reported or reviewed more than once. Over 100 of the cases were reported to involve ingestion of 3-MMC alone (and self-reported ingestion without analytical confirmation). In most cases, the reported clinical features were consistent with sympathomimetic toxicity, including tachycardia, agitation, aggression, hypertension, hallucinations and increased creatine phosphokinase levels (rhabdomyolysis and/or kidney failure).

Between August 2012 and March 2014, 50 of 786 cases of suspected NPS intoxications in Sweden were found to involve 3-MMC *(19)*. Exposure to 3-MMC was confirmed in 49 blood (serum) and 35 urine samples obtained from 50 (38 male and 12 female) patients. In 34 cases (68%), both blood and urine samples were available, and 3-MMC could be detected in both matrices. The age range of the 3-MMC-positive patients was 17–49 years (median, 24; mean, 25.5 years). The 3-MMC concentrations were between 0.002 and 1.49 μg/mL in serum (median, 0.091 μg/mL) and between 0.007 and 290 μg/mL in urine (median: 3.05 μg/mL). Mono-intoxication was found in only four cases (8%). Thus, 27 NPS other than 3-MMC were detected in this subgroup, although two deaths occurred with 3-MMC alone *(19)* (see below).

The main clinical features reported in patients who tested positive for 3-MMC included tachycardia (≥ 100/min) and hypertension (systolic blood pressure, ≥ 140 mm Hg), which were documented in 24 (48%) and 19 (38%) cases, respectively. Furthermore, severe hypertension (systolic blood pressure, ≥ 160 mm Hg) and severe tachycardia (≥ 140/min) were observed separately in five cases each. Other features included hyperthermia (> 39 °C, 6%), seizures (8%), diaphoresis (12%), dilated pupils (24%) and agitation (44%). In 16 patients (32%), a reduced level of consciousness (Glasgow coma scale < 15) was observed, although it was considered that causes other than a direct effect of 3-MMC were present in all cases, including circulatory arrest (2%), postictal state (6%), ethanol (14%), central nervous system-depressing substances (20%) and co-exposure to benzodiazepines (22%). Significant chest pain was not documented in any of the cases *(19)*.

In Slovenia, seven patients were treated for poisoning with 3-MMC in 2013 and 2014. The most common clinical features reported were tachycardia, hypertension and psychological effects such as disturbed perception of surroundings, confusion and restlessness. Treatment was symptomatic, mainly with diazepam. Ingestion of ethanol (three cases) and amphetamines (two cases) was also mentioned *(28)*.

A 34-year old man was involved in a traffic accident and then found sleeping in his car *(46)*. The observed clinical features included glassy and narrow pupils, reddened eyes, disorientation, "washed-out" pronunciation, impaired balance, coordination and fine motor skills, delayed reaction time and deficient concentration. He was treated with methadone. A blood sample taken 8 h later revealed the methadone (127 ng/mL), its metabolite thylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (6.0 ng/mL), lorazepam (25.4 ng/mL) and 3-MMC (35.6 ng/mL) in serum *(46)*.

A review of blood concentrations in 95 cases in which 3-MMC was detected between 2013 and mid-2015 (5200 samples overall) in Poland *(29)* showed that most cases positive for 3-MMC were cases of DUID (66) and traffic accidents (4). The remaining six cases involved intoxication, including fatal poisoning (5), drug possession (9) and 10 others (violence, theft, rape and kidnapping). In 76 of the 95 cases, 3-MMC was not the only substance detected. 3-MMC concentrations ranged from traces (< 1 ng/mL) up to 1.6 µg/mL (mean concentration, 51.3 ng/mL; median, 18.5 ng/mL). The concentrations grouped by type of incident were 1–171 ng/mL (driving DUID), < 1–29 ng/mL (traffic accidents), 2–408 ng/mL (drug possession), < 1–1600 ng/mL (intoxication) and < 1–61 ng/mL (others, including violence, theft, rape and kidnapping). One example was provided in which 3-MMC was detected in the blood of a male patient (21 ng/mL) with benzoylecgonine (58 ng/mL), although no further information was presented. In 19 DUID cases, 3-MMC was the only substance detected. Interestingly, clinical features were found in only six cases, which included uncoordinated movements, tachycardia (100 bpm), aggression, agitation, stuttering, fatigue, verbosity and gaiety. In one non-fatal case in a male subject (no details available), the authors reported blood concentrations of 21 ng/mL 3-MMC and 58 ng/mL benzoylecgonine *(29)*.

In a review of the detection of 3-MMC in biofluids in the cases in Poland described above, Adamowicz et al. *(48)* reported that, in the period 2012–2014, 112 of 1058 samples were found to contain NPS. Of these, 50

contained 3-MMC, with blood concentrations between 1 and 1600 ng/mL (mean, 96; median, 13). As described previously, the observed effects included uncoordinated movements, aggression, agitation, stuttering, verbosity and gaiety. Other drugs were commonly present.

In France, five patients were hospitalized after ingestion of NPS. 3-MMC was stated to have been involved in three cases. The clinical features were reported to include hallucinations (n = 3), agitation (n = 3), tachycardia (n = 3), arterial hypertension (n = 3) and a poison severity score (PSS) of 1 or 2. Symptomatic treatment included sedation in four cases, but all resolved favourably. 3-MMC was detected in three cases: (i) a woman aged 23 years: PSS, 2; 304 µg/L 3-MMC in plasma; methadone, citalopram and possibly 1-(benzofuran-5-yl)-*N*-methylpropan-2-amine (5-MAPB) also detected; (ii) a 36-year-old man, ~7 µg/L 3-MMC in plasma, 2370 µg/L in urine; and (iii) a 19-year-old man, 220 µg/L 3-MMC in whole blood, not detected in urine *(34)*.

In a follow-up publication from France of six intoxications with 3-MMC *(49)*, additional information was provided for some of the cases. A woman aged 22 years who showed confusion, somnolence, myosis, Glasgow Coma Scale = 10 and PSS = 2, was found to have 300 µg/L 3-MMC, 20 µg/L 5-MAPB and 100 µg/L methadone in plasma. In a 35-year-old man, intravenous use resulted in agitation, hypertension, chest pain and tachycardia, PSS = 2 and detection of 7 µg/L 3-MMC in plasma and 2370 µg/L in urine. A 29-year-old man experienced hallucinations and tachycardia (PSS = 2), with detection of 220 µg/L 3-MMC in whole blood and an estimated concentration of 2 µg/L 5F-AKB48 in plasma. A 23-year-old man experienced seizures, with a Glasgow Coma Scale = 3. His plasma contained 3-MMC (1600 µg/L), 4-methylethcathinone (890 µg/L) and methoxetamine (1180 µg/L) and his urine 3-MMC (141 000 µg/L), 4-methylethcathinone (61 000 µg/L) and methoxetamine (39 000 µg/L). A 37-year-old man with a PSS = 2 showed agitation, mydriasis and tachycardia. His plasma contained 3-MMC (60 µg/L), 4-methylethcathinone (240 µg/L), methoxetamine (10 µg/L) and MDMA (110 µg/L), and his urine contained 3-MMC (13 000 µg/L), 4-methylethcathinone (85 000 µg/L), methoxetamine (930 µg/L), MDMA (5,600 µg/L) and MDA (320 µg/L). A 30-year-old man presented with coma, myosis, bradypnoea, Glasgow Coma Scale = 3–5 and PSS = 3. Plasma contained 3-MMC (150 µg/L) and GHB (200 000 µg/L), while urine contained 3-MMC (41 600 µg/L) and GHB (685 000 µg/L) *(49)*.

In Germany in 2014, a 26-yearold woman who was DUID ("conspicuous way of driving") was reported to have pupil abnormalities (slow reaction to light), gazing and appeared to be depressed. The blood concentration of 3-MMC in a blood sample taken 1 h and 10 min after the incident was 39.9 ng/mL. No other substances were detected *(46)*.

A retrospective single-centre study was conducted between January 2010 and January 2016 of 81 patients being treated for acute cathinone intoxication and complications of cathinone use *(50)*. In 10 cases reported between 2014 and 2015, 3-MMC was the sole substance.; additional substances were ingested in three other cases. The reported clinical features included hypertension, tachycardia and increased creatine phosphokinase levels.

A series of cases of intoxication in Poland involved predominantly 4-chloromethcathinone. One DUID case also included detection of amphetamine (15 ng/mL), 3-MMC (450 ng/mL) and THC-COOH (8 ng/mL), in addition to 4-chlorormethcathinone (25.4 ng/mL). The case involved a male of unknown age who was reported to have had slurred speech and red eyes and face. No further information was available *(51)*.

Two non-fatal cases were described in France. One involved a 33-year-old man who was found wandering the streets 24 h after killing his wife and his 2-year-old daughter in an outburst of violence. A blood sample was collected immediately, and chest hair was collected 1 month later. 3-MMC was detected in blood at a concentration of 3 ng/mL; THC (0.5 ng/mL) and THC-COOH (14 ng/mL) were also detected. Hair analysis revealed 3-MMC (14 pg/mg), methoxamine (260 pg/mg), ethylphenidate (41 pg/mg), THC (2229 pg/mg), cocaine (193 pg/mg), pholcodine (239 pg/mg) and zopiclone (416 pg/mg). In the second case, a 31-year-old man was found unconscious, with partial body paralysis and obstruction of one or more coronary arteries. The man was known to engage in drug consumption in the context of sexual activity (chemsex). Blood analysis revealed 3-MMC (392 ng/mL), 4-methylethcathinone (4.5 ng/mL), GHB (234 mg/L), nordiazepam (199 ng/mL), oxazepam (26 ng/mL) and bromazepam (149 ng/mL) *(52)*.

In a review of presentations to emergency departments in Europe between January 2014 and December 2017 for seizures associated with recreational substance use, 1013 of 23 947 cases involved seizures. Of 25 cases involving 3-MMC ingestion, four presented with seizures. The authors concluded

that ingestion of 3-MMC was significantly associated with the likelihood of seizures. It was not stated whether 3-MMC was the only substance ingested *(53)*.

Several non-fatal intoxications have been reported in France with detection of 3-MMC and other substances, especially GHB, in the context of drug consumption, including by injection, and sexual activity (chemsex and slamsex) *(54–56)*. 3-MMC was reported to be one of the most common substances associated with slamsex in France *(57, 58)* (see also section 14).

A 40-year-old man being treated for HIV and a history of substance use, including intravenous use predominantly of GHB and cocaine, and psychiatric treatment, was admitted to intensive care for a reduced state of consciousness (Glasgow Coma Scale = 3), bradypnoea with episodes of apnoea and bilateral miosis. Urine analysis revealed 3-MMC, 4-methylethcathinone and cocaine metabolites. Serum analyses established a GHB concentration of 301 mg/L. No further details were reported *(55)*.

A 35-year-old man was admitted to hospital after having ingested two glasses of alcohol and 3-MMC intranasally. He presented with hallucinations, vomiting and then lost consciousness (blood pressure, 194/91 mm Hg; heart rate, 81 bpm, with no chest pain). Hyperthermia was not noted, and blood sugar was 1.10 g/L. An electrocardiogram showed elevated ST segment in the anterior territory. On admission, the following laboratory values were found: creatinine phosphokinase, 671 IU/L (normal, 0–195 IU/L); myoglobin, 105.8 µg/L (normal, < 90 µg/L); and troponin T-HS, 9.5 ng/L (normal, < 34.2 ng/L). Transthoracic echocardiography showed a normal left ventricular ejection fraction, with no disruption of segmental kinetics or pericardial effusion. The patient was discharged with a prescription for a cardiac examination. Urine screening was negative for amphetamines, cocaine, opiates, methadone and natural cannabinoids but positive for ethanol (0.2 g/L). 3-MMC was detected in urine but was not quantified *(56)*.

A 31-year-old man who confirmed injection of 3-MMC and consumption of GHB but with no known medical history was admitted to hospital with severely impaired consciousness. The Glasgow Coma Scale score was 3, and he exhibited hypothermia (< 35 °C). His pupils reacted normally to light and were of regular width. No other clinical observations were made, and his electrocardiogram was unremarkable. Apart from polynuclear

neutrophilic leukocytosis (12 G/L), the results of standard clinical laboratory tests were also unremarkable. The patient was intubated and mechanically ventilated and recovered after several hours. Analysis of biofluids confirmed the presence of 3-MMC (177 ng/mL and 22 000 ng/mL in blood and urine, respectively) and GHB (131 mg/L and 2000 mg/L in blood and urine, respectively) *(54)*.

A review of toxicological analyses carried out in Poland between 2013 and 2019 included 57 cases (39 fatal and 18 non-fatal) involving use of synthetic cathinones (2). 3-MMC was identified in six non-fatal cases, predominantly DUID, between 2013 and 2014 (Table 3). The concentrations of 3-MMC in the DUID cases ranged from 12 to 344 ng/mL (mean, 226 ng/mL; median, 267 ng/mL).

Table 3. Case reports of non-fatal intoxications associated with 3-MMC in Poland

Sex/age	Comments	3-MMC in blood (ng/mL)
M/41	Man holding a hostage	311
M/unknown	Roadside check; taken a powder labelled "MCH"	12
M/20	Driver; dilated pupils and weak pupillary light reflex noted	293
M/29	Driver; regular pulse, normal pupils and normal pupillary light reflex noted	240
M/25	Driver; regular pulse and rowdy mood noted	344
M/34	Driver; regular pulse, normal pupils, normal pupillary light reflex, positive Romberg test and positive finger–nose test	155

Source: reference *2*. No other drugs were detected.

A 60-year-old man was admitted to hospital with acute kidney injury considered to represent a combination of rhabdomyolysis and pre-renal injury due to existing stage-III chronic kidney disease and 3-MMC use. The patient reported consumption of 3-MMC, but confirmation by biofluid analysis was not reported *(59)*.

In the Netherlands, where increased popularity and use of 3-MMC were observed among certain sectors of the population (e.g., "clubbers"), 3-MMC poisonings reported to the Dutch Poisons Information Centre were reviewed *(21)*. A telephone service was provided for health-care professionals responding to poisoning cases, so that information obtained from patients on their substance use was based of self-reports and confirmation by analysis of biofluids was usually not available. A total of 184 poisonings involving 3-MMC (with and without relevant concomitant

exposure to other substances) were reported between January 2013 and June 2021. Of these, 84 acute poisonings involved self-reported use of 3-MMC only. The reported sympathomimetic effects included agitation (n = 16, 19%), hypertension (n = 17, 20%) and tachycardia (n = 29, 35%). In most patients, initial PSS (information provided during consultations at the Dutch Poisons Information Centre) was minor (n = 37, 44%) to moderate (n = 39, 46%). Severe poisoning (repeated convulsions [n = 1], ventricular fibrillation followed by cardiac arrest [n = 1] and hypertension [systolic blood pressure > 180 mm Hg; n = 3] was observed in five patients during initial consultations. Eight of 16 patients who reported use of 3-MMC only between January 2016 and June 2019 were followed up in a prospective study. The sympathomimetic symptoms included tachycardia, hypertension, chest pain, agitation and perspiration. In one case, the presence of 3-MMC was confirmed in blood at 172 ng/mL after self-reported injection of a solution containing 4500 mg 3-MMC. The PSS was severe, and the clinical features reported were mydriasis, dry mouth, throat and nose, perspiration, tachypnoea (40/min), hypertension (210/142 mm Hg), electrocardiographic abnormalities (prolonged QRS, 110 ms and prolonged QTc, 474 ms), tachycardia (123 bpm), chest pain, anxiety and agitation *(21)*. In one case, 3- and 4-MMC could not be differentiated (2-MMC was not mentioned). One of the cases was followed up outside the prospective cohort study, and blood was found to be positive for 3-MMC and caffeine (no concentrations given). After ingestion of an unknown amount of suspected 3-MMC powder, the patient reported tachycardia (120 bpm), agitation, hyperthermia (38.3 °C), ventricular fibrillation and cardiac arrest in the ambulance. The poisoning was considered severe. The authors stated that the effects of 3-MMC poisoning appear to be short-lived (≤ 24 h), although severe adverse effects and complications of injection can prolong hospitalization *(21)*.

In a qualitative study of the prevalence of visual disturbances after substance use ("visual snow"), 1 of 24 participants identified 3-MMC as a trigger. No more information on substance use was available, and it was not possible to determine whether other substances were involved in the episode thought to have triggered this condition *(60)*.

Scientific literature: fatal cases

Since 2013, at least 34 deaths in which 3-MMC was detected have been identified in the scientific literature (Table 4). Poly-drug use was found in the majority of cases (including psychostimulants and central nervous system depressants such as alcohol and GHB). Some cases were reported

more than once, and some may also have been reported to the EMCDDA. In eight cases, either no other substance was detected or the authors established accidental intoxication with 3-MMC as the cause of death. Three other fatal 3-MMC poisonings involved suicides (two by hanging). Some of these deaths were related to acute 3-MMC intoxication in the context of chemsex practices. Overall, the descriptions included acute circulatory and respiratory failure, deteriorating neurological condition (cerebral oedema consistent with global anoxic brain injury) and cardiac complications.

Table 4. Cases of fatal intoxication with detection of 3-MMC and other substances

Year published	Sex/age (years)[a]	Comments	Reference no.
2014	M/20	Estimated ingestion of about 500 mg 3-MMC and 400 mg 5-APB with 250 mL vodka (40% v/v). Clinical features included hyperthermia, tachycardia, hypertension, bradycardia and seizures; patient died about 4 h after substance use. Cause of death: acute cardiovascular collapse after mixed intoxication with NPS and alcohol. Post-mortem blood concentrations of 1600 ng/mL 3-MMC and 5600 ng/mL 5-APB. Serum alcohol concentration was 1.4 g/L in an ante-mortem sample collected 1 h after admission to the hospital.	*61*
2014	U/U	No specific information reported. Detection of AH-7921 (0.35 µg/g, femoral blood), 3-MMC and buprenorphine (matrix and concentrations not reported).	*62*
2014	U/U	No specific information reported. Deceased was treated in intensive care. Detection of AH-7921 in hair (0.35 µg/g) and femoral blood and 3-MMC (matrix and concentration not reported).	*62*
2014	M/23	No specific information reported; deceased bought the substances on the Internet. Peripheral blood contained AH-7921 (0.43 mg/L), codeine (1.4 µmol/L), 2-FMA (0.041 µmol/L), paracetamol (124 µmol/L) and 3-MMC (0.012 µmol/L). This may be the same case reported by Karinen et al. *(63)*.	*62*
2014	M/20s	Prescribed 400 mg acetaminophen and 30 mg codeine after a minor accident. Ingested powders labelled "3-MMC" and "4-FMA." The decedent fell asleep and died shortly thereafter. Apart from oedematous lungs (weight, 2080 g), no other findings were made at autopsy. Peripheral whole blood analysis showed AH-7921 (0.43 mg/L), codeine (0.42 mg/L), codeine-6-glucuronide (0.77 mg/L), acetaminophen (19 mg/L), 2-FMA (0.0069 mg/L) and 3-MMC (0.0021 mg/L). The cause of death was reported to be intoxication with AH-7921 and other psychoactive substances.	*63*
2014	M/25	Found unresponsive in his room. Autopsy revealed acute bronchitis, pneumonia, brain and lung oedema (weight of lungs, 1256 g) and pulmonary congestion. Drugs detected in femoral blood: AH-7921 (0.35 µg/g) and 3-MMC (no concentration given). Cause of death ruled to be intoxication and the manner of death to be accidental.	*64*

Table 4. *continued*

Year published	Sex/age (years)[a]	Comments	Reference no.
2015	U/U	Ingestion of amphetamine with 3-MMC. Brought to hospital in circulatory arrest. No further information reported.	*19*
2015	M/25	Man with a history of alcohol and amphetamine use and chronic hepatitis C infection was found unresponsive and reported to have taken 3-MMC the previous evening. Was unconscious and wheezing, tachypnoic and cyanotic; systolic blood pressure was 75 mm Hg, and he was tachycardic. A seizure that occurred during transport was treated with diazepam. In hospital, the patient was unconscious (body temperature, 39 °C) and hypotensive (80/40 mm Hg), tachycardic (140/min) and with a respiratory rate of 36/min. During oxygen supplementation, his oxygen saturation was 96%; he also had metabolic acidosis. After treatment with naloxone and flumazenil, his condition remained unchanged; he was intubated and placed on a ventilator. He remained hyperthermic despite sedation, external cooling and administration of cold fluids, and his body temperature peaked at 40.9 °C 20 h after admission. His neurological condition deteriorated, and further examination showed generalized cerebral oedema consistent with a global anoxic brain injury. Patient died 6 days after admission. Blood and urine samples were collected in hospital on the second day, and 3-MMC was found at 2 ng/mL in serum and 85 ng/mL in urine. Other substances detected in urine at low concentrations were buprenorphine, conjugated ethanol metabolites (ethyl glucuronide and ethyl sulfate) and diazepam (probably treatment-related). No other substances were reported.	*19*
2015	U/U	3-MMC was detected in post-mortem blood at a concentration of 4.4 mg/L (no further details reported).	Rojek et al. cited in *31*
2016	M/U	Patient ingested 3-MMC and collapsed; taken to hospital and died the following day. 3-MMC concentration, < 1 ng/mL; MDMA, 33 ng/mL. The authors suggested that the long delay between ingestion and death, the emergency procedures performed and the short half-life of 3-MMC might explain the low concentration.	*29*
2016	U/U	3-MMC (22 ng/mL) and 5-APB (146 ng/mL) detected. A medicinal product containing potassium chloride was found near the cadaver (concentration in stomach, 3.4 mg/g). No further details were provided.	*29*
2016	M/U	Had used 3-MMC and 25I-NBOMe. Blood concentrations were 11 and 3 ng/mL. Reported to have taken "legal highs". The cause of death was ruled as acute respiratory failure caused by pneumonia, which occurred during septic shock, followed by multiple organ failure.	*29*
2016	M/U	Individual found dead in an appartment. 3-MMC (3 ng/mL) detected in conjunction with tramadol at a therapeutic concentration (563 ng/mL). No further details were reported.	*29*

Table 4. *continued*

Year published	Sex/age (years)[a]	Comments	Reference no.
2016	M/30s	Died after consumption of a white powder (no further information provided). Blood contained 3-MMC (78.8 ng/mL), 4-methylethcathinone (124 ng/mL), paracetamol (0.12 µg/mL), paroxetine (0.12 µg/mL), sildenafil (76.4 ng/mL) and ethanol (0.18 g/L). 3-MMC was also detected in cardiac blood, urine, bile and vitreous humour. The authors concluded that death was due to acute intoxication involving 3-MMC.	*65*
2016	M/30s	Died after consumption of a white powder (no further information provided). 3-MMC was detected at 249 ng/mL in peripheral blood and in cardiac blood, urine, bile and vitreous humour. Detection of other substances was not reported. The authors concluded that death was due to acute intoxication involving 3-MMC.	*65*
2016	M/69	While attending a party, the patient vomited and developed cardiopulmonary arrest. 3-MMC and "poppers" (alkyl nitrites) were found at the scene. Peripheral blood analysis showed the presence of 3-MMC (0.33 mg/L), pseudoephedrine (0.03 mg/L) and GHB (576 mg/L). These drugs were also detected in hair, gastric content, bile, urine and cardiac blood.	*31*
2016	U/U	In a fatal case in 2013 due to hanging, 3-MMC was detected (1.1 mg/L) in post-mortem femoral blood, with venlafaxine (1.62 mg/L) and *O*-desmethylvenlafaxine (2.77 mg/L).	Elliott, cited in *9*
2017	M/32	Found dead at home after ingesting white powder intranasally (also known history of GHB consumption). He suffered from headache and warm sensations, lay down and was found dead in the morning. Autopsy revealed no obvious cause of death. Toxicological analysis showed the presence of 3-MMC in various tissues (ng/mL): peripheral blood (249); cardiac blood (609), vitreous humour (2988), bile (1291) and urine (29 694). Cause of death: intoxication; manner of death: accidental. This case may be one of those reported previously *(65)*. No other substances were reported. Analysis of the powdered samples confirmed the presence of 3-MMC.	*66*
2017	U/U	Patient required cardiopulmonary resuscitation by paramedics for cardiac arrest after ingestion of 3-MMC, which was successful; however, cerebral oedema and brain death subsequently ensued. 3-MMC was detected in the patient's urine (no further information reported). Detection of other substances was not reported.	*50*
2019	M/38	Found dead at home with no evidence of violence or traumatic lesions. Femoral blood analysis showed 3-MMC (613 ng/mL), amphetamine (938 ng/mL) and GHB (154 mg/L). Hair analysis showed 3-MMC (17 100 pg/mg) and amphetamine (14 800 pg/mg). The same case was briefly summarized by Ameline et al. *(30)*.	*52*
2019	M/50	Found deceased by hanging in a "swinger's" nightclub; known to participate in chemsex practices. 3-MMC detected in cardiac blood (462 ng/mL), with methoxamine (70 ng/mL), nordiazepam (< 10 ng/mL) and bromazepam (< 10 ng/mL). The same case was summarized by Ameline et al. *(30)*.	*52*

Table 4. *continued*

Year published	Sex/age (years)[a]	Comments	Reference no.
2019	F/19	Subject was found dead in the woods after a quarrel with her boyfriend by telephone, when she suggested committing suicide and appeared agitated and confused. 3-MMC was determined in blood (800 ng/mL), vitreous humour (150 ng/mL), and total stomach contents (5.5 mg). Forensic pathologist excluded any cause of death other than poisoning. Detection of other substances was not reported.	*67*
2020	M/49	Committed suicide by hanging. 3-MMC detected in femoral blood (49 ng/mL), cardiac blood (53 ng/mL), urine (310 ng/mL), stomach contents (74 ng/mL) and bile (205 ng/mL). Traces of diazepam and nordiazepam were also detected. Analysis of pubic hair showed 12 pg/mg MDMA, 4 pg/mg 3-MMC and 28 pg/mg buphedrone. The authors suggested that the 3-MMC concentrations might have been underestimated because of the chemical instability of the drug.	*68*
2020	U/U	Three unpublished cases of fatal intoxications involving 3-MMC (no information provided) at the university hospital in Lille, France.	*69*
2021	F/34	Found dead, apparently under the influence of drugs. Before death, she was agitated, shivering and nervous, and her speech was slurred; she had a history of drug and alcohol dependence. The concentrations of 3-MMC were 391 ng/mL in blood and 64 ng/mL in urine., and those of alcohol were 0.3 mg/mL in blood and 0.6 mg/mL in urine. The cause of death was stated as acute circulatory and respiratory failure after intoxication. Detection of other substances was not reported.	*2*
2021	M/U	Found dead, with needles, a syringe with a depressed plunger, small plastic bags labelled "ruby sand additive 0.5 gram – product imitation", small empty resealable bags with traces of colourless liquid and empty mineral water bottles. Man had a history of using "legal highs", amphetamine and cannabis in the form of smoking mixtures, powders and tablets; he was also allegedly taking steroids. The biofluid concentrations of 3-MMC were 5310 ng/mL in blood (concentration range: 391–5310 ng/mL; mean: 2691 ng/mL; median: 2531 ng/mL) and 1361 ng/mL in urine, and that of amphetamine was 1990 ng/mL in urine. The cause of death was recorded as acute circulatory and respiratory failure after intoxication.	*2*
2021	F/28	Died after taking about 0.4 g 3-MMC crystals dissolved in water, had sex with partner and then had convulsions, nose bleed and loss of consciousness. Had treatment of migraine with hydroxyzine, ketoprofen and other custom-made medicines. Biofluid concentrations of 3-MMC were 3352 ng/mL in blood and 748 ng/mL in vitreous humour; those of caffeine were 300 ng/mL in blood and 100 ng/mL in vitreous humour; and that of codeine was 6 ng/mL in vitreous humour. The cause of death was acute circulatory and respiratory failure after intoxication.	*2*
2021	M/52	The corpse was found without hands and wrists due to "activity of animals". Blood contained 1710 ng/mL 3-MMC, 20 ng/mL diazepam and 6 ng/mL nordiazepam. Cause of death was recorded as acute circulatory and respiratory failure after intoxication in a person with AIDS and pneumonia.	*2*

Table 4. *continued*

Year published	Sex/age (years)[a]	Comments	Reference no.
2022	M/59	Subject found dead at home in a corridor, naked, wearing a black hood and a collar around his neck with a dog leash attached. He had piercings on the testicles and nipples. Several electrodes were posed along the penis and connected to a stimulator and battery. An empty 1-mL syringe was found in a rectal vein on the right of the buttock, which had contained 3-MMC. The femoral blood and urine concentrations of 3-MMC were 1437 and 16 733 ng/mL, respectively. Detection of other xenobiotics was not reported. The cause of death was ruled to be acute 3-MMC poisoning in the context of chemsex. The contents of the syringe also confirmed revealed the presence of 3-MMC.	*20*
2022	55/U	Death stated to be directly related to consumption of 3-MMC during chemsex (no details provided). The concentration of 3-MMC in blood was reported to be 5480 µg/L, and "poppers" were also reported (39% in methaemoglobin).	*70*
2022	54/U	The death was stated to be directly related to consumption of 3-MMC during chemsex (no details provided). The concentration of 3-MMC in blood was reported to be 12 µg/L, and mexedrone was also detected.	*70*
2022	M/55	A man who had sex with men was found dead after a chemsex party with 32 stab wounds. His medical history included cardiovascular disorders treated with amlodipine, valsartan and hydrochlorothiazide. He occasionally took benzodiazepines. Femoral blood contained MXP (606 µg/L) and traces of lidocaine. Urine contained 3-MMC (238 µg/L), MXP (1066 µg/L), lidocaine (traces), valsartan (traces) and oxazepam (750 µg/L); hair contained 3-MMC (< 0.25 ng/mg) and diphenidine (0.25 ng/mg). Two syringes were found to contain 3-MMC and MXP, and one syringe contained diphenidine. The cause of death was ruled as homicide due to stabbing.	*71*

[a] U, unknown or not reported

7. Dependence potential

A. Studies in experimental animals

No information was found.

B. Studies in humans

No information was found.

8. Abuse potential

A. Studies in experimental animals

In studies of locomotor activity in adult male Sprague-Dawley rats (280–300 g), 3-MMC (3 mg/kg intraperitoneally) and methamphetamine

(1 mg/kg intraperitoneally) increased the total distance travelled. When compared with saline, 3-MMC increased activity by 5–30 min and 95–100 min, whereas methamphetamine increased locomotor activity by 5–120 min *(41)*.

In the elevated plus maze test, a single intraperitoneal administration of 3-MMC at a dose of 1, 3, 5 or 10 mg/kg increased the time spent in the open arm at 3 mg/kg, consistent with anxiolytic behaviour. After chronic administration (7 days; 3 mg/kg), the time spent in the open arms was shorter than with saline and methamphetamine, which the authors interpreted as increased anxiety-like behaviour. Acute and chronic administration of methamphetamine (1 mg/kg) showed no significant effect *(41)*.

3-MMC (3 and 10 mg/kg; intraperitoneally) induced conditioned place preference in adult male Sprague-Dawley rats (280–300 g; 8 days of training and tests on day 9), and the conditioned place preference score recorded for the 10-mg/kg dose of 3-MMC was comparable to that of methamphetamine at 1 mg/kg. 3-MMC at 1 mg/kg had no effect *(41)*.

B. Studies in humans

No information was found.

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

No information was found on established uses; however, some patent applications include use of 3-MMC in psychotherapeutic interventions *(25)*. 3-MMC has also been proposed for enhancing the acute emotional effects of LSD, psilocybin and other psychedelics *(72)*. Another patent application suggests its use in the treatment of menstrual cycle-induced disorders and symptoms *(26)*. No current clinical trials were identified on therapeutic use of 3-MMC.

10. Listing on the WHO Model Lists of Essential Medicines

3-MMC is not listed on the 22nd WHO Essential Medicines List or the 8th WHO Essential Medicines List for Children.

11. Marketing authorizations (as a medicinal product)

No information was found.

12. Industrial use

No recorded industrial use was identified.

13. Non-medical use, abuse and dependence

No epidemiological evidence on use of 3-MMC in household surveys was found; however, some information is available from targeted surveys of specific populations, such as users of recreational substances and men who have sex with men who use substances in the context of chemsex or slamsex and from cases of fatal and non-fatal intoxication involving 3-MMC (section 6).

Blood and urine samples were collected from people prosecuted for use of illicit and/or designer drugs in a study in Hungary. Thus, 2744 suspected substance users were sampled in Budapest between July 2012 and June 2013, and 774 people were sampled in south-east Hungary during 2012 and 2013 *(73)*. Nineteen positive samples (0.97%) were identified in Budapest and 24 positive samples (5.07%) in south-east Hungary. All cases were detected in combination with other substances, including pentedrone, benzodiazepines, amphetamine and THC *(73)*.

Over 5 months in Slovenia in 2014, 249 people who currently or previously reported NPS use completed an online survey. The study also included preliminary results obtained from in-depth interviews about drug markets conducted with 26 people who used NPS *(1)*. The results showed that 169 (67.9%) respondents had tried 3-MMC, whereas 35 (14.1%) had used it > 40 times, which was the highest share of frequent users of all NPS. More than one fourth (26.8%) confirmed use for more than 1 year, and one third confirmed use in the past month (n = 168). Over 28% of 3-MMC users had used it once or twice, whereas 20.7% (n = 169) stated that they had used it 40 times or more. The author stated that 3-MMC is used in nightlife settings, open public places and chemsex parties *(1)*.

In a qualitative follow-up study in Slovenia between December 2013 and October 2014, 19 interviews were conducted with 25 individuals on their experiences of NPS use *(24)*. 3-MMC was reported to be the most common drug of choice. Participants reported a wide range of frequencies of use, with some reporting use every weekend and others stating use once every fortnight or every few months; others reported use only on special occasions. Binge use of 3-MMC for several days was reported, with the amount consumed exceeding the amount originally planned.

Younger people reported ready access to 3-MMC, whereas older people reported that it was easier to obtain conventional drugs. One participant reported having experienced withdrawal symptoms while trying to abstain from 3-MMC after more than 1 year of daily use. The reported symptoms included sleep paralysis, "brain zaps", anxiety, insomnia and depression *(24)*.

In a retrospective analysis of 81 cases of intoxications with confirmed use of synthetic cathinones between January 2010 and January 2016 in southern Germany, 13 cases occurring in 2014 and 2015 involved detection of 3-MMC, either alone or in combination with other substances. The clinical features included hypertension and elevated creatine phosphokinase concentration *(50)*.

An Internet-based survey of German-speaking people who reported use of "bath salts" was conducted between June 2016 and January 2017. Of 96 respondents, 48 (50%) were familiar with 3-MMC, and 10 (10%) considered it to be their favourite cathinone; 50 (52%) cited 3,4-methylenedioxypyrovalerone as their favourite *(74)*.

Two cases of substance dependence with confirmed exposure to 3-MMC were reported by one Member State to the EMCDDA in 2021. In one case, the patient reported injecting 3-MMC (slamming) and was hospitalized for withdrawal from 3-MMC and 4-fluoromethylphenidate. In the second case, 3-MeO-PCP and 2F-DCK were also detected in biological samples, and the patient confirmed experimenting with a range of NPS, frequently obtained from the Internet. The same Member State also informed the EMCDDA about three cases of substance dependence with suspected exposure to 3-MMC. In one case, a person was hospitalized for withdrawal from 3-MMC. The patient reported having switched from cocaine to 3-MMC because of the lower price of 3-MMC. The two other cases involved use of 3-MMC in in the context of chemsex and slamsex; in one case, the individual was hospitalized for withdrawal symptoms related to GBL use *(3)*.

Some evidence suggests that 3-MMC circulates at music festivals. In New Zealand, 47 submissions amounting to 305 samples of substances seized between December 2018 and March 2019 were analysed. Five capsules (average dose, 74 mg) containing 3-MMC were found *(75)*. In the United Kingdom, 377 samples considered to resemble MDMA-containing products were collected from music festivals in 2021. Synthetic cathinones were detected in 73 samples (19.4%), and 3-MMC was detected in 16 of 73 (21.9%) *(76)*.

In an analysis of the occurrence of 3-MMC in forensic drug samples, consumer drug samples and exposures reported to poisons centres between 2013 and 2017 in the Netherlands, increasing detections of 3-MMC were reported *(77)*.

According to reports received by the EMCDDA, the drug testing service, Welsh Emerging Drugs and Identification of Novel Substances, received 29 samples containing 3-MMC submitted between December 2014 and September 2021. In the majority of cases, 3-MMC was sold as another substance: 4-fluoroamphetamine (1), 3-fluorophenmetrazine (1), ketamine (1), cocaine (2), 2C-B (2), MDMA (6) or mephedrone (9). The effects reported by people who believed they had taken 3-MMC were in agreement with those reported for other synthetic cathinones and included agitation, increased energy, euphoria, chest pains, paranoia, confusion, visual hallucinations and irregular heartbeat *(3)*. One sample received in March was confirmed to contain this substance *(78)*. Drug testing services in Austria, the Netherlands, Switzerland and the USA reported detection of 3-MMC in at least 40 cases. The products were sometimes sold as 3-MMC *(79)*.

In a study of the detection of NPS in influent wastewater samples collected bimonthly between October 2017 and June 2018 and October 2019 and February 2020 in Australia, 3-MMC was detected once in one territory *(80)*. In a snapshot analysis of influent wastewater collected from 14 sites in eight countries during the New Year period of 2019–2020, 3-MMC was detected in three countries (Italy, the Netherlands and Spain) *(81)*. In an extended study, 144 influent wastewater samples were collected from 25 sites in 10 countries during the 2020–2021 New Year period. 3-MMC (together with eutylone) was detected most frequently and at the highest mass loads. Although methcathinone was detected in every country, this might have been due to oxidation of ephedrine or pseudoephedrine. 3-MMC was detected in three European countries and New Zealand *(82)*. 3-MMC is available in its own right and is advertised for sale by some Internet retailers.

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

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

According to the EMCDDA, four Member States (Denmark, France, Hungary and Sweden) and Norway reported 45 cases of suspected DUID

with confirmed exposure to 3-MMC, including four traffic accidents *(3)*. As described in section 6, 3-MMC has been detected in cases of DUID, in some cases with evidence of impairment. 3-MMC was commonly detected with other substances *(2, 46, 47, 51, 83, 84)*.

In a retrospective study of the numbers of self-reported 3-MMC poisonings to the Dutch Poisons Information Centre between 2013 and June 2021, the annual number increased from 1 in 2013 to 63 in 2020. The majority (n = 158, 86%) were reported after 2018, with 70 poisonings reported during the first half of 2021, which suggests increased use of 3-MMC in the Netherlands. 3-MMC was placed under national control in the country in October 2021 *(21)*.

According to the EMCDDA and the published literature cited below, the circumstances under which substances (including 3-MMC) are consumed should be considered to identify new patterns and settings. Those attracting increasing attention in the context of 3-MMC use are chemsex and slamsex. Most such cases have been reported by researchers in France (see also section 6). The health concern is not only poisoning due to overdosing via the intravenous route and infections associated with injection sites and extravasation but also co-administration of other drugs to enhance the user's experience. In addition, the risk of sexually transmitted diseases is increased, as the people who use substances such as 3-MMC in these contexts may engage in sexual behaviour that increases the risks for transmission of HIV and hepatitis C virus. Furthermore, chemsex has been associated with a high risk of nonconsensual sex, anal and rectal trauma and penile abrasion (85). Polydrug use has been reported to be common (including combinations with GHB and GBL), and 3-MMC is one of the commonly used synthetic cathinones in this context (see also section 6) *(3, 20, 54–56, 58, 69–71, 85, 86)*.

Information from drug testing services in Europe and the USA suggests that 3-MMC is present in products acquired or sold as other substances, including MDMA *(79)*. This suggests that people who use certain types of recreational drugs may be exposed unintentionally to 3-MMC, either alone or in combination with other substances, which might add additional risks of harm (e.g., potential exacerbation of a psychostimulant toxidrome).

Between 1 January 2012 and 28 September 2021, nine European Union Member States reported 672 samples containing 3-MMC to the EMCDDA:

Spain (3), Belgium (3), Czechia (4), Portugal (8), Austria (20), Poland (40), Slovenia (52), France (99) and the Netherlands (443). Of these samples, 14 were collected in 2012, 35 in 2014, 28 in 2015, 25 in 2016, 72 in 2017, 101 in 2018, 133 in 2019, 166 in 2020 and 98 in 2021 (until October). The samples of 3-MMC were mostly in powder form (577), but tablets (36), capsules (28) and samples in liquid form (16) were also reported. Most of the samples (590) were collected by drug testing services but also by the Polish National Medicinal Institute (29) and by the Slovenian National Laboratory of Health, Environment and Food (23). In 628 cases (94%), 3-MMC was the only substance detected. It has been detected in combination with other substances an average of six times a year since 2015. In 2016, 3-MMC was detected in combination with other substances in 16 collected samples. Almost all contained "methylethcathinone" without specification of the isomer *(3)*.

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

15. Licit production, consumption and international trade

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

16. Illicit manufacture and traffic and related information

According to the EMCDDA *(3)*, a total of 9038 seizures were reported by 25 countries in Europe representing 2820 kg of the material in all its physical forms between 1 January 2012 and 8 October 2021, with 1930 kg between 2012 and 2019 and 747 kg (27% of all material seized) in 2020. In 2021, 138 kg were seized. Most of the seizures reported (n = 8343; 92%) were of powders, amounting to 2630 kg. Seizure of other forms was also reported: blotters (7), herbal material (16), liquids (33), other or unknown physical forms (79) and tablets and capsules (560 cases). As reported by the EMCDDA *(3)*, in a case reported by the Netherlands in 2019, approximately 350 kg of *N*-acetyl-3-MMC imported from India was seized, with 154 kg of 3-MMC at a "dealer/producer" site. *N*-Acetyl-3-MMC is an uncontrolled chemical that can readily be converted into 3-MMC (section 2D).

Information from law enforcement authorities suggests that at least 55 illicit cathinone laboratories have been dismantled in Europe since 2011. About 50% were seized between 2019 and 2021, indicating increasing

interest in producing cathinones in Europe. Three sites were reported to be involved in the production of 3-MMC. One was seized in Slovakia (2013), and two were seized in the Netherlands (2017 and 2020). The laboratory in Slovakia was considered an operational site, whereas the Dutch sites were considered to be storage and packaging units. According to Europol, a number of abandoned clandestine laboratories for the production of 3-MMC were seized in Slovakia in 2018. One site exploded due to "incompetent handling", resulting in "environmental damage" *(3)*.

In a study in Italy, 479 drug samples suspected to contain NPS were found in 212 seized postal parcels collected between May and October 2020. Synthetic cathinones were found in 117 items (24.4%), 89 of which were attributed to 3-MMC, which was the predominant cathinone (76%) *(87)*. An analysis of samples seized in the Tuscany area (Italy) between 2006 and 2016 indicated that 3-MMC use emerged in Italy in 2015 *(88)*.

The numbers of countries that have reported detections of 3-MMC to the UNODC Early Warning Advisory on NPS database since its first detection were: three in 2012, 32 in 2013, 21 in 2014, 22 in 2015, 26 in 2016, 20 in 2017, 21 in 2018, 30 in 2019, 31 in 2020, 14 in 2021 and 2 so far in 2022. In some instances, several entries from the same country have been counted for the same year *(89)*.

3-MMC was first reported to the US National Forensic Laboratory Information System in 2012, and three reports were listed in 2021 *(90)*.

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

17. Current international controls and their impact

3-MMC is currently not controlled under the 1961, 1971 or 1988 United Nations conventions.

18. Current and past national controls

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

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

None.

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3.2 Pre-review reports

3.2.1 Zopiclone

1. Substance identification

A. International nonproprietary name

Zopiclone

B. Chemical Abstracts Service registry number

Zopiclone free base: 43200-80-2

C. Other chemical names

Zopiclone free base; 5*H*-pyrrolo[3,4-*b*]pyrazine, 1-piperazinecarboxylic acid deriv. (ZCI); (±)-Zopiclone; Amoban; Amovane; Hypnor; Imoclone; Imovance; Imovane; RP 27267; Sopivan; Zimovane; Zopiclone

D. Trade names

Adco-Zopimed; Alchera; Alpaz; Amoban; Amobanters; Amvey; Datolan; Descanil; Dobroson; Dopareel; Dopareel; Eurovan; Foltran; Genclone; Good-Knight; Imoclone; Imolone; Imovane; Imozop; Imrest; Insomnium; Insopin; Jin Meng; Limovan; Losopil; Lyzop; Metorom; Milovan; Neo-Cone; Noctidem; Nocturno; Normason; Optidorm; Ozal; Piclodorm; Piklon; Qing Er Qi; Qualivane; Relaxon; Rhovane; San Chen; Senzop; Siaten; Slipvell; Somnal; Somnol; Somnosan; Sonnat; Sonoesan; Synovane; Torson; Veneco; Ximovan; z-Dorm; Zetix; Zileze; Zimoclone; Zimovane; Zolief; Zolinox; Zolium; Zolon; Zometic; Zomni; Zonix; Zoperil; Zopicalma; Zopicon; Zopigen; Zopinil.Zopinox; Zopistad; Zopitabs; Zopitan; Zopitidin; Zopitin; Zopivane; Zorclone; ACT Zopiclone; Apo-Dream; Apo-Zopiclone; Austell-Zopiclone; Chemmart Zopiclone; Docilen; DOM-Zopiclone; Dormex; Drimolin; Ecodorm; Hypnor; Jamp Zopiclone; Mar-Zopiclone; Mint-Zopiclone; Mylan-Zopiclone; Optimal; Phamzopic; Priva-zopiclone; Pro-Zopiclone; RAN-Zopiclone; ratio-Zopiclone; Riva-Zopiclone; Sandoz Zopiclone; Somnogama; Somnols; Sonlaks; Sonlax; Sonlaks; Terry White Chemists Zopiclone; Uniclone; Yi Tan Ning; Zalepla; Ziclone; Zopiclodura; Zopiclon; Zopiclona; Zopiklon; Zopitran; Zosleep-Humanity

E. Street names

Zopiclone; Z-drug; zops; zoppies *(1)*; zim-zims *(2)*

F. Physical appearance

Zopiclone has been reported as a white or slightly yellowish powder *(3)*.

G. WHO review history

Zopiclone was pre-reviewed by the Expert Committee on Drug Dependence at its 29th meeting, when it recommended that surveillance be continued but that a critical review was not required. In view of the abuse liability of the drug and the significant number of reports of adverse drug reactions (ADRs) related to abuse reported to the WHO international drug monitoring programme, zopiclone was pre-reviewed by the Committee at its 33rd meeting, when it recommended a critical review. Zopiclone was critically reviewed at the 34th meeting, in 2006, when the Committee rated its abuse liability as low and its therapeutic usefulness considerable and recommended continued surveillance by WHO.

2. Chemistry

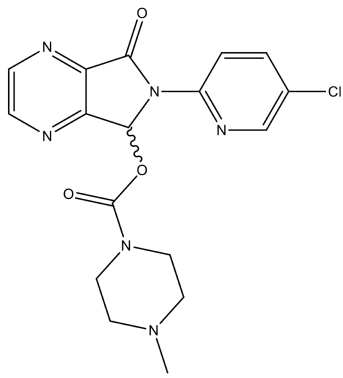
A. Chemical name

IUPAC name:
Zopiclone free base: (5RS)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate

Chemical Abstracts Service index name:
Zopiclone free base: 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl ester (9CI, ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{17}H_{17}ClN_6O_3$
Molecular weight: 388.81 g/mol

C. Stereoisomers

The presence of an asymmetric carbon atom gives rise to the (5R)- and (5S)-enantiomers of zopiclone. The racemic mixture is referred to as "zopiclone". The (+)-(5S)- enantiomer of zopiclone is referred to as "eszopiclone".

D. Methods and ease of illicit manufacture

Zopiclone is a nonbenzodiazepine hypnotic drug of the cyclopyrrolone class. The chemical structure is a pyrrolo[3,4-*b*]pyrazine with a 4-methylpiperazine-1-carboxyl group at the 5-position, a 5-chloropyridin-2-yl group at the 6-position and an oxo-substituent at the 7-position.

The first synthesis of zopiclone was described in a patent by Rhône-Poulenc SA *(4)*. The reaction of pyrazine-2,3-dicarboxylic anhydride with 2-amino-5-chloropyridine produces pyrazine-2-carboxylic acid amide, which, after ring closure with thionyl chloride, results in the 5,7-dioxopyrrolopyrazine imide derivative. Selective potassium borohydride reduction of one of the carbonyl groups leads to the chiral 6-(5-chloropyrid-2-yl)-5-hydroxy-7-oxo-5,6-dihydropyrrolo[3,4-*b*] pyrazine, which reacts with 1-chloro-carbonyl-4-methylpiperazine to produce zopiclone as a racemic mixture.

Alternatively, the chiral 6-(5-chloropyrid-2-yl)-5-hydroxy-7-oxo-5,6-dihydropyrrolo[3,4-*b*]pyrazine reacts with phenylchloroformate leading to 6-(5-chloropyrid-2-yl)-7-oxo-5-phenoxycarbonyloxy-5,6-dihydropyrrolo[3,4-*b*]pyrazine, which in turn reacts with 1-methylpiperazine giving the racemic mixture of zopiclone.

Other patents are for improvements of zopiclone synthesis, although they do not substantially modify the scheme described above *(5–9)*.

All the syntheses reported in the literature, although simple, require the equipment of a chemical synthetic laboratory and qualified personnel.

E. Chemical properties

Melting-point:
178 °C *(4)*

Boiling-point:
No information was found.

Solubility:
Zopiclone is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and practically insoluble in ethanol (96%). It dissolves in dilute mineral acids *(3)*.

F. Identification and analysis

Synthetic zopiclone was characterized by proton and carbon nuclear magnetic resonance, mass spectrometry (MS), infra-red spectroscopy, ultraviolet (UV) spectroscopy *(10)*, fluorescence spectroscopy *(11)* and electrochemical properties *(12)*.

Zopiclone is available as a reference material, as are two of its metabolites, zopiclone-N-oxide and N-desmethylzopiclone, as a deuterated derivative and as (S)- and (R)-enantiomers, from commercial suppliers for routine analysis in forensic, clinical and research investigations (e.g., *13*). Identification and analytical assays of zopiclone and of eszopiclone in bulk preparations or tablets are reported in various pharmacopoeias, such as the European Pharmacopoeia *(3)*, the United States Pharmacopeia *(14)* and the British Pharmacopoeia *(15)*.

Several analytical procedures have been reported for the determination of zopiclone and its metabolites in various biological matrices *(16)*. GC coupled with MS was used to analyse urine samples *(17, 18)*; GC coupled to a nitrogen–phosphorous detector to analyse human post-mortem blood and plasma *(19, 20)*; liquid chromatography (LC) coupled to a fluorescence detector to analyse zopiclone in human plasma, serum and urine *(21, 22)*; LC coupled to diode array detection to analyse human plasma, blood, urine and post-mortem tissue *(23–25)*; and capillary electrophoresis coupled to UV laser-induced fluorescence detection to analyse urine and saliva *(26)*. Several human biological specimens, such as whole blood, hair, plasma, exhaled breath aerosol, serum, post-mortem liver, urine, gastric contents and meconium, were analysed by LC-MS *(27–35)*. Radioimmunoassay methods were developed for the determination of zopiclone and its metabolites in urine *(36)*.

Various chiral analytical methods have been developed for the determination of single enantiomers of zopiclone in bulk drug, pharmaceutical preparations and biological fluids, such as capillary electrophoresis (e.g., *37*), thin-layer chromatography (e.g., *38*) and high-performance LC with chiral stationary phases *(39, 40)*.

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

Several reviews on the general pharmacology of zopiclone were consulted *(41–44)*a new class of psychotherapeutic agents possessing a pharmacological profile of high efficacy and low toxicity similar to that of the benzodiazepines. Binding is thought to occur to the benzodiazepine receptor complex, or to a site closely linked to this complex. Although zopiclone exhibits anticonvulsant, muscle relaxant and anxiolytic properties in animals, it finds better use as an hypnotic because of marked sedating effects. In clinical trials, zopiclone (usually 7.5 mg. Additional publications are cited when clarifications were necessary or when they provided further information.

In the early 1980s, a new class of psychotherapeutic agents, cyclopyrrolones, was developed, of which zopiclone was the first. Zopiclone was introduced onto the market in 1986 by Rhone-Poulenc, which is now part of Sanofi-Aventis, the largest world-wide pharmaceutical manufacturer. The defining properties of this class of agents is a pharmacological profile of high efficacy and low toxicity similar to that of the benzodiazepines but purportedly with a lower dependence profile than that associated with benzodiazepines. Zopiclone binds to sites on or closely linked to the benzodiazepine receptor complex, giving benzodiazepine-like hypnotic, anxiolytic, anticonvulsant and myorelaxant properties. Specifically, zopiclone acts in a competitive manner as a full agonist at the $GABA_A$ receptor complex, where it decreased the affinity of the receptors for the $GABA_A$ antagonist flumazenil without affecting the number of binding sites *(45)*. Although zopiclone and the benzodiazepines appear to bind to the same recognition site, enhancing the function of the $GABA_A$ receptor, differences in receptor function observed after binding suggest that zopiclone and the benzodiazepines interact with separate binding domains and/or induce different conformational changes in the $GABA_A$ receptor complex.

A. Routes of administration and dosage

In the 1980s, zopiclone was prescribed at 7.5 mg/dose per day to be taken orally 30–60 min before retiring to improve sleep, purportedly with minimal adverse effects. Doses > 7.5 mg were prescribed when indicated. No reduction of the dose was suggested for elderly patients. Clinical trials

at that time found minimal "next day" effects, but patients were warned of the possibility of impaired mental alertness and psychomotor skills and were advised to exercise caution. By the 1990s, enough evidence had accumulated of "hangover effects" that a dose of 3.75 mg/day was recommended for elderly patients, which could be increased if necessary to 7.5 mg/day if the patient did not respond to the lower dose. In patients with severe or persistent insomnia, 15 mg was recommended. A new recommendation for a dose of 3.75 mg/day was added for patients with hepatic impairment or severe renal insufficiency, in whom metabolism may be slowed.

As with all hypnotics, long-term, regular use of zopiclone is not recommended. The manufacturers state that the treatment duration should not exceed 4 weeks, while the general recommendation is that zopiclone should be used only intermittently. Nonetheless, many patients with chronic insomnia use zopiclone regularly for extended periods *(46)*.

Doses of up to 225 mg (30 tablets) were described in 20 cases of intentional zopiclone overdose. The effects included only mild drowsiness *(47)*.

Case studies in the literature describe instances in which higher doses were either prescribed or taken. A man was initially prescribed 7.5 mg once a day for insomnia, which was increased to 7.5 mg four times a day *(48)*. In other cases, individuals themselves increased their dose; one woman being treated for insomnia related to depression increased her dose to 22.5 mg/day, while a woman with bipolar affective disorder increased her dose to 7.5 mg/day four times per day *(48)*. In another case, a woman with a history of recurrent depressive disorder had been prescribed zopiclone in increasing doses for insomnia and for several months was taking up to nine tablets of 7.5 mg/day in three divided doses *(49)*. A review of clinical case reports of abuse or dependence indicated that some individuals took amounts that were 30–120 times greater than the recommended dose *(50)*. In a more recent study, Schifano et al. *(51)* cited reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions of doses of 450–2250 mg.

In a case study, a male intravenous drug user was reported to have crushed zopiclone tablets and subsequently injected them (dose unknown). The person reported relaxation followed by sleep. His use appears to have been intermittent and subject to availability, as several alternative drugs included temazepam, diazepam and dihydrocodeine *(52)*.

B. Pharmacokinetics

At the recommended oral dose of 7.5 mg, zopiclone is rapidly absorbed (> 95% is absorbed within 1 h; peak plasma concentration, 60–70 μg/L). Its bioavailability is 80%, suggesting no significant first-pass effect. Distribution to body tissues, including the CNS, breast milk, placenta and salivary glands, is rapid and extensive, with a volume of distribution of 100 L in healthy subjects. Binding to plasma proteins is 45%. Zopiclone undergoes extensive metabolism in the liver, most biotransformation pathways involving cytochrome P450-dependent monooxygenase enzymes. Oxidation, demethylation and oxidative decarboxylation are significant mechanisms of metabolism. The *N*-oxide derivative, which is less active than the parent compound, accounts for 11% of a dose, and the inactive derivative, *N*-desmethyl zopiclone, about 15% of a dose; 4–7% is excreted unchanged in the urine. About 50% of a dose undergoes oxidative decarboxylation, and the resulting inactive metabolic products are excreted via the lungs. Neither the drug nor its metabolites are detectable in plasma 48 h after administration. In most studies, the half-life was reported to be 3.5–6 h, although it may be up to 8 h in individuals with poor liver function and the elderly. In volunteers given several oral doses of zopiclone, the elimination half-life was 6.5 h (53). The half-life is not affected in people with poor kidney function. The elimination half-life of the active metabolite is similar to that of the parent drug. Plasma clearance of zopiclone is about 14 L/h in healthy subjects and is not affected by haemodialysis. The milk:plasma ratio in lactating women after a 7.5-mg dose is approximately 50%. Zopiclone administered intravenously undergoes biphasic elimination, with a half-life of 5 h *(54)*.

In humans, rats and dogs, zopiclone kinetics are similar in males and females *(54)*.

C. Pharmacodynamics

At a dose of 7.5 mg, zopiclone is efficacious in the treatment of insomnia in adults, including the elderly, who often experience insomnia *(55)*. It is at least as effective as other benzodiazepines in improving many sleep parameters, including in patients with chronic insomnia.

Because of its action at the benzodiazepine receptor complex, zopiclone has sedative, anxiolytic, anticonvulsant and myorelaxant properties similar to those of benzodiazepines in studies in experimental animals. Zopiclone is, however, less effective than benzodiazepines in treating anxiety, although it has shown anxiolytic activity in clinical trials in

patients with generalized anxiety disorder and insomnia. No studies on its anticonvulsant or myorelaxant properties in humans were identified.

At medically prescribed doses, people with insomnia experience some deterioration of psychomotor function 1–2 h after administration, which, however, subsides within 8–10 h. Co-administration of alcohol and 7.5 mg zopiclone has an additive effect on impairment of psychomotor function after 1.5 h, which is negligible after 8 h. Other studies showed impaired driving skills the day after a dose of 7.5 mg zopiclone in people with insomnia and residual psychomotor impairment in healthy volunteers who received zopiclone at 7.5 mg/day. In a review of 16 psychometric studies in healthy volunteers and insomniac patients given the standard dose of 7.5 mg/day, no residual effects were reported in most studies *(56)*. In those studies that did find effects, they were of modest magnitude and did not persist for > 12 h after dosage. This review, which concluded that "zopiclone possesses few if any residual effects of clinical relevance", was published in 1995 and states that "the studies reviewed failed to meet current methodological standards and may have left some important questions unanswered".

Both earlier and later studies showed that at medically prescribed doses zopiclone can cause slight immediate memory loss but little or no "morning after" amnesia *(41, 57, 58)*.

5. Toxicology

Plasma concentrations of zopiclone during therapeutic use are typically < 100 µg/L *(59)* but are frequently > 100 µg/L in drivers arrested for impaired driving and may exceed 1000 µg/L in acutely poisoned patients *(60)*. Post-mortem blood concentrations in victims of fatal acute overdose are usually in a range 400–3900 µg/L *(60)*.

Like other benzodiazepine receptor agonists, zopiclone is generally not the only drug present in poisoning deaths, and, although it may contribute, it is generally not the causal agent. Fatalities have, however, occurred (described below) when the dose is high enough and in vulnerable populations.

In a monitoring study of prescription events in 13 177 patients, 20 cases of intentional zopiclone overdose were reported. The highest recorded dose was 225 mg (30 tablets). The effects included only mild drowsiness *(47)*. In early case reports, the estimated maximum dose ingested during a

suicidal overdose death was 420 mg, combined with heavy alcohol use *(61)*, and 450 mg in a case complicated by concomitant use of diazepam *(62)*. In a severely debilitated elderly man, 90 mg zopiclone resulted in suicidal death *(63)*. The ingested dose was not stated in two other cases, one of which was complicated by concomitant alcohol use *(64)*.

In an overview of fatalities due to overdose conducted in England and Scotland for the period 1983–1999, information was collected on fatal poisonings due to use of a single anxiolytic or sedative drug *(65)*. A total of 23 deaths were attributed to zopiclone. The authors calculated a "fatal toxicity index", expressed as the number of deaths per million prescriptions for zopiclone, of 2.1, which was lower than those for flurazepam (20.5), flunitrazepam (10.8), temazepam (9.9), triazolam (4.7) and nitrazepam (3.6) but higher than those for loprazolam (1.6) and lormetazepam (1.4). A time-course analysis presented for zopiclone with this method of assessing toxicity indicated that the fatal toxicity index of zopiclone was similar to that of the benzodiazepines as a group (> 7) within the first few years of marketing. A study conducted in New Zealand of deaths attributable to sedatives during 2001 *(66)* found that, of 200 deaths due to poisoning, 39 involved sedatives, of which 12 involved zopiclone, ranking it as the sixth most common cause of poisoning in New Zealand in that year. The fatal toxicity index was lower than that observed in the United Kingdom but similar for zopiclone (1.04) and all benzodiazepines (0.59).

6. Adverse reactions in humans

Few adverse reactions were found in clinical trials of 7.5 mg/day zopiclone. The most frequent events are bitter taste, dry mouth and difficulty in rising in the morning (all < 4%) *(42)*. Nightmares, nausea and sleepiness have been reported in fewer than 1% of cases *(42)*. For example, in a post-marketing study of 20 513 patients with insomnia, 9.2% experienced at least one adverse event while receiving zopiclone at 3.75 mg/day (elderly patients, 10.5% of the study cohort) or 7.5 mg/day for 21 days. Adverse events were reported spontaneously by patients, rather than according to a checklist. They included a bitter taste (3.6%) difficulty in waking in the morning (1.3%), dry mouth (1.6%), sleepiness (0.5%), nightmares (0.5%) and nausea (0.5%) *(67)*. The results of other large trials are generally consistent *(44)*.

Isolated reports of adverse events after zopiclone overdose included atrioventricular block in a patient after voluntary ingestion of 127.5 mg *(42)* and coma after zopiclone overdose by a psychiatric patient who

was also receiving treatment with chlorpromazine, amitriptyline, trifluoperazine and procyclidine. The coma was successfully treated with flumazenil *(68)*.

Detrimental clinical effects (such as difficulty in waking, impaired daytime well-being and reduced morning coordination) may occur the morning after hypnotic treatment if the duration of clinical action extends beyond night-time (or the normal period of sleep). These effects are lower with short-acting benzodiazepines. The results of several investigations indicate that next-day impairment is similar or superior with zopiclone to the short-acting benzodiazepine triazolam *(44)*.

Adverse effects include a withdrawal syndrome even at a medically prescribed dose of 7.5 mg/day *(42)*. Withdrawal symptoms occurred 12–21 days after the last dose in healthy volunteers and included increased anxiety, morning discomfort and awake time and decreased sleep latency and quality. In patients with insomnia and generalized anxiety disorder, rebound anxiety was the most commonly reported symptom (< 1%). Nervousness and vertigo were also reported by a few subjects during zopiclone withdrawal. Most studies of zopiclone that included a withdrawal phase did not provide data on adverse events occurring during this period *(44)*.

In a study of over 500 000 people, patients treated with a Z-drug (zolpidem, zopiclone, zaleplon) concomitantly with prescription opiates were at significant risk of accidental overdose in comparison with patients who were taking prescription opiates only *(69)*.

VigiBase:
VigiBase is the WHO global database of individual case safety reports (ICSRs). An ICSR is an adverse event report for a suspected medicine or vaccine in an individual patient. As of September 2022, over 150 Member States and territories had contributed to the VigiBase. Given the nature of the database, VigiBase provides a statement of reservations and limitations to be considered. VigiBase was searched for ICSRs of drug abuse and dependence (with standardized MedDRA queries12) after use of zopiclone (as an active ingredient, generic name), and 1348 ICSRs were extracted between 1 January 2017 and 27 July 2022, of which 1030

[12] Standardized MedDRA queries (SMQs) facilitate retrieval of MedDRA-coded data. Over 100 SMQs have been created, including "Drug abuse, dependence". The definition can be found at https://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=20000101

(76%) were considered serious:13 death, 155 (11.5%); life-threatening, 75 (5.6%); caused or prolonged hospitalization, 644 (47.8%); disabling or incapacitating, 10 (0.7%); congenital anomaly or birth defect, 2 (0.1%); and other medically important conditions, 324 (24%). The outcomes were fatal in 162 (12.0%) of all cases. Most cases were reported by physicians (35%), health professionals other than physicians and pharmacists (35%) and pharmacists (20%).

Cases were in adults aged 18–44 (34%), 45–64 (24%), ≥ 65 (13%) or unknown (28%). Women accounted for 60% of all cases. Most cases occurred in France (48%), Sweden (26%), the United Kingdom (7%), Germany (6%), Canada (4%), Australia (1%), Japan (1%), Norway (1%) and < 1% in several other countries.

Frequently reported reactions included 406 (30%) cases of intentional overdose, 308 (23%) cases of drug dependence, 304 (23%) cases of toxicity to various agents, 204 (15%) cases of drug abuse, 126 (9%) cases of overdose, 122 (9%) cases of intentional product misuse, 67 (5%) cases of prescription form tampering, 39 cases (3%) of drug use disorder, 28 cases of intentional product use or misue (2%), 25 cases (2%) of accidental overdose, 20 cases (2%) of dependence and 102 (7.4%) cases of miscellaneous origin.

Cases were co-reported with the following MedDRA terms14 at ≥ 2%: intentional self-injury, 259 (19.2%); somnolence, 168 (12.5%); suicide attempt, 79 (5.9%); fatigue, 71 (5.3%); depressed level of consciousness, 66 (4.9%); coma 57 (4.2%); loss of consciousness, 49 (3.6%); hypotension, 46 (3.4%); tachycardia, 43 (3.2%); withdrawal syndrome, 40 (3.0%); drug ineffective, 38 (2.8%); completed suicide, 34 (2.5%); confusional state, 34 (2.5%); drug interaction, 33 (2.4%).

The 10 drugs as either suspected or concomitant were: propiomazine, 192 (14%); oxazepam, 170 (13%); diazepam, 152 (11%); promethazine, 142 (11%); alprazolam, 123 (9%); alimemazine, 90 (7%); tramadol, 84 (6%); ethanol, 80 (6%); paracetamol, 78 (6%); and pregabalin, 76 (6%).

[13] A serious adverse event is any event that: is fatal, is life-threatening, is permanently or significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly, or requires intervention to prevent permanent impairment or damage *(70)*.

[14] MedDRA is clinically validated international medical terminology used by regulatory authorities throughout the lifecycle of a drug.

The large number of cases in France is a concern. It is probably related to a requirement instituted in April 2017 that prescriptions for the Z-drug zolpidem be obtained on tamper-resistant, secure forms, similar to those used for narcotics *(71)*. A time-series analysis of data acquired from the French national health-care system in 2018 showed a sharp decrease in prescriptions of zolpidem and a concomitant increase in prescription of zopiclone *(72)*.

7. Dependence potential

A. Studies in experimental animals

Zopiclone suppressed barbital withdrawal signs in rhesus monkeys, and discontinuation of zopiclone elicited a withdrawal syndrome in crab-eating monkeys treated with the drug for several weeks *(73)*.

Zopiclone has been tested in two models of physical dependence in mice. The results in a model based on measurement of convulsant seizures suggested that it did not cause physical dependence: Zopiclone did not modify the sensitivity of the GABA receptor complex to the partial inverse agonist FG 7142 after withdrawal *(74)*. In the other model, zopiclone did cause physical dependence, and administration of the antagonist, flumazenil, precipitated withdrawal as expressed in reduced electroshock-induced seizure thresholds in animals treated with a high dose for 3 days *(75)*. In an attempt to understand the discrepant results, the two sets of experiments are described in more detail below.

A model of a purported index of physical dependence was used to test whether zopiclone could cause dependence on the basis of the finding that chronic treatment in mice with the benzodiazepine flurazepam or midazolam enhanced their sensitivity to the proconvulsant effect of the partial inverse agonist FG 7142 after withdrawal of these compounds *(74)*. The compounds being investigated or their vehicle were injected intraperitoneally into mice (n = 10 per dose) four times daily for 3 days, and the animals were examined 2 days after the last dose of compound. The compounds were administered at doses of 2, 4, 8, or 16 mg/kg (lorazepam and triazolam) and 4, 8, 16 or 40 mg/kg (diazepam and flunitrazepam); cyclopyrrolones were given at 4, 8, 16, 40, 80 or 400 mg/kg (zopiclone) and 4, 16, 40, 80 or 400 mg/kg (suriclone). The mice then received intraperitoneal injections of 40 mg/kg FG 7142. No convulsions were seen in the control (vehicle pretreated) mice or in mice treated with zopiclone or suriclone, whereas those treated with the benzodiazepines had seizures after administration of FG 7142.

Zopiclone caused physical dependence in the other model *(75)*, in which mice were injected subcutaneously twice a day with zopiclone at 150 mg (morning) and 300 mg (afternoon). A starting dose of 150 mg/kg per day was followed by 15 and 1.5 mg/kg per day in subsequent assays. Flumazenil (2.5 mg/kg) was given intravenously 24 h after the last dose, and the mice were tested 5 min later for electroshock seizure thresholds in an up–down titration method. Flumazenil-precipitated withdrawal was manifested by a lowering of the seizure threshold. This model was developed specifically to test the dependence potential of compounds with benzodiazepine agonist properties. The authors noted that the lowest effective dose of compounds with greater in-vivo affinity and intrinsic activity at benzodiazepine receptors, such as several of the benzodiazepine compounds and zopiclone, lowered the seizure threshold and that the effects were dose-related. In contrast, compounds with greater in-vivo affinity and intrinsic activity at benzodiazepine receptors such as zolpidem, the pyrazolopyridine tracazolate and the triazolopyridazine CL 218872 did not cause physical dependence by this criterion.

In a study of cross-tolerance to and dependence on various compounds, rats were made dependent on triazolam. Chronic triazolam treatment produced tolerance to the depressant effects of triazolam, lorazepam and zopiclone *(76)*.

B. Studies in humans

Only sporadic accounts of zopiclone dependence in humans were reported before 2019. These consisted mainly of single case reports, small numbers of participants or post hoc reports. A common finding was that a subset of people begin treatment with zopiclone as prescribed for sleep problems, then escalate the dose over time, either because the doses lose their efficacy, to reduce anxiety, in conjunction with substance abuse and psychiatric difficulties or a combination of these reasons *(77)*. After cessation of extreme doses, some people experienced withdrawal symptoms, including insomnia, craving, anxiety, tachycardia, tremor and occasional seizures. "Doctor shopping" to obtain more drug is common, and widespread purchase of excessive amounts has been reported *(77)*.

An early, short (4-week) clinical trial did not address the development of tolerance to the sleep-inducing effects of 7.5 mg oral zopiclone *(41)*. A later small 8-week trial showed that tolerance developed, while a second small 17-week trial did not. Rebound insomnia, which may indicate withdrawal, was observed after treatment in some of the trials. The general consensus

in the 1980s and 1990s was that zopiclone had no abuse potential, although further study was recommended *(41, 42, 44)*.

A study was conducted in 1983 of nine healthy male volunteers to examine the dependence liability of zopiclone. The participants were assigned in random sequence to treatment with 21 consecutive nightly oral doses of 7.5 mg zopiclone, followed by 7 nights of placebo (withdrawal period) or a 21-night treatment period with placebo, similarly followed by 7 nights of placebo. Discontinuation of zopiclone was associated with increased anxiety and lighter sleep on days 2 and 4 of withdrawal. Heart rate, systolic and diastolic blood pressure, hand tremor and measured variables in auditory-evoked electroencephalography were not significantly different from placebo during withdrawal from zopiclone. No other physical or mental symptoms were observed during zopiclone treatment. Eight participants reported subjective effects throughout the study, but only two were able to identify the period of active drug treatment correctly. The authors concluded that "similar changes occur with other hypnotic drugs of relatively low dependence liability" *(78)*.

Seven cases (total incidence, 0.05%) of possible dependence, none of which was confirmed, were reported during monitoring of prescription events in over 13 000 patients *(47)*. Forms were posted to physicians in England who prescribed zopiclone between March and July 1991 enquiring about events that had occurred in patients prescribed zopiclone. An event was defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction or any other complaint that was considered of sufficient importance to be entered in the patient's notes. The response rate was modest (55%).

In a review in 1999 of clinical trials of therapeutic doses of zopiclone, no significant rebound insomnia was found, and there were few withdrawal reactions. The authors concluded that the risk of dependence was insignificant, although abuse potential should be considered in people with a history of addiction or psychiatric illness *(58)*.

In a review of clinical case reports of abuse or dependence in 1966–2002, 22 cases were included *(50)*. The proportions of males and females were similar, and cases were reported in all age groups. Extreme doses were 30–120 times the recommended dose. Most patients had a history of substance use disorder and/or other psychiatric conditions.

8. Abuse potential

A. Studies in experimental animals

Monkeys self-administered zopiclone but not a control suspension given either intragastrically or intravenously *(73)*.

In a discriminative stimulus test in monkeys trained to discriminate the benzodiazepine, midazolam, zopiclone had midazolam-like discriminative stimulus effects that were antagonized by the $GABA_A$ antagonist flumazenil *(79)*.

In another study, rats were trained to discriminate a zopiclone-induced interoceptive stimulus (3.2 mg/kg intraperitoneally) from saline. The zopiclone discriminative stimulus could be generalized to the benzodiazepines diazepam (1.8 mg/kg), nitrazepam (10 mg/kg) and alprazolam (10 mg/kg) and was blocked by the benzodiazepine antagonist Ro 15-1788 (1 mg/kg) *(80)*.

In another study, rats were trained to discriminate a dose of 5 mg/kg of the $GABA_A$ agonist chlordiazepoxide from saline. The chlordiazepoxide cue was antagonized by the $GABA_A$ antagonist flumazepil and was generalized to a variety of anxiolytic and sedative drugs, including zopiclone *(81)*.

B. Studies in humans

Case reports from as early as 1995 that include subjective reports from patients suggest that zopiclone has abuse potential. One patient reported increased euphoria when zopiclone was combined with alcohol, and another reported that it induced a sense of drunkenness and well-being, also when used with alcohol *(52)*.

In 1999, a study in Norway *(82)* (only the abstract was available in English) showed that 60% of drivers suspected of driving under the influence of drugs had concentrations of zopiclone in their blood higher than therapeutic levels, indicating misuse. Most of the drivers also tested positive for illegal drugs, prescription drugs with abuse potential or alcohol.

Widespread purchase of excessive amounts of zopiclone, an indicator of abuse potential, has been reported. A cross-sectional study of claims data from the German health insurer Gmuender ErsatzKasse was conducted to examine use of the Z-drugs zopiclone and zolpidem *(83)* (only the

abstract was available in English). Between July and December 2004, 6959 individuals bought at least one pack of zolpidem or zopiclone, including 21% containing 90 daily doses or more. High usage, defined as at least 180 daily doses, was identified for 501 subjects (7%).

The reinforcing properties of zopiclone (3.75 mg) and triazolam (0.25 mg) were compared in 40 recently abstinent (but not in withdrawal) alcohol-dependent inpatient men in a double-blind cross-over study *(84)*. No difference in mood or in items in the Addiction Research Centre Inventory (a standardized questionnaire for assessing subjective effects of psychoactive drugs *(85)*) was observed, and neither drug induced significant side-effects. However, individuals preferred triazolam to zopiclone.

A study with a similar cross-over design conducted in recently abstinent (but not in withdrawal) alcohol-dependent men was designed to determine whether a dose of zopiclone or triazolam could substitute for a drink of alcohol *(86)*. Patients were given eight doses of 0.25 mg triazolam or 3.75 mg zopiclone for 2 days each, followed by a washout period, and instructed to take one tablet whenever they wanted alcohol. The tablets of zopiclone or triazolam differed in colour. Their preference for triazolam over zopiclone was nonsignificant, and there was no difference in subjective feelings of the intensity of the two drugs or in mood states. None of the volunteers developed a desire for zopiclone after withdrawal of the medication.

A latent class analysis was used to examine the database of a French regional health insurance organization to characterize zolpidem and zopiclone users in real-life situations and identify problem use *(87)*. Four clinical subtypes of users were identified for zolpidem: non-problematic users, users with associations with hypnotics/anxiolytics or with associated mental disorders, and problematic users. Problematic use was not identified in zopiclone users (n = 21 860).

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

Zopiclone is widely prescribed and is marketed in at least 39 countries (see section 11).

Zopiclone is prescribed to patients with chronic insomnia to shorten sleep latency, decrease the frequency of waking and improve the duration and

quality of sleep. It was also shown to be effective in aiding sleep the night before surgery *(88)*.

The sedative efficacy of zopiclone was found to be at least as good as that of the long-acting benzodiazepines nitrazepam and flunitrazepam, the intermediate-acting benzodiazepine temazepam and the short-acting benzodiazepines triazolam and midazolam *(44)*.

Louzada et al. *(89)* conducted a systematic review to compare the efficacy and safety of zopiclone to treat sleep disorders in older adults with those of other sedative-hypnotics, placebo and non-pharmacological interventions. The study was conducted according to PRISMA guidelines, and its methodological quality was assessed with the "Risk of bias" tool in the Cochrane Reviewers' Handbook. The search resulted in 12 randomized, placebo-controlled clinical trials, two open studies and two observational reports. Overall, the studies suggested that zopiclone treatment in elderly people is effective in treating insomnia by reducing sleep latency, nocturnal waking and wake time after sleep onset while increasing total sleep time, with probable effects on sleep architecture. Zopiclone was found to be reasonably well tolerated, to have few adverse effects with a non-severe impact on psychomotor or cognitive performance and to cause no major harm to overall well-being and daily living ability. The quality of most of the studies was, however, classified as low or unclear. The authors concluded that, although the studies indicate benefits of zopiclone use, high-quality trials are required on its long-term effects, tolerability and safety in the treatment of older adults.

A study of the use of zopiclone in Australia comprised almost 2 million people who had attended one of 404 Australian general practices at least three times in 2 consecutive years between 2011 and 2018. In both years, the rates of prescription of any Z-drug were lower (4.4% and 3.5%) than those for all benzodiazepines (56.6% and 41.8%) per 1000 consultations. Zopiclone prescription increased from 5.0% to 22.6% between 2011 and 2018. Repeat prescriptions for zopiclone that exceeded recommended doses increased by 31.4% during the period *(90)*.

A study in Finland included all 408 527 legal purchases of benzodiazepines and Z-drugs between 2006 and 2014 from the Finnish Social Insurance Institution. Sedative use was defined as one or more purchases in 1 year; long-term use was defined as purchase of at least 180 daily doses and two or more separate purchases in 1 year; high-dose use was defined as

purchase of at least 1000 daily doses on at least two separate occasions in 1 year. By 2014, 9.3% of the Finnish adult population used sedatives, 3.6% were long-term users, and 0.3% were high-dose users. For zopiclone, use, long-term use and high-dose use were 4.1%, 1.8% and 0.6% respectively. Overall, use of most of the benzodiazepines and Z-drugs, including zopiclone, decreased over the course of the study. Nonetheless, in each year, zopiclone was the most frequently used hypnotic substance, despite the decrease in its use. Although long-term use of any sedative is not recommended, zopiclone use persisted for many years after initial use: 29% at 3 years, 15% at 5 years and 11% at 9 years *(91)*.

10. Listing on the WHO Model Lists of Essential Medicines

Zopiclone is not listed on the 22nd WHO Model List of Essential Medicines or the 8th Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Zopiclone is marketed in at least 39 countries (2):

Zopiclon Actavis, PUREN Pharma, Germany

Zopiclon AL Aliud, Pharma, Germany

Zopiclon Apotex, Apotex Nederland, Netherlands

Zopiclon Aristo, Aristo Pharma, Germany

Zopiclon Aurobindo, Aurobindo, Netherlands

Zopiclon axcount, Axcount, Germany

Zopiclon CF, Centrafarm, Netherlands

Zopiclon Focus, Focus, Netherlands

Zopiclon Genthon, Genthon, Netherlands

Zopiclon Heumann, Heumann, Germany

Zopiclon Hexal, Hexal, Germany

Zopiclon Jubilant, Jubilant, Netherlands

Zopiclon Mylan, Mylan, Netherlands

Zopiclon PCH, Pharmachemie, Netherlands

Zopiclon Sandoz, Hexal, Germany; Sandoz, Netherlands

Zopiclon Stada, STADA, Germany; STADA Nordic, Denmark; STADA Nordic, Sweden

Zopiclon Synthon, Synthon, Netherlands

Zopiclon Teva, Teva Nederland, Netherlands

Zopiclona, Humax, Colombia; Recipe, Colombia

Zopiclona Cevallos, Cevallos, Argentina

Zopiclona Genfar, Genfar SA, Costa Rica; Genfar S.A., Guatemala; Genfar S.A., Honduras; Genfar SA, Panama

Zopiclona Interpharma, Interpharma, Chile

Zopiclona La Santé, La Santé, Colombia

Zopiclona MK, MK, Colombia

Zopiclona Qualigen, Qualigen, Spain

Zopiclon-CT, AbZ-Pharma, Germany

Zopiclone Actavis UK, United Kingdom; Crescent, United Kingdom; Flamingo Pharma, United Kingdom; Generics UK, United Kingdom; Kent Pharmaceuticals, United Kingdom; Milpharm, United Kingdom; Sawai Seiyaku, Japan; Tatsumi Yakuhin, Japan; Towa Yakuhin, Japan

Zopiclone Actavis, Actavis, Denmark; Actavis, Norway; Actavis, Sweden; Actavis Group, Iceland; Teva, New Zealand

Zopiclone Alter, Alter, France

Zopiclone Aristo, Aristo, United Kingdom

Zopiclone Arrow, Arrow, France

Zopiclone Biogaran, Biogaran, France

Zopiclone Cristers, Cristers, France

Zopiclone EG, EG, Italy; EG Labo, France; Eurogenerics, Belgium

Zopiclone EG-7.5, Eurogenerics, Luxembourg

Zopiclone Eva, Eva, Egypt

Zopiclone GH, Generic Health, Australia

Zopiclone Jubilant, Jubilant, Denmark; Medical Valley, Sweden

Zopiclone Mylan, Mylan, Belgium; Mylan, France

Zopiclone Orion, Orion Pharma, Sweden

Zopiclone Ranbaxy, Ranbaxy, France

Zopiclone Sandoz, Sandoz, France

Zopiclone Sanis Health, Sanis Health, Canada

Zopiclone Sivem, Sivem Pharmaceuticals, Canada

Zopiclone Synthon, Synthon, Singapore

Zopiclone Teva, Teva Pharma Belgium, Belgium

Zopiclone Teva Sante, Teva Santé, France

Zopiclone Tianping, Tianping, China

Zopiclone Zentiva, Sanofi-Aventis, France

Zopiclone Zentiva 7.5mg, Helvepharm, Switzerland

Zopiclone Zydus, Zydus, France

Zopiclon-neuraxpharm 3,75mg, neuraxpharm Arzneimittel, Germany

Zopiclon-neuraxpharm 7,5mg, neuraxpharm Arzneimittel, Germany

Zopiclon-ratiopharm, ratiopharm, Germany; Ratiopharm GmbH, Netherlands

Zopiclon-Takeda, Takeda, Bulgaria

Zopicon, Intas, India

Zopigen, Xixia, South Africa

Zopigen 7.5 mg, Generics, Hungary

Zopiklon, Mylan, Norway

Zopiklon Mylan, Mylan, Iceland; Mylan, Norway; Mylan, Sweden

Zopiklon Pilum, Pilum Pharma, Sweden

Zopinox, Orion Pharma, Finland

Zopistad 7.5, Stada-VN JV, Viet Nam

Zopitidin 7.5 mg, Vitabalans, Hungary

Zopitin, Vitabalans, Czechia; Vitabalans, Estonia; Vitabalans, Lithuania; Vitabalans, Latvia; Vitabalans, Norway; Vitabalans, Slovakia; Vitabalans Oy, Poland

Zopitran, Alembic, India

Zopivane, Cipla Medpro, South Africa

Zosleep-Humanity, Celogen, Georgia

12. Industrial use

There does not appear to be any industrial use for zopiclone.

13. Non-medical use, abuse and dependence

In the early 1990s, there was some indication of voluntary non-medical use, abuse and physical dependence on zopiclone. In their review, Wadsworth and McTavish *(42)* reported a case review that included

239 cases of voluntary overdose in which CNS depression was the most frequently reported event (abstract not available). Other reported adverse effects of overdose included hyperkalaemia, hyperglycaemia and slight hyperbilirubinaemia. Isolated reports of physical dependence described symptoms of anxiety *(92)* and convulsions *(93)* during withdrawal from zopiclone at doses up to 90 mg/day in patients with a history of substance abuse. In a case study in 1991, recurrence of physical and psychological symptoms of craving for opioids was reported after ingestion of a single dose of 7.5 mg zopiclone by a patient who had withdrawn from the opioid pethidine 12 months previously. The craving led to a full narcotic relapse. The patient was a medical practitioner with insight into the significance of this event *(94)*.

Early reports of non-medical use were substantiated later. Bannan et al. *(95)* examined the prevalence of non-medical use of zopiclone (and other drugs) in 158 clients attending a methadone maintenance programme in Dublin, Ireland. Thirty-seven (23%) clients tested positive for zopiclone. Re-testing at 4–5 months indicated persistent non-medical use of zopiclone in 17%. Benzodiazepines were the most popular drug used concomitantly, followed by heroin and other opiates. None of the clients had injected zopiclone, although the majority had injected other drugs.

Zopiclone is readily available without prescription on the Internet. Ho et al. conducted an internet snapshot survey with the methods of the European Monitoring Centre for Drugs and Drug Addiction *(96)*. Thirty-seven websites that sold zopiclone tablets in quantities of up to 2000 daily doses were identified. Most (24) provided information or warnings about dosage. A prescription for purchase was not required on 22 of the websites, 14 did not mention whether a prescription was necessary, and 1 stated that a prescription was necessary.

Schifano et al. *(97)* examined reports on Z-drugs to the European Medicines Agency Database of Suspected Adverse Drug Reactions, providing systematic data for identification and analysis of zopiclone misuse, abuse, dependence and withdrawal. Of the total number of ADRs, 9283 (14%) were related to zopiclone misuse, abuse, dependence or withdrawal. Most of those related to zopiclone were reported by physicians in countries outside the European Economic Area (45.8%); pharmaceutical companies were the usual reporting agencies (51.4%). The most common ADRs were intentional overdose (30%), overdose (23%) and drug use disorder (23%). The majority of ADRs were found in women.

Of these cases, 24% involved only zopiclone, 21% involved concomitant use of benzodiazepines, 15% antidepressants, 11% antipsychotics and 3% opiates or opioids. A few cases included use of other drugs (cannabis, 12; cocaine, 6; and methamphetamine, 1). Suicidal behaviour was reported in 27% of the cases. When doses were reported, they were > 15 mg in 577 cases (360 individuals), including 205 ADRs (120 cases) in which the dose ingested was 450–2250 mg.

Several online forums were consulted for information on the misuse, abuse and dependence potential of zopiclone.

Bluelight is a web forum and research portal dedicated to harm reduction in drug use for people aged ≥ 13 years. As of May 2022, it claimed over 455 000 registered users. Between April 2020 and July 2022 there were only three threads (conversations) on zopiclone *(98)*, which involved only a few commenters. Most used it medicinally for sleep, although a few used it at high doses (~ 30 mg) to hallucinate, in combination with other drugs. The commenters cautioned others not to stop zopiclone abruptly and offered titrating schedules. Some comments described tolerance, withdrawal symptoms and rebound insomnia after daily use for as little as 2 weeks. Several commenters mentioned the bitter taste, and some provided antidotes.

Erowid is a publicly available Internet resource on psychoactive plants and chemicals *(99)*. Anyone can submit a report; however, reports are reviewed and are required to be descriptive, informative and written at a level of at least 8th grade (13–14 years). Over 2 million people use Erowid every month to post reports of their experience with a drug, including whether they combined it with other drugs. Between 1995 and 2022, there were 43 reports on zopiclone, in the following categories: general, 6; first use, 5; combination with other psychoactive substances, 19; experiences, 3; addiction, 3; and medical use to sleep, 10. Most of the reports are from 2005–2010. In contrast, 334 and 426 reports included the search terms "caffeine" and "heroin", respectively, during the same period.

Reddit is the largest Internet forum on which people discuss and comment and provide news and information on drugs *(100)*. Zopiclone has its own online forum (i.e., "subreddit"); however, the only posts are by the advertiser, Zopic.co.uk., an online pharmacy that purportedly fills prescriptions for sleep medications, including zopiclone. Zopiclone is mentioned in a few other forums, most discussions centering on its

medical use for insomnia; others include how to avoid withdrawal and the optimal dose for sleep. About 10% of the comments are on non-medical use, and about 20% of the comments are from the advertiser, Zopic.co.uk.

Drugs-forum.com is a forum for discussion of all aspects of medical and recreational drug use *(101)*. As of 26 July 2022, there were 1.7 million contributions and 285 000 members. A keyword search on zopiclone for 26 July 2021–26 July 2022 resulted in 18 zopiclone-related comments (withdrawal, 6; sleep, 4; dependence, 3; tolerance, 0; dose, 3; addiction, 2; weaning, 0; titrating, 0), whereas a search on caffeine and heroin during the same period resulted in 27 and 140 comments, respectively.

Thus, although zopiclone is widely prescribed throughout the world, there has been very little discussion on online forums on its medical or non-medical use.

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

A meta-analysis was conducted in 2005 of studies of the risks and benefits of sedative hypnotics in older people with insomnia. The objective was to quantify and compare potential benefits (subjective reports of sleep variables) and risks (adverse events and morning-after psychomotor impairment) of short-term treatment with sedative hypnotics. Statistically significant improvements in sleep were found with sedative use, but the effect was small. The risk of adverse events was statistically significantly increased and potentially clinically relevant in older people at risk of falls and cognitive impairment. The authors concluded that the ratio of benefit:risk is small, particularly if the patient has additional risk factors for cognitive or psychomotor adverse events *(102)*. The analysis did not distinguish among different sedatives however, and is included here only to provide historical background.

Nishtala and Chyou *(103)* conducted a population-based, case-crossover study in New Zealand of the use of zopiclone and the risk of fractures in 74,787 elderly people with a first fracture between 1 January 2005 and 31 December 2015. The risk of fracture was found to be significantly higher (RR = 1.45) with use of zopiclone than with non-use and remained significant after adjustment for concomitant use of α-blockers, antipsychotics, β blockers, benzodiazepines and tricyclic antidepressants. The effect increased with age.

A systematic review and meta-analysis of the risk of vehicle accidents associated with use of psychoactive drugs, which included zopiclone, found that zopiclone increased the risks of an accident involving only property damage, a fatal accident and an accident involving only injury *(104)*. These findings were substantiated in a descriptive review of studies on driving and zopiclone use and studies on psychomotor performance in general *(56)*. The author concluded that patients who took zopiclone have over twice the risk of motor vehicle collisions than unexposed drivers and that psychomotor impairment, falls and hip fractures are more likely, especially at higher (15 mg) doses and when zopiclone is mixed with other psychoactive substances, including alcohol.

15. Licit production, consumption and international trade

Zopiclone is widely used throughout the world as a sedative hypnotic. A search identified 119 trade names (see section 1.D), and there are probably more. Zopiclone is manufactured by 70–100 pharmaceutical companies (see section 11).

16. Illicit manufacture and traffic and related information

The Medicines and Healthcare Products Regulatory Agency in the United Kingdom estimated that between 2013 and 2016 up to £200 million worth of prescription medicines, including diazepam and zopiclone, had been diverted to the criminal market for supply *(105)*.

Only one incidence of suspicious shipment of, trafficking in or manufacture or production of zopiclone before 2006 has been reported to IONICS, in which zopiclone was diverted to illicit channels and abused in Argentina *(106)*.

In a report to WHO prepared by the Organe international de contrôle des stupéfiants (International Agency for Drug Control) of the International Narcotics Control Board, zopiclone was identified as a significant concern to Member States throughout the world: 599 incidents involving zopiclone between January 2020 and March 2022 were communicated through IONICS by 11 governments in Africa, East and South-East Asia, West Asia, Oceania, West and Central Europe and North America. The previous report included 58 incidents between January 2019 and March 2021 communicated by eight governments in West Asia, Oceania and West and Central Europe, indicating the spread of zopiclone to other regions of the world.

The 24 countries or territories of origin of the incidents between January 2020 and March 2022 were in nine regions (Africa, East and South-East Asia, South Asia, West Asia, Oceania, West and Central Europe, North America, Central America and the Caribbean, and South America). The previous report (January 2019–March 2021) identified eight countries in five regions (Africa, South Asia, Oceania, Southeast Europe, and West and Central Europe) as the origins of incidents.

Zopiclone was reported through IONICS for the first time in 2020. The number of communicated incidents involving the substance increased from 36 incidents in 2020 to 537 in 2021.

17. Current international controls and their impact

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

18. Current and past national controls

See Annex 1.

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

No other matters were identified.

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

ADB-BUTINACA

Of the 77 countries that agreed to provide data, 34 had information on ADB-BUTINACA (Table A1).

Table A1. Numbers of countries providing information on ADB-BUTINACA

Region	No. of countries that had no information	No. of countries that had information
African	3	1
Americas	6	3
South-East Asia	3	0
European	9	21
Eastern Mediterranean	5	3
Western Pacific	3	6
Total	29	34

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for ADB-BUTINACA. No countries reported that ADB-BUTINACA was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). None reported use for industrial purposes.

Epidemiology of non-medical use

Twenty countries (14 European, 2 Americas, 2 Western Pacific, 1 African and 1 Eastern Mediterranean) reported evidence from law enforcement and health professionals of the use of ADB-BUTINACA for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived primarily from data on seizures and customs (n=15).

Routes of administration and formulations

The most common reported route of administration was smoking, followed by oral and inhalation (Table A2).

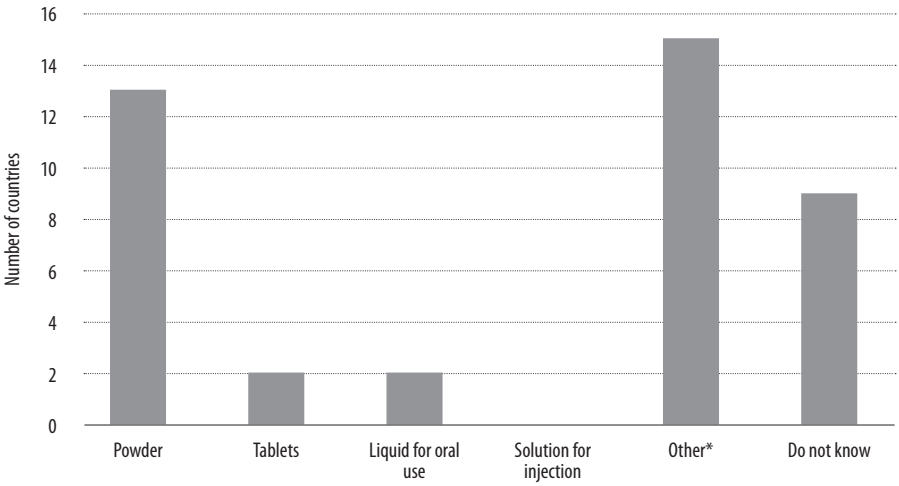
Table A2. Reported routes of ADB-BUTINACA administration

Route of administration	No. of countries
Smoking	10
Oral	6
Inhalation	2
Sniffing	0
Injection	0
Other[a]	1
Do not know	6

[a] Vaping (n=1)

The most common known formulations of ADB-BUTINACA reported were as a powder and as part of a herbal mixture (Fig. A1).

Fig. A1. Formulations of ADB-BUTINACA

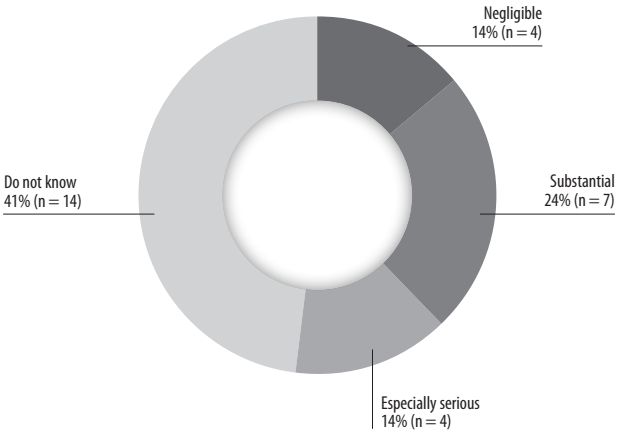


*Other formulations most commonly referred to were herbal mixture or plant material (n=8) and e-liquid (n=2). One member state also referenced 'impregnated on paper' whilst another member state mentioned 'unintentional smoking of cannabis laced with ADB-BUTINACA'.

Perceived negative health impact

Ten countries (5 European, 2 Americas, 2 Eastern Mediterranean, 1 Western Pacific) reported that the negative health impact of non-medical consumption of ADB-BUTINACA was "especially serious" or "substantial" (Fig. A2). Two countries reference that ADB-BUTINACA has been involved in serious intoxications. One member state referenced that ADB-BUTINACA has been identified in a few low THC products sold as cannabis. One member state referenced that ADB-BUTINACA has been identified in 202 samples taken from persons dependent on drugs.

Fig. A2. Negative health impacts of non-medical consumption of ADB-BUTINACA



Emergency department visits

Six countries (3 European, 1 African, 1 Americas, 1 Western Pacific) were aware of emergency department visits related to ADB-BUTINACA. Two countries reported side-effects to include hallucinations, unconsciousness, altered mental state and excitement. One country in Europe noted 15 intoxications between 2021 and 2022 that were mostly reported in combination with other substances.

Deaths

Four countries (2 European, 1 Americas, 1 Western Pacific) reported a total of 16 ADB-BUTINACA related deaths in 2021. Four countries (2 European, 1 Americas, 1 Western Pacific) reported a total of 13 ADB-BUTINACA deaths in 2021 that involved other substances. Two countries (1 European, 1 Western Pacific) reported three deaths in 2021 in which ADB-BUTINACA was the only substance involved.

Drug dependence

Two countries (1 European region, 1 Eastern Mediterranean) reported that people presented for treatment of drug dependence in their country due to use of ADB-BUTINACA.

Current national controls

Twenty-six countries (16 European, 4 Western Pacific, 3 Americas, 2 Eastern Mediterranean, 1 African) responded that the availability of ADB-BUTINACA was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A3 shows the main reported activities for ADB-BUTINACA.

Table A3. Reported activities involving ADB-BUTINACA for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	12
Smuggling (from other countries)	8
Internet sales (other or location of sellers and website unknown)	5
Direct sales	4
Internet sales (from abroad to buyers in respondent's country)	4
Internet sales (seller or website located in respondent's country)	3
Manufacture of the substance by chemical synthesis	2
Production of consumer products containing the substance	2
Manufacture of the substance by extraction from other products	1
Diversion	1
Do not know	14
Other[a]	1

[a] Includes "Several seizures".

Seizures

Eleven countries (9 European, 1 Western Pacific, 1 Americas) reported seizures in 2022. The number of seizures per country ranged from 1 to 295 and the amounts seized ranged from 0.28 g to 7.4 kg (Table A4). One European country also reported six tablets containing ADB-BUTINACA. Sixteen countries (14 European, 1 Western Pacific, 1 Americas) reported seizures in 2021. The number of seizures per country ranged from 1 to 4418 and the amounts seized from 1 g to 81 kg. One European country reported one seizure of 1960 ml of ADB-BUTINACA. Six countries (4 European, 1 Western Pacific, 1 Americas) reported seizures in 2020. The number of seizures per country ranged from 1 to 207 and the amounts seized from 12.99 g to 2.1 kg. One country (European) also reported one seizure of 528 ml in 2022 and 3 seizures totalling 505 ml in 2021. One country (European) also reported six tablets containing ADB-BUTINACA in 2022 and one tablet in 2021.

Table A4. Reported seizures of ADB-BUTINACA

Year	No. of countries that reported seizures	No. of seizures
2022	11	787
2021	16	6092
2020	6	309

Twenty-two countries (18 European, 3 Western Pacific, 2 South-East Asia, 1 Eastern Mediterranean, 1 Americas) reported that they had the laboratory capacity to analyse ADB-BUTINACA.

Adinazolam

Of the 77 countries that agreed to provide data, 17 had information on adinazolam (Table A5).

Table A5. Numbers of countries providing information on adinazolam

Region	No. of countries that had no information	No. of countries that had information
African	2	1
Americas	7	2
South-East Asia	3	0
European	17	9
Eastern Mediterranean	7	0
Western Pacific	3	5
Total	39	17

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for adinazolam. No countries reported that a dinazolam was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). None reported use for industrial purposes.

Epidemiology of non-medical use

Seven countries (3 European, 2 Americas and 2 Western Pacific) reported evidence from law enforcement and health professionals of the use of adinazolam for non-medical purposes (outside the medical, industrial or scientific context).

Routes of administration and formulations

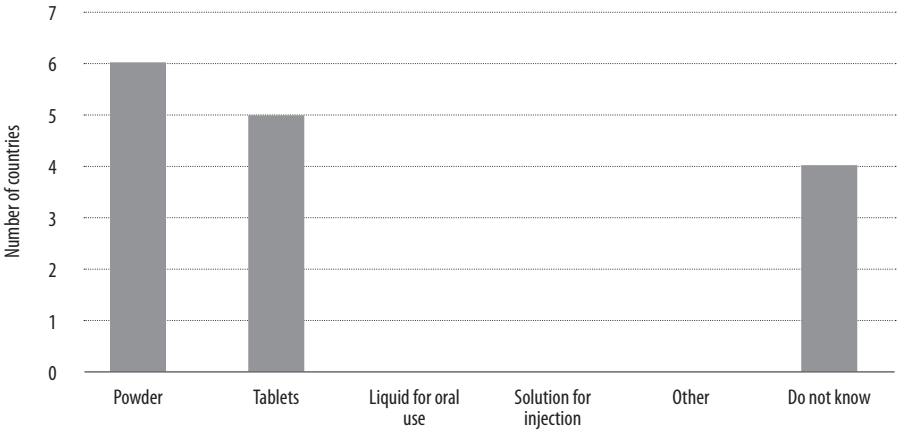
The only reported route of administration was oral (Table A6).

Table A6. Reported routes of adinazolam administration

Route of administration	No. of countries
Smoking	0
Oral	5
Inhalation	0
Sniffing	0
Injection	0
Other	0
Do not know	6

The most common known formulations of adinazolam reported were as a powder and as a tablet (Fig. A3).

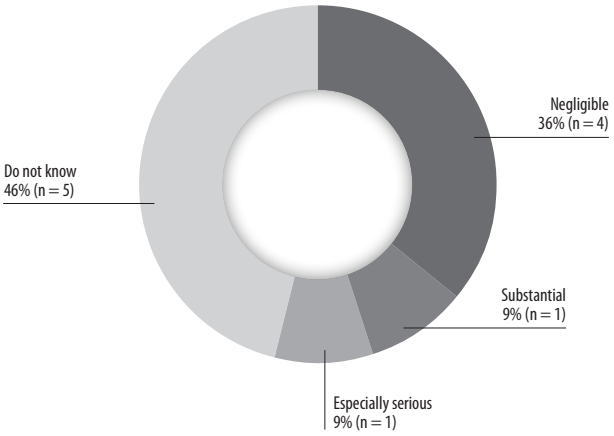
Fig. A3. Formulations of adinazolam



Perceived negative health impact

Two countries (1 European, 1 Americas) reported that the negative health impact of non-medical consumption of adinazolam was "especially serious" or "substantial" (Fig. A4). One country (Americas) described adinazolam as generally abused for its sedative/hypnotic effects and has been identified in 42 toxicology cases (a death, non-fatal overdoses and driving under the influence) between 2020 and 2021.

Fig. A4. Negative health impacts of non-medical consumption of adinazolam



Emergency department visits

Two countries (1 European, 1 Americas) were aware of emergency department visits related to adinazolam.

Deaths

One country (Americas) reported a total of 1 adinazolam-related death that involved other substances between 2020 and 2022.

Drug dependence

No countries reported that people presented for treatment of drug dependence in their country due to use of adinazolam.

Current national controls

Nine countries (5 European, 3 Western Pacific, 1 Americas) responded that the availability of a dinazolam was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A7 shows the main reported activities for adinazolam.

Table A7. Reported activities involving adinazolam for purposes other than medical, scientific or industrial use

Activity	No. of countries
Smuggling (from other countries)	3
Trafficking	3
Internet sales (other or location of sellers and website unknown)	3
Internet sales (from abroad to buyers in respondent's country)	1
Manufacture of the substance by chemical synthesis	1
Internet sales (seller or website located in respondent's country)	0
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion	0
Do not know	4
Othera	1

[a] Includes "Seizures".

Seizures

Three countries (2 European, 1 Americas) reported adinazolam seizures in 2022. The number of seizures per country ranged from 1 to 30 and the amounts seized ranged from 0.27 g to 725.3 g (Table A8). Five countries (4 European, 1 Americas) reported seizures in 2021. The number of seizures per country ranged from 1 to 87 and the amounts seized from 47.4 g to 735 g. One country (European) reported 197 tablets seized in 2021. Five countries (4 European, 1 Americas) reported adinazolam, seizures in 2020. The number of seizures per country ranged from 1 to 347 and the amounts seized from 804.52 g to 2719.5 g. One country (European) reported 481 tablets seized in 2020.

Table A8. Reported seizures of adinazolam

Year	No. of countries that reported seizures	No. of seizures
2022	3	122
2021	5	125
2020	5	380

Fourteen countries (8 European, 4 Western Pacific, 2 Americas) reported that they had the laboratory capacity to analyse adinazolam.

Bromazolam

Of the 77 countries that agreed to provide data, 23 had information on bromazolam (Table A9).

Table A9. Numbers of countries providing information on bromazolam

Region	No. of countries that had no information	No. of countries that had information
African	4	1
Americas	5	3
South-East Asia	3	0
European	13	13
Eastern Mediterranean	6	0
Western Pacific	4	5
Total	35	24

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for ADB-BUTINACA. No countries reported that bromazolam was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). None reported use for industrial purposes.

Epidemiology of non-medical use

Eleven countries (6 European, 3 Americas and 2 Western Pacific) reported evidence from health professionals and law enforcement of the use of bromazolam for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived primarily from data on seizures and toxicology reports (n=11).

Routes of administration and formulations

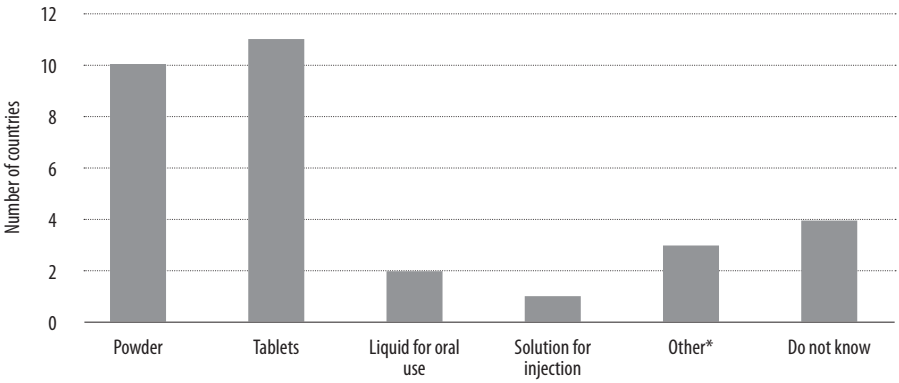
The most common reported route of administration was oral, followed by sniffing and injection (Table A10).

Table A10. Reported routes of bromazolam administration

Route of administration	No. of countries
Oral	11
Sniffing	1
Injection	1
Smoking	0
Inhalation	0
Other	0
Do not know	6

The most common known formulations of bromazolam reported were as a powder and as a tablet (Fig. A5).

Fig. A5. Formulations of bromazolam

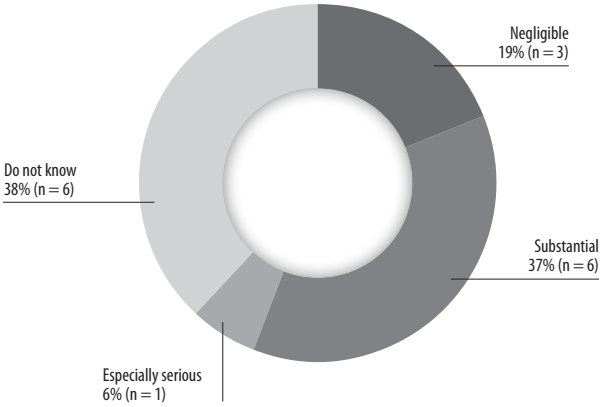


*Other formulations referred to were gummy bears (n=1) or a residue, rock like solid (n=1).

Perceived negative health impact

Seven countries (6 European, 2 Western Pacific, 1 Americas, 1 Eastern Mediterranean, 1 South-East Asia) reported that the negative health impact of non-medical consumption of bromazolam was "especially serious" or "substantial" (Fig. A6). Two countries (1 European, 1 Western Pacific) reported that bromazolam was a growing concern, and had been detected in counterfeit benzodiazepine tablets. An additional country (Americas) reported that it has been identified in at least 150 death investigations, and was commonly identified with other sedative/hypnotics.

Fig. A6. Negative health impacts of non-medical consumption of bromazolam



Emergency department visits

Three countries (3 European) were aware of emergency department visits related to bromazolam. One country in Europe described 43 emergency presentations by people who had consumed bromazolam with other substances, with a wide range of symptoms, hypertension, hypothermia, agitation, extreme agitation, cardiac arrest, psychosis, seizure, chest pain, arrhythmia, low consciousness. Another European country reported one case of severe acute intoxication in an emergency room with dysarthria and cognitive deficit. One African country reported vomiting, nausea and drowsiness.

Deaths

Four countries (2 Americas, 2 European) reported a total of 160 bromazolam-related deaths between 2020 and 2022. One country (Americas) reported one hundred and fifty-two deaths in 2022 in which it was unknown if other substances were involved.

Drug dependence

No countries reported that people presented for treatment of drug dependence in their country due to use of bromazolam.

Current national controls

Fourteen countries (9 European, 3 Western Pacific, 1 Americas) responded that the availability of bromazolam was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A11 shows the main reported activities involving bromazolam.

Table A11. Reported activities involving bromazolam for purposes other than medical, scientific or industrial use

Activity	No. of countries
Smuggling (from other countries)	7
Trafficking	6
Internet sales (from abroad to buyers in respondent's country)	3
Internet sales (other or location of sellers and website unknown)	3
Internet sales (seller or website located in respondent's country)	1
Manufacture of the substance by chemical synthesis	1
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion	0
Do not know	5
Other[a]	1

[a] Includes "Seizures".

Seizures

Eleven countries (3 European, 1 Western Pacific, 1 South-East Asia) reported seizures in 2022. The number of seizures per country ranged from 1 to 407 and the amounts seized ranged from 174.04 g to 5.1 kg. In addition, amounts seized in tablets ranged from 25 pills to 2275 pills (Table A12). One country (European) reported seizures of bromazolam as a liquid totalling 867 ml. Ten countries (8 European, 2 Americas) reported bromazolam seizures in 2021. The number of seizures per country ranged from 1 to 757 and the amounts seized from 33 g to 5.7 kg. In addition, amounts seized in tablets ranged from 9 pills to 207 pills. Nine countries (6 European, 1 African, 1 Americas, 1 Western Pacific) reported bromazolam seizures in 2020. The number of seizures per country ranged from 1 to 33 and the amounts seized from 0.9 g to 30.2 g. In addition, amounts seized in tablets ranged from 10 pills to 102 pills.

Table A12. Reported seizures of bromazolam

Year	No. of countries that reported seizures	No. of seizures
2022	11	607
2021	10	961
2020	9	59

Twenty countries (18 European, 3 Western Pacific, 2 South-East Asia, 1 Eastern Mediterranean, 1 Americas) reported that they had the laboratory capacity to analyse bromazolam.

Protonitazene

Of the 77 countries that agreed to provide data, 16 had information on protonitazene (Table A13).

Table A13. Numbers of countries providing information on protonitazene

Region	No. of countries that had no information	No. of countries that had information
African	2	1
Americas	6	2
South-East Asia	3	0
European	21	4
Eastern Mediterranean	6	0
Western Pacific	3	5
Total	41	16

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for protonitazene. No countries reported that protonitazene was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). No country reported use for industrial purposes.

Epidemiology of non-medical use

Five countries (3 European, 2 Americas) reported evidence of the use of protonitazene for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived primarily from data on seizures (n=4), with the last country further specifying "law enforcement encounters and medical examiner reports".

Routes of administration and formulations

The most commonly reported routes of administration were oral, sniffing and injection (Table A14).

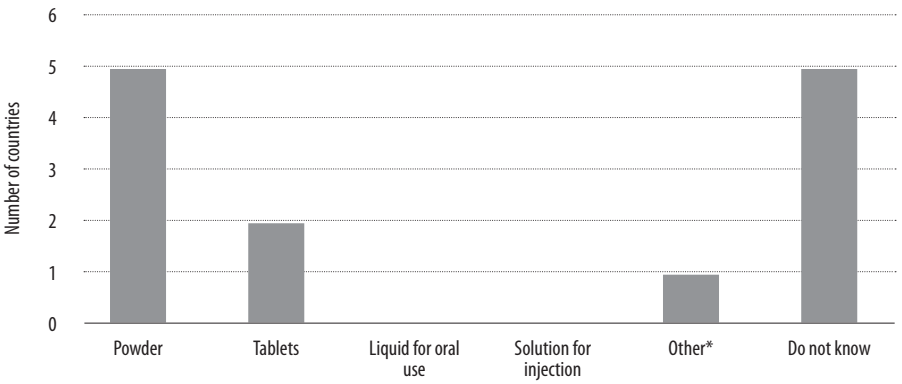
Table A14. Reported routes of protonitazene administration

Route of administration	No. of countries
Oral	4
Sniffing	2
Injection	2
Inhalation	1
Smoking	1
Other[a]	1
Do not know	6

[a] Nasal spray

The most common known formulations of protonitazene reported were as a powder and tablet (Fig. A7).

Fig. A7. Formulations of protonitazene

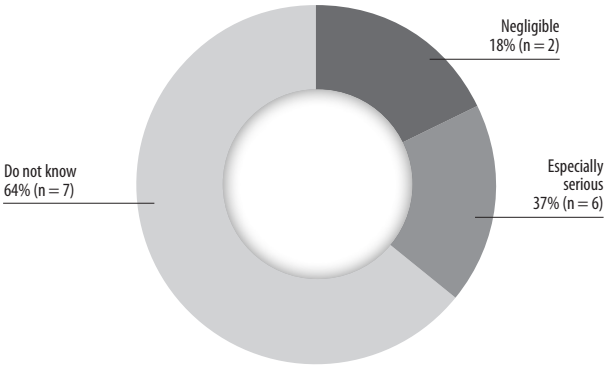


*One country mentioned "residue, syringe".

Perceived negative health impact

Two countries (1 European, 1 Americas) reported that the negative health impact of non-medical consumption of protonitazene was "especially serious" (Fig. A8). One country (European) reported their source of evidence as being from seizures, and one country (Americas) cited protonitazene "has been identified in postmortem and toxicology cases (driving under the influence)".

Fig. A8. Negative health impacts of non-medical consumption of protonitazene



Emergency department visits

No countries were aware of emergency department visits related to protonitazene.

Deaths

Three countries (1 African, 2 Americas) reported a total of 25 protonitazene-related deaths. One country (African) reported 1 death where protonitazene was the only substance involved, 3 where other substances were involved and 4 where it was unknown whether other substances were involved. One country (Americas) reported that in 2021 there was 1 death where protonitazene and other substances were involved and 9 where it was unknown whether other substances were involved. Another country (Americas) reported that in 2021 there were 9 deaths where protonitazene and other substances were involved.

Drug dependence

No countries were aware of people who presented for treatment of drug dependence in their country due to use of protonitazene.

Current national controls

Ten (6 European, 2 Western Pacific, 2 Americas) responded that the availability of protonitazene was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A15 shows the main reported activities for protonitazene.

Table A15. Reported activities involving protonitazene for purposes other than medical, scientific or industrial use

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

One country from the Western Pacific reported protonitazene being used for industrial or other non-medical/non-scientific purposes in their country, as a "material for synthesis of psychoactive drugs".

Seizures

Three countries (2 European, 1 Americas) reported seizures in 2022. The number of seizures per country ranged from 1 to 6 and the amounts seized ranged from 1.2 g to 989 g (Table A16). Two countries (1 European, 1 Americas) reported seizures in 2021. The number of seizures ranged from 1 to 21, and the amounts seized ranged from 1 g to 44 g.

Table A16. Reported seizures of protonitazene

Year	No. of countries that reported seizures	No. of seizures
2022	3	10
2021	2	22

Twelve countries (7 European, 3 Western Pacific, 2 Americas) reported that they had the laboratory capacity to analyse protonitazene.

Etazene

Of the 77 countries that agreed to provide data, 20 had information on etazene (Table A17).

Table A17. Numbers of countries providing information on etazene

Region	No. of countries that had no information	No. of countries that had information
African	2	1
Americas	6	2
South-East Asia	3	0
European	16	12
Eastern Mediterranean	6	0
Western Pacific	3	5
Total	36	20

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for etazene. No countries reported that etazene was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard).

Epidemiology of non-medical use

Five countries (3 European, 2 Americas) reported evidence of the use of etazene for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived from data on seizures/law enforcement encounters (n=5) and medical examiner reports/blood samples in cases of death (n=2).

Routes of administration and formulations

The most commonly reported routes of administration were oral, sniffing and injection (Table A18).

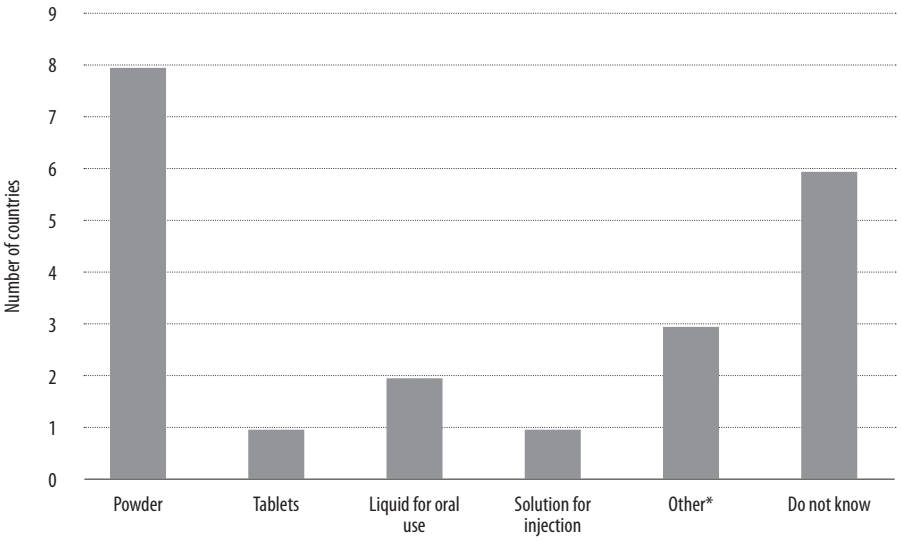
Table A18. Reported routes of etazene administration

Route of administration	No. of countries
Oral	3
Sniffing	3
Injection	3
Smoking	1
Inhalation	0
Other[a]	1
Do not know	10

[a] Nasal spray

The most common known formulation of etazene reported was as a powder (Fig. A9).

Fig. A9. Formulations of etazene

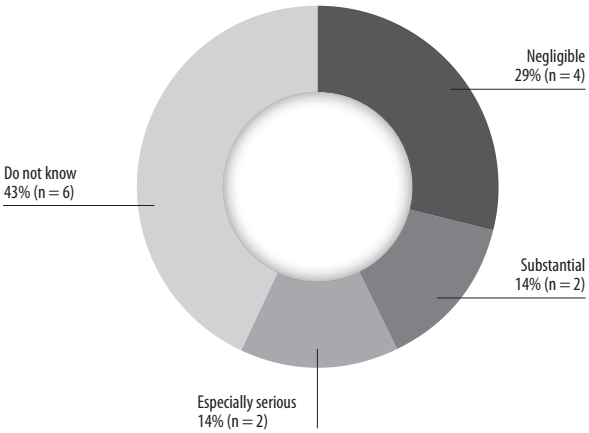


*Seizures of liquid. No information about if the liquid/solution was for oral administration/use or for injection, purple-red paste, residue, syringe, material, and herbal material.

Perceived negative health impact

Two countries (1 European, 1 Americas) reported that the negative health impact of non-medical consumption of etazene was "especially serious" (Fig. A10). Two countries (2 European) reported their source of evidence as being from seizures, two countries (1 European, 1 Americas) reported postmortem investigations, and one country (1 Americas) reported one of their sources as toxicology identification as a part of driving under the influence cases.

Fig. A10. Negative health impacts of non-medical consumption of etazene



Emergency department visits

No countries were aware of emergency department visits related to etazene.

Deaths

Four countries (2 Americas, 2 European) reported a total of 10 etazene-related deaths in 2021. Two countries (1 Americas, 1 European) respectively reported 6 and 2 deaths that involved etazene and other substances. Two countries (1 Americas, 1 European) both reported 1 death for their country where it was unknown if other substances were involved.

Drug dependence

No countries were aware of people who presented for treatment of drug dependence in their country due to use of etazene.

Current national controls

Fifteen (11 European, 2 Western Pacific, 2 Americas) responded that the availability of etazene was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A19 shows the main reported activities involving etazene.

Table A19. Reported activities involving etazene for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	5
Smuggling (from other countries)	3
Internet sales (other or location of sellers and website unknown)	2
Internet sales (seller or website located in respondent's country)	1
Internet sales (from abroad to buyers in respondent's country)	0
Manufacture of the substance by chemical synthesis	0
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	0
Do not know	7
Other	0

One country (Western Pacific) reported etazene being used for industrial or other non-medical/non-scientific purposes in their country, as a "material for synthesis of psychoactive drugs".

Seizures

Three countries (2 European, 1 Americas) reported etazene seizures in 2022. The number of seizures per country ranged from 1 to 2 and the amounts seized ranged from 1.5 g to 185 g (Table A20). Five countries (4 European, 1 Americas) reported etazene seizures in 2021. The number of seizures ranged from 1 to 53, and the amounts seized ranged from 0.5 g to 298 g. Five countries (4 European, 1 Americas) reported etazene seizures in 2020. The number of seizures ranged from 1 to 12, and the amounts seized ranged from 1 g to 302 g.

Table A20. Reported seizures of etazene

Year	No. of countries that reported seizures	No. of seizures
2022	3	4
2021	5	104
2020	5	25

Fifteen countries (10 European, 3 Western Pacific, 2 Americas) reported that they had the laboratory capacity to analyse etazene.

Etonitazepyne

Of the 77 countries that agreed to provide data, 19 had information on etonitazepyne (Table A21).

Table A21. Numbers of countries providing information on etonitazepyne

Region	No. of countries that had no information	No. of countries that had information
African	2	1
Americas	6	2
South-East Asia	3	0
European	17	10
Eastern Mediterranean	6	0
Western Pacific	3	5
Total	37	19

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for etonitazepyne. No countries reported that etonitazepyne was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard).

Epidemiology of non-medical use

Seven countries (4 European, 2 Americas, 1 Western Pacific) reported evidence of the use of etonitazepyne for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived from data on seizures/law enforcement encounters (n=5), medical examiner reports (n=1), and drug checking services (n=1).

Routes of administration and formulations

The most commonly reported route of administration was oral (Table A22).

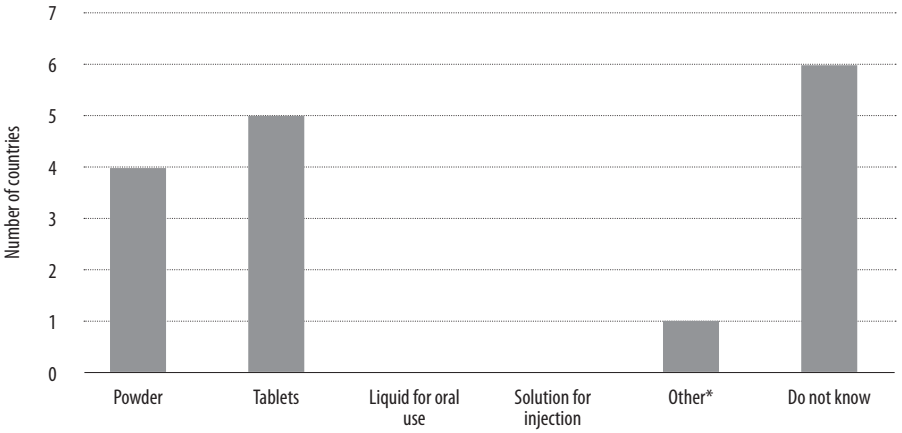
Table A22. Reported routes of etonitazepyne administration

Route of administration	No. of countries
Oral	5
Sniffing	3
Injection	2
Smoking	1
Inhalation	1
Other[a]	1
Do not know	7

[a] Vaping

The most common known formulation of etonitazepyne reported was as tablets or powder (Fig. A11).

Fig. A11. Formulations of etonitazepyne



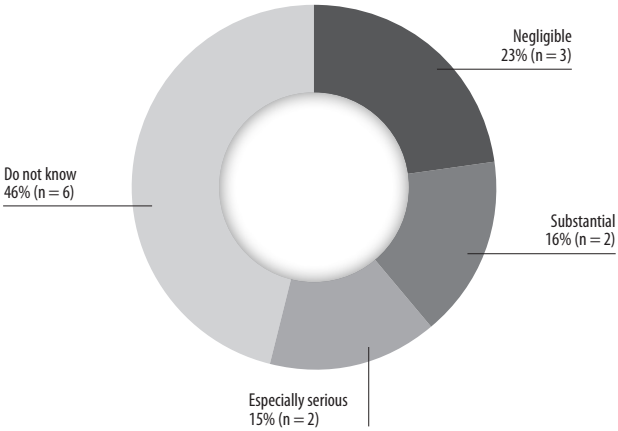
*Residue in a syringe of unknown formulation.

Perceived negative health impact

Two countries (1 European, 1 Americas) reported that the negative health impact of non-medical consumption of etonitazepyne was "especially serious" (Fig. A12). Two countries (2 European) reported their source of evidence as from seizures, one country (European) reported emergency department presentations and associated deaths, one country (Americas) reported evidence from toxicology

identification as a part of postmortem and driving under the influence cases, and one country (Western Pacific) reported etonitazepyne as being sold as counterfeit oxycodone tablets.

Fig. A12. Negative health impacts of non-medical consumption of etonitazepyne



Emergency department visits

One country (European) was aware of emergency department visits related to etonitazepyne. This country reported 3 patients in 2022 and 2 patients in 2021 who presented to the emergency department with etonitazepyne and other substances. Their symptoms included cardiac arrest, respiratory insufficiency, loss of consciousness, tachycardia, and respiratory distress.

Deaths

Three countries (1 African, 1 Americas, 1 European) reported a total of 29 etonitazepyne-related deaths for the most recent completed year data was available (i.e. 2021 for most countries). Two countries (1 African, 1 Americas) respectively reported 3 and 17 etonitazepyne-related deaths where other substances were involved. One country (African) reported 5 deaths where it was unknown whether other substances were involved.

Drug dependence

No countries were aware of people who presented for treatment of drug dependence in their country due to use of etonitazepyne.

Current national controls

Eleven (6 European, 3 Western Pacific, 2 Americas) responded that the availability of etonitazepyne was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A23 shows the main reported activities involving for etonitazepyne.

Table A23. Reported activities involving etonitazepyne for purposes other than medical, scientific or industrial use

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

One country (Western Pacific) reported etonitazepyne being used for industrial or other non-medical/non-scientific purposes in their country, as a "material for synthesis of psychoactive drugs".

Seizures

Five countries (4 European, 1 Americas) reported seizures in 2022. The number of seizures per country ranged from 1 to 40 and the amounts seized ranged from 0.5 g to 29 g (Table A24). Four countries (3 European, 1 Americas) reported seizures in 2021. The number of seizures ranged from 1 to 131, and the amounts seized ranged from 5 g to 214 g.

Table A24. Reported seizures of etonitazepyne

Year	No. of countries that reported seizures	No. of seizures
2022	5	44
2021	4	135

Fifteen countries (10 European, 4 Western Pacific, 1 Americas) reported that they had the laboratory capacity to analyse etonitazepyne.

2-methyl-AP-237

Of the 77 countries that agreed to provide data, 17 had information on 2-methyl-AP-237 (Table A25).

Table A25. Numbers of countries providing information on 2-methyl-AP-237

Region	No. of countries that had no information	No. of countries that had information
African	3	0
Americas	6	2
South-East Asia	3	0
European	17	11
Eastern Mediterranean	6	0
Western Pacific	5	4
Total	40	17

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for 2-methyl-AP-237. One country (Americas) reported that 2-methyl-AP-237 was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). No country reported other use of 2-methyl-AP-237 for industrial or other non-medical/non-scientific purposes in their country.

Epidemiology of non-medical use

Five countries (3 European, 2 Americas) reported evidence of the use of 2-methyl-AP-237 for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived from data on seizures/law enforcement encounters (n=4), medical examiner reports/detection in blood (n=2), emergency department presentations (n=1), and poison information calls (n=1).

Routes of administration and formulations

The most commonly reported route of administration was sniffing (Table A26).

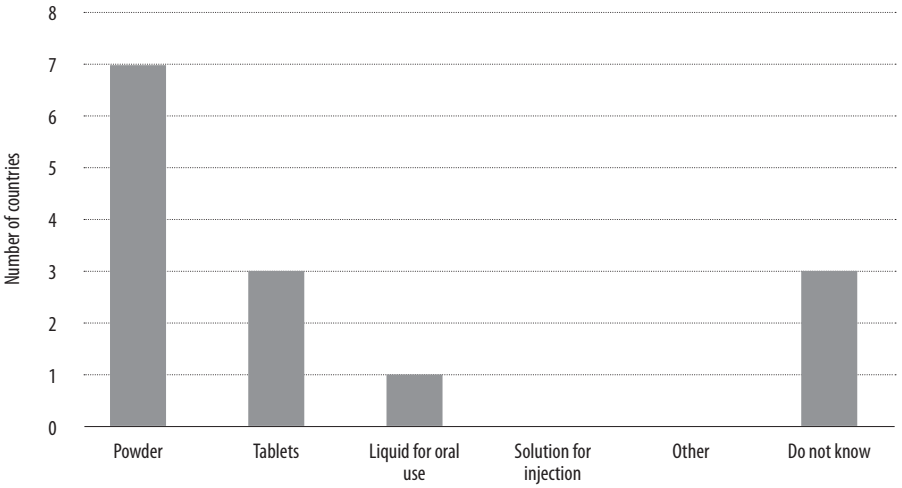
Table A26. Reported routes of 2-methyl-AP-237 administration

Route of administration	No. of countries
Sniffing	4
Oral	2
Injection	2
Smoking	2
Inhalation	0
Othera	2
Do not know	5

[a] Rectal administration (n = 1) and as a nasal spray (n = 1).

The most common known formulation of 2-Methyl-AP-237 reported was powder (Fig. A13).

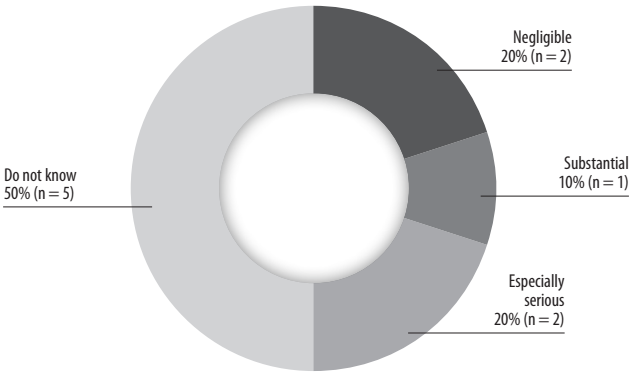
Fig. A13. Formulations of 2-methyl-AP-237



Perceived negative health impact

Two countries (1 European, 1 Americas) reported that the negative health impact of non-medical consumption of 2-methyl-AP-237 was "especially serious" (Fig. A14). One country (European) reported their sources of information as being from femoral blood, poisons information related to hospitalisations, and seizures. Another country (Americas) reported their information as from deaths related to extramedical use of drugs and medical examiner reports.

Fig. A14. Negative health impacts of non-medical consumption of 2-methyl-AP-237



Emergency department visits

Three countries (2 European, 1 Americas) were aware of emergency department visits related to 2-methyl-AP-237. The adverse effects that patients presented with at emergency departments included respiratory failure/difficulty breathing, high pulse, and miosis.

Deaths

Two countries (1 European, 1 Americas) reported a total of seven 2-methyl-AP-237-related deaths for the most recent completed year data was available. One country (European) reported one 2-methyl-AP-237-related death in 2019 where other substances were involved. One country (Americas) reported six 2-methyl-AP-237-related deaths in 2021 where other substances were involved. This country (Americas) further noted that the types of drugs co-identified in 2-methyl AP-237 associated fatal and nonfatal overdose cases were often prescription opioid analgesics, heroin, tramadol, depressants, fentanyl, and other synthetic opioid substances.

Drug dependence

No countries were aware of people who presented for treatment of drug dependence in their country due to use of 2-methyl-AP-237.

Current national controls

Eleven (8 European, 3 Western Pacific) responded that the availability of 2-methyl-AP-237 was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A23 shows the main reported activities involving 2-methyl-AP-237.

Table A27. Reported activities involving 2-methyl-AP-237 for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	4
Smuggling (from other countries)	3
Internet sales (other or location of sellers and website unknown)	2
Internet sales (from abroad to buyers in respondent's country)	1
Internet sales (seller or website located in respondent's country)	1
Manufacture of the substance by chemical synthesis	0
Direct sales	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion (from legal supply chain)	0
Do not know	4
Other	0

Seizures

Five countries (4 European, 1 Americas) reported seizures in 2022. The number of seizures per country ranged from 1 to 2 and the amounts seized ranged from 0.8 g to 45 g (Table A28). Two countries (1 European, 1 Americas) reported 2-methyl-AP-237 seizures in 2021. The number of seizures ranged from 2 to 47, and the amounts seized ranged from 8 g to 9 g. Two countries (1 European, 1 Americas) reported 2-methyl-AP-237 seizures in 2020. The number of seizures ranged from 3 to 5, and the amounts seized ranged from 3 g to 10 g.

Table A28. Reported seizures of 2-methyl-AP-237

Year	No. of countries that reported seizures	No. of seizures
2022	5	7
2021	2	49
2020	2	8

Twelve countries (9 European, 2 Western Pacific, 1 Americas) reported that they had the laboratory capacity to analyse 2-methyl-AP-237.

α-PiHP

Of the 77 countries that agreed to provide data, 26 had information on α-PiHP (Table A29).

Table A29. Numbers of countries providing information on α-PiHP

Region	No. of countries that had no information	No. of countries that had information
African	3	0
Americas	5	3
South-East Asia	3	0
European	11	17
Eastern Mediterranean	6	0
Western Pacific	3	6
Total	31	30

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for α-PiHP. No countries reported that α-PiHP was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). No countries reported use for industrial purposes.

Epidemiology of non-medical use

Fourteen countries (9 European, 3 Americas and 2 Western Pacific) reported evidence from law enforcement or health professionals of the use of α-PiHP for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived primarily from data on seizures and toxicology reports (n=14).

Routes of administration and formulations

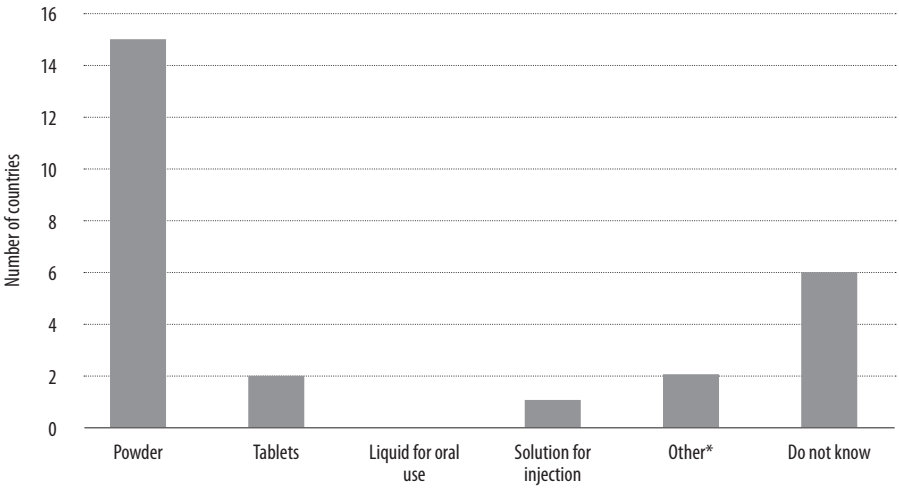
The most common reported route of administration was sniffing, followed by oral, injection and smoking (Table A30).

Table A30. Reported routes of α-PiHP administration

Route of administration	No. of countries
Smoking	7
Oral	5
Inhalation	4
Sniffing	4
Injection	0
Other[a]	0
Do not know	6

The most common known formulations of α-PiHP reported were as a powder and as a tablet (Fig. A15).

Fig. A15. Formulations of α-PiHP



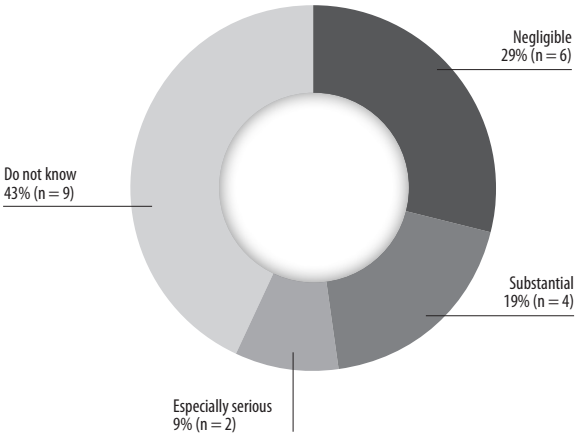
*Other formulations referred to were herbal mixture or liquid (unknown if for oral use or injection).

Other formulations referred to were herbal mixture or liquid (unknown if for oral use or injection).

Perceived negative health impact

Six countries (4 European, 2 Americas) reported that the negative health impact of non-medical consumption of α-PiHP was "especially serious" or "substantial" (Fig. A16). Three countries (2 European, 1 Americas) reported the occurrence of seizures and identification in toxicology cases.

Fig. A16. Negative health impacts of non-medical consumption of α-PiHP



Emergency department visits

One country (European) was aware of emergency department visits related to α-PiHP and described side-effects to include headache, sweating, vertigo, anxiety, reduced blood pressure, tremors, overactivity, anxiety and increased body temperature. Two cases report on individuals that injected the substance and had discomfort at the injection site or high pulse, increased blood pressure and chest pain.

Deaths

Four countries (3 European, 1 Americas) reported a total of 18 α-PiHP-related deaths between 2020 and 2022. Two countries (1 European, 1 Americas) reported 10 deaths in 2021 in which it was unknown if other substances were involved. One country (European) reported 3 α-PiHP-related deaths in which another substance was also involved, also in 2021.

Drug dependence

No countries reported that people presented for treatment of drug dependence in their country due to use of α-PiHP.

Current national controls

Twenty-one countries (13 European, 5 Western Pacific, 3 Americas) responded that the availability of α-PiHP was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A31 shows the main reported activities involving α-PiHP.

Table A31. Reported activities involving α-PiHP for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	10
Smuggling (from other countries)	6
Internet sales (from abroad to buyers in respondent's country)	2
Internet sales (other or location of sellers and website unknown)	2
Internet sales (seller or website located in respondent's country)	1
Manufacture of the substance by chemical synthesis	1
Direct sales	1
Diversion	1
Manufacture of the substance by extraction from other products	0
Production of consumer products containing the substance	0
Do not know	6
Other	0

Seizures

Nine countries (8 European, 1 Americas) reported α-PiHP seizures in 2022. The number of seizures per country ranged from 1 to 181 and the amounts seized ranged from 3 g to 1.3 kg (Table A32). Eight countries (6 European, 1 Western Pacific, 1 Americas) reported α-PiHP seizures in 2021. The number of seizures per country ranged from 1 to 341 and the amounts seized from 11 g to 35.7 kg. Seven countries (6 European, 1 Americas) reported α-PiHP seizures in 2020. The number of seizures per country ranged from 1 to 200 and the amounts seized ranged from below 1 g to 613.2 g.

Table A32. Reported seizures of α-PiHP

Year	No. of countries that reported seizures	No. of seizures
2022	9	318
2021	8	409
2020	7	280

Twenty-two countries (15 European, 5 Western Pacific, 2 Americas) reported that they had the laboratory capacity to analyse α-PiHP.

3-MMC

Of the 77 countries that agreed to provide data, 31 had information on 3-MMC (Table A33).

Table A33. Numbers of countries providing information on 3-MMC

Region	No. of countries that had no information	No. of countries that had information
African	2	0
Americas	5	3
South-East Asia	3	0
European	7	22
Eastern Mediterranean	6	0
Western Pacific	3	6
Total	26	31

Approved medical, scientific or industrial use

No countries reported approved therapeutic indications for 3-MMC. No countries reported that 3-MMC was currently used in medical or scientific research, such as in clinical trials for any human or veterinary indication (except as an analytical standard). No countries reported use for industrial purposes.

Epidemiology of non-medical use

Nineteen countries (14 European, 3 Americas and 2 Western Pacific) reported evidence from health professionals, law enforcement or drug checking services of the use of 3-MMC for non-medical purposes (outside the medical, industrial or scientific context).

Routes of administration and formulations

The most common reported route of administration was oral, followed by sniffing and injection (Table A34).

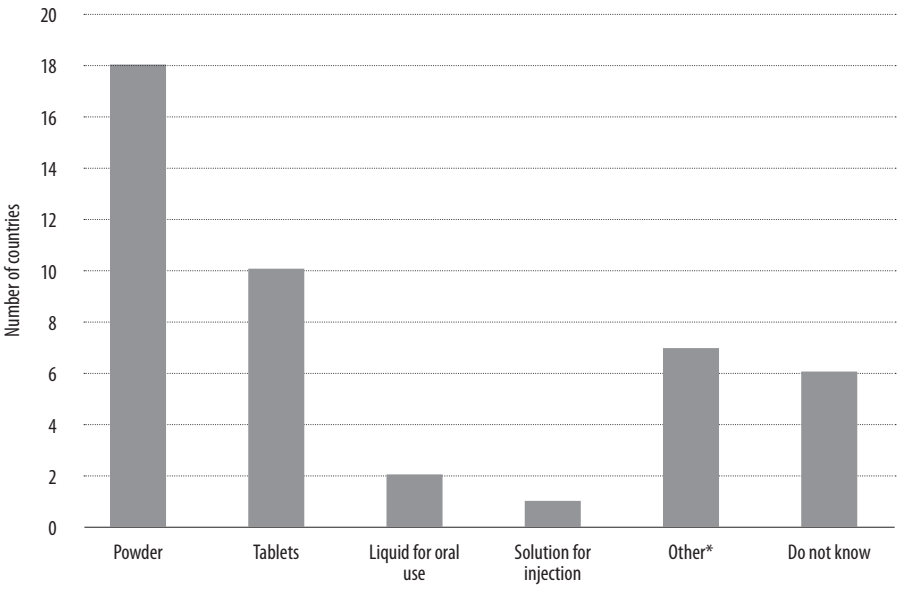
Table A34. Reported routes of 3-MMC administration

Route of administration	No. of countries
Oral	10
Sniffing	9
Injection	3
Smoking	1
Inhalation	0
Other[a]	1
Do not know	13

[a] Rectal

The most common known formulations of 3-MMC reported were as a powder and as a tablet (Fig. A17).

Fig. A17. Formulations of 3-MMC

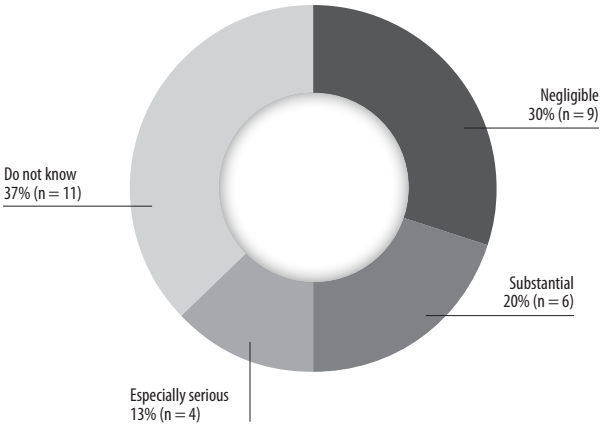


*Other formulations referred to were a crystalline substance (n = 3) and blotters or paper (n = 2).

Perceived negative health impact

Ten countries (8 European, 2 Americas) reported that the negative health impact of non-medical consumption of 3-MMC was "especially serious" or "substantial" (Fig. A18). One European country reported that 3-MMC had been found in tablets or powders sold as MDMA at festivals and nightclubs. Two European countries mentioned that 3-MMC had been detected in intoxications. One European country mentions that 3-MMC is used by various user groups and is readily, freely available and sold at a low price.

Fig. A18. Negative health impacts of non-medical consumption of 3-MMC



Emergency department visits

Four European countries were aware of emergency department visits related to 3-MMC. One European country reported side-effects from 3-MMC to include confusion, dissociation and paraesthesia. Another European country described three intoxications with a number of side effects to include increased heart rate (2 cases), increased body temperature, hallucinations, change in behaviour, tight chest, and anxiety.

Deaths

Five countries (4 European, 1 Western Pacific) reported a total of 18 3-MMC-related deaths between 2018 and 2020. One country (European) reported six deaths during 2021 and 2022 that involved other substances as well as six deaths during 2021 and 2022 in which 3-MMC was the only substance involved.

Drug dependence

Two European countries reported that people presented for treatment of drug dependence in their country due to use of 3-MMC.

Current national controls

Twenty-nine countries (17 European, 6 Western Pacific, 3 Americas) responded that the availability of 3-MMC was currently regulated under national legislation.

Illicit manufacture and trafficking-related information

Table A35 shows the main reported activities involving 3-MMC.

Table A35. Reported activities involving 3-MMC for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	13
Smuggling (from other countries)	9
Internet sales (other or location of sellers and website unknown)	5
Internet sales (from abroad to buyers in respondent's country)	3
Direct sales	2
Manufacture of the substance by chemical synthesis	2
Internet sales (seller or website located in respondent's country)	1
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Diversion	0
Do not know	8
Other	0

Seizures

Thirteen countries (3 European, 1 Western Pacific, 1 South-East Asia) reported 3-MMC seizures in 2021. The number of seizures per country ranged from 1 to 34 and the amounts seized ranged from 0.5 g to 5.9 kg (Table A36). In addition, one European country seized 15,297 tablets. Sixteen countries (14 European, 1 Western Pacific, 1 Americas) reported 3-MMC seizures in 2021. The number of seizures per country ranged from 1 to 89 and the amounts seized from 6 g to 610 kg. Twelve countries (11 European, 1 Americas) reported 3-MMC seizures in 2020. The number of seizures per country ranged from 1 to 87 and the amounts seized from 2 g to 613.5 kg.

Table A36. Reported seizures of 3-MMC

Year	No. of countries that reported seizures	No. of seizures
2022	13	119
2021	16	327
2020	12	252

Twenty-nine countries (22 European, 5 Western Pacific, 2 Americas) reported that they had the laboratory capacity to analyse 3-MMC.

Zopiclone

Of the 77 countries that agreed to provide data, 43 had information on zopiclone (Table A37).

Table A37. Numbers of countries providing information on zopiclone

Region	No. of countries that had no information	No. of countries that had information
African	2	2
Americas	3	8
South-East Asia	3	1
European	7	21
Eastern Mediterranean	4	3
Western Pacific	1	8
Total	20	43

Approved medical, scientific or industrial use

Medical use

Forty-one of the countries (21 European, 8 Americas, 8 Western Pacific, 3 Eastern Mediterranean, 2 African, 1 South-East Asia) reported approved therapeutic indications for zopiclone. Thirty-six countries (17 European, 8 Western Pacific, 7 Americas, 3 Eastern Mediterranean, 2 African, 1 South-East Asia) reported that zopiclone was used in the treatment of insomnia or sleep disorders. One country (European) reported that zopiclone was used for post-acute withdrawal syndrome.

Veterinary use

No countries reported that zopiclone was approved as a veterinary product.

Scientific research

Three countries (2 European, 1 Western Pacific) reported that zopiclone is used in medical or scientific research, including two countries reporting ongoing clinical trials.

Industrial use

One country (Western Pacific) reported industrial use of zopiclone.

Epidemiology of non-medical use

Eleven countries (5 European, 3 Americas and 3 Western Pacific) reported evidence from law enforcement or health professionals of the use of zopiclone for non-medical purposes (outside the medical, industrial or scientific context).

Routes of administration and formulations

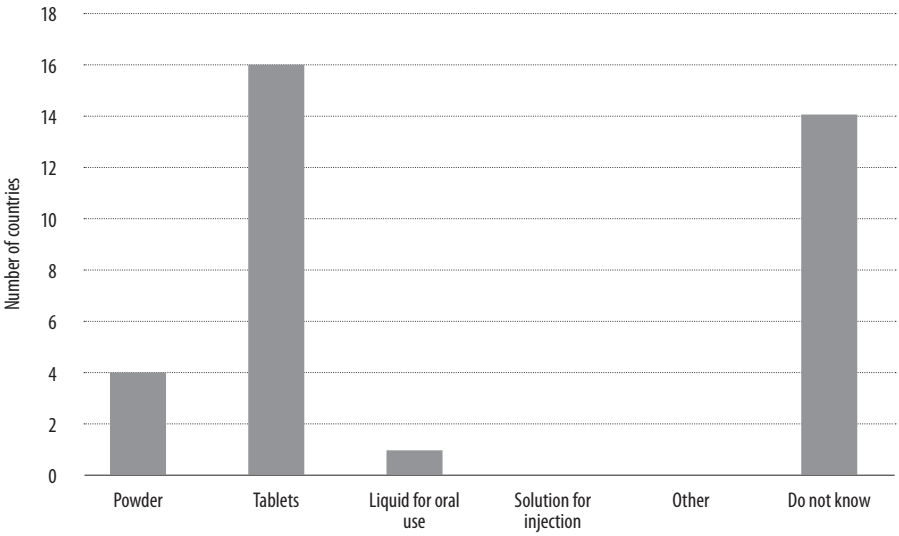
The most common reported route of administration was oral (Table A38).

Table A38. Reported routes of zopiclone administration

Route of administration	No. of countries
Smoking	10
Oral	6
Inhalation	2
Sniffing	0
Injection	0
Other[a]	1
Do not know	6

The most common known formulations of zopiclone reported were as a tablet (Fig. A19).

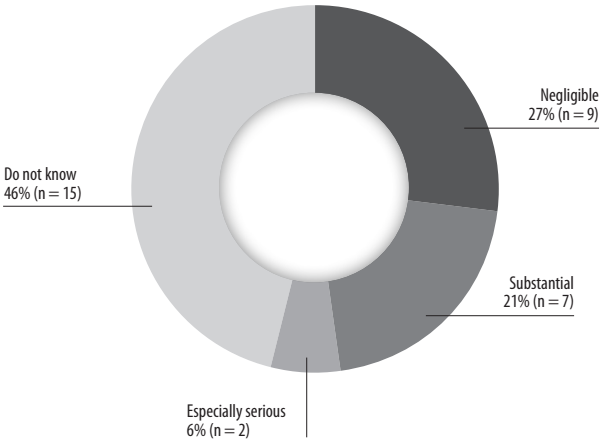
Fig. A19. Formulations of zopiclone



Perceived negative health impact

Nine countries (3 European, 2 Western Pacific, 3 Americas, 1 Eastern Mediterranean) reported that the negative health impact of non-medical consumption of zopiclone was "especially serious" or "substantial" (Fig. A20). Two countries (1 European, 1 Western Pacific) reported hospital admissions as a result of zopiclone use. One country (Western Pacific) reported evidence of oversupply and overprescribing of zopiclone as well as evidence of zopiclone for sale on social media platforms.

Fig. A20. Negative health impacts of non-medical consumption of zopiclone



Emergency department visits

Five countries (2 European, 2 Western Pacific, 1 Americas) were aware of emergency department visits related to zopiclone. Three countries (2 European, 1 Americas) reported side-effects to include amnesia, memory loss, anxiety, agitation, decreased consciousness, chest pain, respiratory insufficiency or psychosis. One Western Pacific country mentioned that zopiclone had been used in self-harm or suicide attempts. One Western Pacific country reported 12 cases of drug dependence and two overdoses.

Deaths

Four countries (1 European, 1 Western Pacific, 1 Americas) reported a total of 155 zopiclone-related deaths between 2020 and 2022. One European country reported one hundred and fifteen deaths in 2020.

Drug dependence

Seven countries (3 Western Pacific, 2 European region, 1 Americas, 1 Eastern Mediterranean) reported that people presented for treatment of drug dependence in their country due to use of zopiclone.

Current national controls

Thirty-two countries (15 European, 7 Western Pacific, 5 Americas, 3 Eastern Mediterranean, 2 African) responded that the availability of zopiclone was currently regulated under national legislation. Table A40 shows the main reported control activities for zopiclone.

Illicit manufacture and trafficking-related information

Table A39 shows the main reported activities involving zopiclone.

Table A39. Reported activities involving zopiclone for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	6
Smuggling (from other countries)	3
Diversion	3
Direct sales	3
Internet sales (from abroad to buyers in respondent's country)	2
Internet sales (other or location of sellers and website unknown)	2
Internet sales (seller or website located in respondent's country)	1
Manufacture of the substance by chemical synthesis	0
Production of consumer products containing the substance	0
Manufacture of the substance by extraction from other products	0
Do not know	21
Other	0

Seizures

Six countries (4 European, 1 Western Pacific, 1 Americas) reported zopiclone seizures in 2022. The number of seizures per country ranged from 1 to 71 and the amounts seized ranged from 9 tablets to 1426 tablets (Table A4). In addition, two countries (1 European, 1 Americas) reported 28.06 g and 20 g of powder seized. Eleven countries (6 European, 3 Western Pacific, 1 Eastern Mediterranean, 1 Americas) reported zopiclone seizures in 2021. The number of seizures per country ranged from 1 to 191 and the amounts seized from 13 tablets to 25 390 tablets. In addition, four countries (2 European, 1 Western Pacific, 1 Americas) reported amounts seized from 0.67 g to 817.6 g. Six countries (4 European, 2 Western Pacific) reported zopiclone seizures in 2020. The number of seizures per country ranged from 1 to 129 and the amounts seized ranged from 14 tablets to 9026 tablets. In addition, one country (European) reported 125.21 g of powder seized.

Table A40. Reported seizures of zopiclone

Year	No. of countries that reported seizures	No. of seizures
2022	6	110
2021	11	336
2020	6	258

Thirty-eight countries (20 European, 7 Western Pacific, 6 Americas, 2 Eastern Mediterranean, 2 African, 1 South-East Asia) reported that they had the laboratory capacity to analyse zopiclone.

Annex 2. List of participants

Expert Committee members

Patrick M. Beardsley, Department of Pharmacology and Toxicology and Centre for Biomarker Research and Personalized Medicine, Virginia Commonwealth University, USA

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Simon Elliott, Elliott Forensic Consulting, England, United Kingdom

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Pamela Kaduri, Department of Psychiatry, University of Toronto and adjunct faculty, Muhimbili University of Health and Allied Sciences, United Republic of Tanzania (Rapporteur)

Junichi Kitanaka, Laboratory of Drug Addiction and Experimental Therapeutics, Hyogo College of Medicine, Japan

Antonio Pascale Prieto, Department of Toxicology, Faculty of Medicine, Uruguay

Afarin Rahimi-Movaghar, Iranian National Centre for Addiction Studies, Tehran University of Medical Sciences, Islamic Republic of Iran (Co-Chair)

Sutisa Nudmamud-Thanoi, Centre of Excellence in Medical Biotechnology, Naresuan University, Thailand

Jason White, School of Pharmacy and Medical Sciences, Division of Health Sciences, University of South Australia, Australia (Chair)

Representatives of the International Narcotics Control Board, Vienna, Austria

Galina Korchagina, Member

Hanifa Rebbani, Member

Representatives of the United Nations Office of Drugs and Crime, Vienna, Austria

Conor Crean, Laboratory and Scientific Division

WHO secretariat (WHO Headquarters, Geneva, Switzerland)

Alma Alic, Compliance and Risk Management and Ethics

Andrew Ball, Department of Communicable and Noncommunicable Diseases

Gilles Forte (Secretary), Access to Medicines and Health Products Division

Claudia Nannini, International, Constitutional and Global Health Law

Suzanne Nielsen (Temporary adviser), Access to Medicines and Health Products Division

Dilkushi Poovendran, Access to Medicines and Health Products Division

Vladimir Poznyak, Alcohol, Drugs and Addictive Behaviours

Mariângela Simão, Access to Medicines and Health Products Division

Thomas Le Ruez, Access to Medicines and Health Products Division

Annette Verster, Testing, Prevention and Populations

The Forty-fifth Meeting of the World Health Organisation (WHO)'s Expert Committee on Drug Dependence (ECDD) was convened from 10 to 14 October 2022 and was coordinated from the WHO headquarters in Geneva.

The Forty-fifth WHO ECDD critically reviewed nine new psychoactive substances: including one synthetic cannabinoid receptor agonist (ADB-BUTINACA), two benzodiazepines (adinazolam, bromazolam), four novel synthetic opioids (protonitazene, etazene, etonitazepyne, 2-Methyl-AP-237), and two cathinones/stimulants (α-PiHP, 3-MMC). A critical review to consider international scheduling measures was undertaken for each substance so that the Expert Committee could consider whether information about these substances may justify the scheduling or a change in scheduling of a substance in the 1961 or 1971 Conventions.

In addition, the Forty-fifth ECDD carried out a pre-review of zopiclone to consider whether current information justified a critical review.

This report summarizes the findings of the forty-fifth ECDD meeting.

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