

WHO Expert Committee on Drug Dependence

Forty-fourth report



World Health
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This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization



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Authors of critical and pre-review reports:

4F-MDMB-BICA: Giuseppe Cannazza^{1*}, Cinzia Citti^{2*}, Jenny Wiley

Benzyllone: Simon Brandt³

Brorphine: Simon Brandt³

Eutylone: Giuseppe Cannazza^{1*}, Cinzia Citti^{2*}, João Silva⁴

Kratom, mitragynine, 7-hydroxymitragynine: Giuseppe Cannazza^{1*}, Cinzia Citti^{2*}, David Gorelick⁵

Metonitazene: Giuseppe Cannazza^{1*}, Cinzia Citti^{2*}, Jermaine Jones⁶

Phenibut: Giuseppe Cannazza^{1*}, Cinzia Citti^{2*}, Teresa Franklin⁷

¹ University of Modena and Reggio Emilia, Italy

² Institute of Nanotechnology of the National Council of Research, Italy

³ Liverpool John Moores University, UK

⁴ University of Porto, Portugal

⁵ University of Maryland, USA

⁶ New York State Psychiatric Institute / Columbia University Medical Center, USA

⁷ University of Pennsylvania, USA

*The indicated authors led the development of the chemistry sections

44th ECDD Committee Members: Patrick Beardsley, Wim Best, Sandra Comer, Ifeoma Ekwere, Simon Elliott, Raka Jain, Pamela Kaduri (Rapporteur), Junichi Kitanaka, Antonio Pascale Prieto, Afarin Rahimi-Movaghar (Co-Chair), Sutisa Thanoi and Jason White (Chair).

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Abbreviations and acronyms

4-ANPP	4-anilino- <i>N</i> -phenethyl piperidine
CB ₁	cannabinoid
CFSRE	Center for Forensic Science Research and Education (USA)
CND	Commission on Narcotic Drugs
CYP	cytochrome P450
DAMGO	[D-Ala ² , <i>N</i> -mePhe ⁴ , Gly-ol]-enkephalin
DART	direct analysis in real time
DAT	dopamine receptor transporter
DEA	Drug Enforcement Administration (USA)
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DUID	driving under the influence of drugs
EC ₅₀	half maximal effective concentration
ECDD	Expert Committee on Drug Dependence
ED ₅₀	median effective dose
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
GABA	γ-aminobutyric acid
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
5-HT	5-hydroxytryptamine



IC ₅₀	half maximal inhibitory concentration
INCB	International Narcotics Control Board
ip	intraperitoneal
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
K _i	inhibitory constant
LC	liquid chromatography
MDMA	±-3,4-methylenedioxymethamphetamine
MDMB	methyl 2,3-dimethyl butanoate
MDMB-4en-PINACA	methyl (S)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3-carboxamido)butanoate
MOR	μ-opioid receptor
MS	mass spectrometry
NET	norepinephrine receptor transporter
NFLIS	National Forensic Laboratory Information System (USA)
NMR	nuclear magnetic resonance
NPS	new psychoactive substance
SERT	serotonin receptor transporter
THC	Δ ⁹ -tetrahydrocannabinol
TLC	thin-layer chromatography
TOF	time of flight
UHPLC	ultra-high-performance liquid chromatography
UNODC	United Nations Office on Drugs and Crime
UV	ultraviolet

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-fourth meeting, the ECDD critically reviewed five new psychoactive substances, comprising one synthetic cannabinoid receptor agonist (4F-MDMB-BICA), two novel synthetic opioids (brophine and metonitazene) and two cathinones/stimulants (eutylone and benzylone). These substances had not previously been reviewed formally by WHO and are currently not under international control. A critical review of the use of each substance and its effects was undertaken so that the Expert Committee could determine whether the information available on these substances justified scheduling or a change in scheduling from that in the 1961 or 1971 Convention. In addition, the meeting pre-reviewed kratom, mitragynine and 7-hydroxymitragynine and phenibut to determine whether the current information justified a critical review.

After the Forty-fourth 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	Alternative name	International Union of Pure and Applied Chemistry (IUPAC) name
To be added to Schedule I of the Single Convention on Narcotic Drugs (1961)	Brorphine		3- {1- [1- (4-bromophenyl) ethyl] piperidin-4-yl} -1H-benzimidazol-2-one
	Metonitazene		<i>N,N</i> -Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1 <i>H</i> -benzo[<i>d</i>]imidazol-1-yl) ethan-1-amine
To be added to Schedule II of the Convention on Psychotropic Substances (1971)	Eutylone	3,4-Methylenedioxy- <i>a</i> -ethylamino butiophenone	1-(Benzo[<i>d</i>][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one
To be kept under surveillance	4F-MDMB-BICA	4F-MDMB-BUTICA	Methyl 2-({[1-(4-fluorobutyl)-1 <i>H</i> -indol-3-yl] carbonyl}amino)-3,3-dimethylbutanoate Methyl 2-(1-(4-fluorobutyl)-1 <i>H</i> -indole-3- carbaxamido)-3,3-dimethylbutanoate
	Benzylone	3,4-Methylenedioxy- <i>N</i> -benzylcathinone	1-(Benzo[<i>d</i>][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one
	Kratom, mitragynine, 7-hydroxymitragynine		
	Phenibut	4-Amino-3-phenylbutyric acid	4-Amino-3-phenylbutanoic acid

1. Information session

On 11 October 2021, before the Expert Committee convened, an information session was held so that the Committee could hear presentations and question representatives of interested parties about data that had been provided on the substances under review.

The session was opened 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 (CND) about the appropriate level of international control. When relevant, the ECDD also considers whether a substance has a medical or scientific application. This mandate is reinforced by several resolutions of the United Nations General Assembly and the CND. WHO fulfils its mandate through the ECDD in accordance with WHO guidance on the review of psychoactive substances for international control. The processes and procedures were developed by the World Health Assembly, and revisions were approved by the WHO Executive Board in 2010.

The 44th ECDD heard oral presentations by the following individuals: Don Land, Wat Ku Daeng Wat Yang Temple, Thailand; Greg Fryett, Fryett, Thailand; Ekkasit Kumarnsit, Prince of Songkla University, Thailand; Evgeny Krupitsky, V.M. Bekhterev National Medical Center for Psychiatry and Neurology, Russian Federation; Fabian Pitter Steinmetz, European Coalition for Just and Effective Drug Policies, Germany; Christopher McCurdy, University of Florida, USA; David Heldreth, Panacea Plant Sciences, USA; Jack Henningfield, USA; Mac Haddow, American Kratom Association, USA; Marilyn Huestis, USA; and Walter Prozialeck, Midwestern University, USA.

Additionally, the secretariat received written statements from the following individuals, which were presented to the 44th ECDD: Fabian Pitter Steinmetz, European Coalition for Just and Effective Drug Policies, Germany; Christopher McCurdy, University of Florida, USA; David Heldreth Jr, Panacea Plant Sciences, USA; Marilyn Huestis, USA; Walter Prozialeck, Midwestern University, USA; Mac Haddow, American Kratom Association, USA; Jakub Zientala, Zientala, Netherlands; Evgeny Krupitsky, V.M. Bekhterev National Medical Center for Psychiatry and Neurology, Russian Federation; Daniel Wang, Pinney Associates, Inc., USA; Lora Romney, International Plant and Herbal Alliance, USA; Peter Candland, American Kratom Association, USA; Christopher Deaney, Christopher's Organic Botanicals, USA; Marek Chawarski, USA; Denise Sigelkow, USA; Mohammad Farris Iman Leong Bin Abdullah, Malaysia; Martin Jelsma, Transnational Institute, Netherlands; Konstantin Kunts, Smart Solutions Integration Agency, Russian Federation; Gloria Lai, International Drug Policy Consortium, Thailand; and Lukáš Vlasák, Czech Republic.

2. Meeting report of the 44th Expert Committee on Drug Dependence

The forty-fourth meeting of the WHO Expert Committee on Drug Dependence (ECDD) was convened virtually on 11–15 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 (1) and the 1971 Convention on Psychotropic Substances (2), which is to assess psychoactive substances with potential for abuse and dependence that harm health and, when relevant, to assess therapeutic use of the substances. She recalled that evidence-based assessment of psychoactive substances as mandated by the international drug control conventions is central to the work of the ECDD. She reminded participants that they were acting in their personal capacities and not as representatives of their governments.

Claudia Nannini of the WHO Office of the Legal Counsel recalled that the Expert Committee is convened in accordance with WHO's regulations for expert advisory panels (3) and the guidance on WHO review of psychoactive substances for international control (4). 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 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 44th meeting of the ECDD considered that the disclosed interests were not in conflict with any of the issues to be discussed at the meeting or with the recommendations to be issued by the Expert Committee. No other interests declared by members of the Expert Committee or temporary advisers were deemed relevant to the work of the group.

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 by the 41st ECDD on cannabis and cannabis-related substances

Dr Forte reported on the discussions that were held at the CND in Vienna on WHO recommendations on cannabis and cannabis-related substances made by the ECDD at its 41st meeting. WHO communicated the recommendations to the CND in January 2019 for further dissemination to Member States. At its 62nd regular session in March 2019, the CND decided to postpone voting on the WHO recommendations in order to provide Member States with more time to consider the recommendations (Decision 62/14).

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

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

In December 2020, the 63rd Reconvened CND voted upon the recommendations on cannabis and cannabis-related substances made by the 41st ECDD. The Commission voted to delete cannabis and cannabis resin from Schedule IV of the 1961 Convention. Cannabis and cannabis remain in Schedule I of the 1961 Convention and thus remain subject to control under

that Convention. The Commission voted not to accept the other cannabis-related recommendations made by the 41st ECDD, leaving their control under international drug control conventions unchanged.

2.1.2 Recommendations by the 43rd ECDD

The 64th CND voted in April 2021 to accept the following recommendations made by the 43rd ECDD, thereby placing the substances under international control:

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

- Isotonitazene

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

- CUMYL-PEGACLONE
- MDMB-4en-PINACA
- 3-methoxyphencyclidine
- Diphenidine

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

- Clonazolam
- Diclazepam
- Flubromazolam

In addition, the 43rd ECDD recommended that WHO keep the following substances under surveillance:

- 2-methoxydiphenidine
- 5-methoxy-*N,N*-diallyltryptamine (5-MeO-DALT)
- 3-fluorophenmetrazine

2.1.3 Recommendations by the 9th ECDD Working Group

The 9th ECDD Working Group, convened in April 2021, recommended that the following substances be placed under WHO surveillance:

- 2-methyl AP-237
- 3-methylmethcathinone (3-MMC)
- 5-(2-aminopropyl)benzofuran (5-APB)
- 5,6-methylenedioxy-2-aminoindane (MDAI)

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 CND has explicitly requested a review of a substance;
- a pre-review of a substance has resulted in an Expert Committee recommendation for critical review; or
- information has been brought to WHO’s attention that a substance is manufactured clandestinely, is an especially serious risk to public health and society and is of no recognized therapeutic use by any Party.

2.2.1 4F-MDMB-BICA (4F-MDMB-BUTICA)

Substance identification

The chemical structure of 4F-MDMB-BICA (IUPAC chemical name: Methyl 2-({[1-(4-fluorobutyl)-1H-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate) is similar to those of a number of synthetic cannabinoids. It has been identified in seized materials as a white, off-white, brown or orange powder and has been identified in herbal blends, vaping solutions and infused onto paper. It is also available as a reference material as a crystalline solid.

WHO review history

4F-MDMB-BICA has not been formally reviewed by WHO and is not currently under international control. Information was brought to WHO's attention that this substance is manufactured clandestinely, poses a risk to public health and has no recognized therapeutic use.

Similarity to known substances and effects on the central nervous system

4F-MDMB-BICA is a synthetic cannabinoid, structurally related to 5F-MDMB-PICA, a synthetic cannabinoid that is included in Schedule II of the United Nations Single Convention on Psychotropic Substances of 1971. Some data suggest that 4F-MDMB-BICA has activity at the cannabinoid (CB1) receptor, but this action may not be identical to that exerted by other CB1 agonists. The effects of 4F-MDMB-BICA have not been evaluated in animals or humans, and there are insufficient data on overdose cases to confirm that it has typical cannabinoid effects.

Dependence potential

No studies have been reported in animals or humans on the dependence potential of 4F-MDMB-BICA.

Actual abuse and/or evidence of likelihood of abuse

No studies have been reported in animals or humans to indicate the likelihood of abuse of 4F-MDMB-BICA. A number of countries in various regions have reported use of 4F-MDMB-BICA. Its use has been associated with deaths and emergency department visits, although many substances were present in biological samples, and the relationship between 4F-MDMB-BICA exposure and cause of death was not established.

Therapeutic usefulness

4F-MDMB-BICA is not known to have any therapeutic use.

Recommendation

The structure of 4F-MDMB-BICA is similar to those of other synthetic cannabinoids, but its mechanism of action has yet to be confirmed. The magnitude of harm due to 4F-MDMB-BICA alone is unclear, and its effects and abuse potential have not been studied in animals or humans. In view of the limited information available on abuse, dependence and risks to public health, there is insufficient evidence to justify placing 4F-MDMB-BICA under international control.

Recommendation: The Committee recommended that 4F-MDMB-BICA (IUPAC chemical name: Methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl} amino)-3,3-dimethylbutanoate) be kept under surveillance by the WHO secretariat.

2.2.2 Brorphine

Substance identification

The chemical structure of brorphine (IUPAC chemical name: 3- {1- [1-(4-bromophenyl) ethyl] piperidin-4-yl} -1*H*-benzimidazol-2-one) is similar to that of bezitramide, an opioid listed in Schedule I of the 1961 Convention. Brorphine free base has been described as a white or off-white solid and the hydrochloride salt as a neat solid, with seized samples described as white, yellowish, grey, purple or white powder or in crystal form. It is also found in tablets and capsules as falsified opioid medicines. It is reported to be used by oral, inhalation and intravenous (iv) routes of administration.

WHO review history

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

Similarity to known substances and effects on the central nervous system

Brorphine is a full agonist at the μ -opioid receptor (MOR), with greater potency than morphine and less potency than fentanyl. It has analgesic effects that are reversed by an opioid antagonist and, based on its mechanism of action, it would be expected to produce other typical opioid effects such as respiratory depression and sedation. Brorphine may be convertible to bezitramide, which is an opioid listed in Schedule I of the 1961 Single Convention on Narcotic Drugs.

Dependence potential

No controlled studies in animals or humans have examined the dependence potential of brorphine. As a potent μ -opioid agonist, it would be expected to produce dependence similar to other opioid substances. Unverified online reports describe tolerance and withdrawal after repeated brorphine use.

Actual abuse and/or evidence of likelihood of abuse

In an animal model for predicting abuse potential, brorphine had effects similar to those of morphine and fentanyl.

Deaths involving bupropion have been reported in several countries. Deaths commonly occur after use of bupropion in combination with other opioids or with benzodiazepines such as flunitrazepam. Bupropion has been identified in falsified opioid medicines, suggesting that its use may sometimes be unintentional. Fatal and non-fatal intoxications due to bupropion share features with intoxications due to other opioids, such as pulmonary oedema. Bupropion has been detected with other substances in biological fluids in cases of driving under the influence of drugs (DUID).

Seizures have been reported in multiple countries and regions.

Therapeutic usefulness

Bupropion is not known to have any therapeutic use.

Recommendation

The mechanism of action of bupropion indicates that it is likely to have similar abuse potential and ill effects as opioids that are controlled under Schedule I of the 1961 Single Convention on Narcotic Drugs. Its use has been reported in a number of countries and has been associated with adverse effects, including death. It has no known therapeutic use and is likely to cause substantial harm.

Recommendation: The Committee recommended that bupropion (IUPAC chemical name: 3- [1- [1- (4-bromophenyl) ethyl] piperidin-4-yl] -1*H*-benzimidazol-2-one) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.2.3 Metonitazene

Substance identification

Metonitazene (IUPAC chemical name: *N,N*-diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl)ethan-1-amine) belongs to the series of 2-benzylbenzimidazole opioid compounds. It is a white, off-white, beige or coloured powder and is sometimes crystalline. Reports suggest that it is used intranasally and by iv injection.

WHO review history

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

Similarity to known substances and effects on the central nervous system

Metonitazene is a chemical analogue of etonitazene and isotonitazene, both of which are Schedule I compounds under the Single Convention on Narcotic Drugs, 1961. Metonitazene is a potent opioid analgesic with rapid onset of action and greater potency than fentanyl and hydromorphone. Limited early clinical research demonstrated that metonitazene produces analgesia and typical opioid adverse effects, including sedation, respiratory depression, nausea and vomiting. The effects of metonitazene have been shown to be reversed by an opioid antagonist.

Dependence potential

Studies in animals show that metonitazene suppresses opioid withdrawal and has potent μ -opioid agonist effects. No controlled human studies have been reported on the dependence potential of metonitazene, but, as it is a potent μ -opioid agonist, it would be expected to produce dependence similarly to other opioids.

Actual abuse and/or evidence of likelihood of abuse

No controlled studies have been reported on the abuse potential of metonitazene, but, as it is a potent μ -opioid agonist, it would be expected to have high abuse liability. Online reports by people who have used metonitazene describe its euphoric and opioid-like effects.

A number of deaths have been reported in association with use of metonitazene. In many of these cases, metonitazene was used in combination with other opioids or benzodiazepines; however, in some fatalities, metonitazene was the sole substance identified in analysed biological samples.

Trafficking and use of metonitazene have been reported from a number of countries in several regions.

Therapeutic usefulness

Metonitazene is not known to have any therapeutic use.

Recommendation

The mechanism of action and effects of metonitazene indicate that it is liable to have abuse potential and ill effects similar to those of 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 been associated with adverse effects, including death. Metonitazene has no known therapeutic use and is likely to cause substantial harm.

Recommendation: The Committee recommended that metonitazene (IUPAC chemical name: *N,N*-diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-

benzo[d]imidazol-1-yl)ethan-1-amine) be added to Schedule I of the 1961 Single Convention on Narcotic Drugs.

2.2.4 Eutylone (3,4-methylenedioxy- α -ethylamino butiophenone)

Substance identification

Eutylone (IUPAC chemical name: 1-(Benzo[d][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one) is a synthetic cathinone of the phenethylamine class. The hydrochloride salt of eutylone has been described as a crystalline solid. Eutylone is found mainly as tablets, capsules and crystals. It is used orally and intranasally.

WHO review history

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

Similarity to known substances and effects on the central nervous system

Eutylone is a synthetic cathinone with a mechanism of action and effects similar to those of other cathinones and stimulants such as methamphetamine. Related cathinones, such as methylone and N-ethylnorpentylone, are listed under Schedule II of the Convention on Psychotropic Substances of 1971. The clinical features described are similar to those with other cathinones, including sympathomimetic effects and psychostimulant effects such as euphoria, insomnia, tachycardia, agitation, anxiety, delirium and psychosis.

Dependence potential

No studies have been conducted in animals or humans on the dependence potential of eutylone. In view of its overall profile of effects, eutylone would be expected to produce dependence similarly to other psychostimulants.

Actual abuse and/or evidence of likelihood of abuse

In an animal model that predicts abuse potential, eutylone was shown to produce effects similar to those of methamphetamine. Online reports from people reporting use of eutylone suggest that it has high abuse potential.

Eutylone has been detected in biological samples from forensic, post-mortem and DUID cases. Published case reports describe fatalities as a result of eutylone use. In addition to the effects described above, reported adverse events in these cases have included rhabdomyolysis, hyperthermia, hypertension and seizures.

Eutylone has been detected in seized materials in multiple countries in several regions.

Therapeutic usefulness

Eutylone is not known to have any therapeutic use.

Recommendation

Eutylone has effects similar to those of related cathinones listed under Schedule II of the Convention on Psychotropic Substances of 1971.

There is evidence that this substance is used in multiple countries in various regions. Eutylone causes substantial harm, including severe adverse events and fatal intoxications. Its mode of action suggests the likelihood of abuse, and it poses a substantial risk to public health. It has no known therapeutic use.

Recommendation: The Committee recommended that eutylone (IUPAC chemical name: 1-(benzo[*d*][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one) be added to Schedule II of the Convention on Psychotropic Substances of 1971.

2.2.5 Benzylone (3,4-methylenedioxy-*N*-benzylcathinone)

Substance identification

Benzylone (IUPAC chemical name: 1-(benzo[*d*][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one) is a ring-substituted synthetic cathinone. Benzylone is a white powder, and the hydrochloride salt is a crystalline solid.

WHO review history

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

Similarity to known substances and effects on the central nervous system

The mode of action of benzylone suggests stimulant effects similar to those of other cathinones; however, these effects are relatively weak, and it did not produce stimulant effects in animal models.

Limited information is available on its effects in humans.

Dependence potential

No information was available on the dependence potential of benzylone in animals or humans.

Actual abuse and/or evidence of likelihood of abuse

In an animal model that predicts abuse potential, benzylone did not produce effects similar to those of 3,4-methylenedioxymethamphetamine (MDMA), and its similarity to methamphetamine is unclear. No human studies have been conducted to assess abuse liability.

Benzylone has been detected in seized materials in multiple countries across several regions.

Little information was available on the adverse effects of benzylone. Although it has been detected in post-mortem samples with other substances, there is no evidence that benzylone had a causative role in the deaths.

Therapeutic usefulness

Benzylone is not known to have any therapeutic use.

Recommendation

Benzylone is a synthetic cathinone that has some effects in common with substances listed under Schedule II of the Convention on Psychotropic Substances of 1971. However, its effects are relatively weak and there is no consistent evidence supporting the likelihood of abuse or dependence. In addition, there is no consistent evidence of the extent of public health and social problems related to use of benzylone.

Recommendation: The Committee recommended that benzylone (IUPAC chemical name: 1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one) be kept under surveillance by the WHO secretariat.

2.3 Recommendations on preliminary reviews (pre-reviews)

2.3.1 Kratom, mitragynine, 7-hydroxymitragynine

Substance identification

Kratom is the common term for *Mitragyna speciosa*, a tree native to South-East Asia. Kratom is used almost exclusively orally, typically by chewing the leaves, ingesting powdered leaf, drinking an infusion or decoction or by ingesting powdered leaf as a capsule or pill or dissolved in a beverage. Other forms such as extracts and resins are also used.

Several alkaloids have been detected in kratom plants. The main known psychoactive components are mitragynine and 7-hydroxymitragynine, both of which are found in the leaves of *M. speciosa*. Mitragynine is the most abundant alkaloid in kratom. While 7-hydroxymitragynine is a minor alkaloid, it is also a metabolite of mitragynine.

WHO review history

Kratom has been under ECDD surveillance since 2020, when a national report indicated the potential for abuse, dependence and harm to public health from mitragynine and 7-hydroxymitragynine, and a report from an international organization documented fatalities associated with kratom use. A pre-review on kratom, mitragynine and 7-hydroxymitragynine was initiated after consideration of those reports.

Similarity to known substances and effects on the central nervous system

Mitragynine and 7-hydroxymitragynine are partial agonists at the μ -opioid receptor. The analgesic effects of kratom have been demonstrated in humans, while kratom extract, mitragynine and 7-hydroxymitragynine have been shown to be antinociceptive in animal models. The antinociceptive effects are reversed by an opioid antagonist.

Mitragynine also binds to adrenergic, serotonergic and dopamine receptors. Although there is limited information on its effects at these receptors, kratom extracts and mitragynine have been reported to have a variety of non-opioid-like behavioural effects in animals, including antidepressant and antipsychotic effects.

Reported adverse effects after kratom intoxication have included neuropsychiatric (agitation, confusion, sedation, hallucinations, tremor, seizure, coma), cardiovascular (tachycardia, hypertension), gastrointestinal (abdominal pain, nausea, vomiting) and respiratory (respiratory depression) symptoms. A number of cases of kratom-associated liver toxicity have been documented.

Dependence potential

In animal models, repeated dosing with mitragynine produced dependence, evidenced by naloxone-precipitated withdrawal. The withdrawal syndrome from kratom appeared to be less severe than that from morphine.

In humans, opioid-like withdrawal symptoms have been reported after cessation of kratom use. Limited epidemiological evidence indicates that withdrawal is usually mild. A few cases of neonatal opioid withdrawal symptoms have been reported in neonates born to mothers who used kratom regularly.

Actual abuse and/or evidence of likelihood of abuse

Kratom extracts did not show abuse liability in one animal model. Mitragynine and 7-hydroxymitragynine had effects indicative of abuse liability in some animal models but not in others. Mitragynine is not self-administered by animals, while 7-hydroxymitragynine has been shown to be self-administered, supporting likely abuse liability.

Kratom can produce serious toxicity in people who use high doses, but the number of cases is probably low as a proportion of the total number of people who use kratom. Although mitragynine has been analytically confirmed in a number of deaths, almost all involved use of other substances, and the contribution of kratom use to the fatalities is unclear.

Kratom and mitragynine have been associated with cases of DUID, but their role in driving impairment could not be established in most instances.

Multiple countries across various regions report nonmedical use of kratom. Seizures of kratom and related products have been reported in several countries.

Therapeutic usefulness

People report using kratom to self-medicate for a variety of disorders and conditions, including pain, opioid withdrawal, opioid use disorder, anxiety and depression. Kratom is used in traditional medicine in some countries.

Research is under way to determine the basic pharmacology and potential therapeutic value of kratom, mitragynine and 7-hydroxymitragynine.

Recommendation

Kratom contains multiple alkaloids. The two main known psychoactive alkaloids, mitragynine and 7-hydroxymitragynine, have at least some effects similar to those of opioids under international control. Mitragynine, the most abundant of these alkaloids, also has non-opioid activity, the significance of which is unclear. There is mixed evidence on the abuse liability of mitragynine in animal models. Kratom is used for self-medication for a variety of disorders but there is limited evidence of abuse liability in humans. Cessation of regular use of kratom may lead to withdrawal symptoms.

The Committee considered information on traditional use and investigation into possible medical applications of kratom.

The Committee concluded that there is insufficient evidence to recommend a critical review of kratom. With respect to mitragynine and 7-hydroxymitragynine, the Committee, except for one member, also concluded that there is insufficient evidence to recommend a critical review at this time.

Recommendation: The Committee recommended that kratom, mitragynine and 7-hydroxymitragynine be kept under surveillance by the WHO secretariat.

2.3.2 Phenibut (4-amino-3-phenyl-butyric acid)

Substance identification

Phenibut (IUPAC chemical name: 4-amino-3-phenylbutanoic acid) is a structural analogue of baclofen and gabapentin. It is produced in various formulations, including tablets and powder for oral use and a crystalline form. Phenibut is a

registered pharmaceutical in some countries and is also marketed online for a number of uses, including as a sleep aid, mood enhancer, treatment for anxiety and a cognitive enhancer.

WHO review history

Phenibut has not been formally reviewed by WHO and is not currently under international control. Phenibut has been under ECDD surveillance since 2017 after reports from Member States of its abuse and dependence potential. A pre-review was initiated after consideration of those reports.

Similarity to known substances and effects on the central nervous system

Phenibut acts primarily as an agonist at the γ -aminobutyric acid (GABA_B) receptor, similar to baclofen, and at the $\alpha 2$ - δ subunit of voltage-dependent calcium channels, similar to gabapentin.

In animal studies, phenibut has dose-dependent analgesic, antidepressant and anxiolytic effects, which are mediated both by its GABA_B agonist effects and actions at voltage-dependent calcium channels.

Phenibut intoxication can result in central nervous system depressive symptoms, including decreased level of consciousness, muscle tone, stupor, depressed respiration, temperature dysregulation, hyper- or hypotension and coma. Other individuals have presented with agitation, hallucinations, seizures and delirium.

Dependence potential

No studies have been conducted in animals on the dependence potential of phenibut. People who use phenibut describe escalating dosing, suggesting tolerance, and difficulty in cessation.

There have been a few case reports of withdrawal symptoms after abrupt discontinuation of high doses of phenibut. The reported symptoms included insomnia, psychomotor agitation, delusions, psychosis, disorganized thought patterns, auditory/visual hallucinations, anxiety, depression, fatigue, dizziness, seizures, decreased appetite, nausea and vomiting, palpitations and tachycardia. In most cases, use of phenibut was not verified analytically, and the clinical picture was complicated by use of other drugs.

Actual abuse and/or evidence of likelihood of abuse

No controlled studies in animals or humans have examined the abuse potential of phenibut.

Adverse effects due to nonmedical use of phenibut have been reported from different countries. The doses taken in medically unsupervised use of phenibut

obtained on the Internet are often much higher than those used clinically; however, many cases involve multiple drugs and the role of phenibut in these cases remains unclear.

Multiple countries over several regions have reported seizure of phenibut. The extent of non-medical use is unknown.

Therapeutic usefulness

Phenibut is approved in a few countries as a medicine for various psychiatric and neurological conditions.

Recommendation

The Committee noted that concern has been raised in several countries on nonmedical use of phenibut. While there have been reports of adverse effects and of a withdrawal syndrome after cessation of use, the information on these cases is very limited. In addition, there is very little information on the abuse liability of phenibut, on the magnitude of its misuse or abuse and on its similarity to currently internationally controlled substances.

The Committee also noted that phenibut is used therapeutically in a few countries.

Recommendation: The Committee recommended that phenibut (IUPAC chemical name: 4-amino-3-phenylbutanoic acid) not be critically reviewed but should be kept under surveillance by the WHO secretariat.

3. Critical review and pre-review reports

3.1 Critical review reports

3.1.1 4F-MDMB-BICA

1. Substance identification

A. International Nonproprietary Name (INN)

Not available.

B. Chemical Abstract Service Registry Number

2666932-37-0 (free base)

2682867-53-2 ((S)-enantiomer)

C. Other chemical names

Methyl 2-{{1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]amino}-3,3-dimethylbutanoate

Methyl 3,3-dimethyl-2-[1-(4-fluorobutyl)-1*H*-indole-3-carboxamido]butanoate

Methyl 3-methyl-*N*-[1-(4-fluorobutyl)-1*H*-indole-3-carbonyl]valinate

Methyl 3,3-dimethyl-2-{{1-(4-fluorobutyl)-1*H*-indol-3-yl]formamido}butanoate

Methyl *N*-{{1-(4-fluorobutyl)-1*H*-indole-3-yl]carbonyl}-3-methylvalinate

Methyl 2-[1-(4-fluorobutyl)-1*H*-indole-3-carboxamido]-3,3-dimethylbutanoate

Methyl 2-{{1-(4-fluorobutyl)indol-3-yl]formamido}-3,3-dimethylbutanoate

Methyl 2-{{1-(4-fluorobutyl)indole-3-carbonyl]amino}-3,3-dimethyl-butanoate

Methyl *N*-{{1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}-3-methylvalinate

Methyl 2-{{1-(4-fluorobutyl)indol-3-yl]formamido}-3,3-dimethylbutanoate

N-(1-Methoxy-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobutyl)-1*H*-indole-3-carboxamide

MDMB-4F-BICA

4F-MDMB-2201

MDMB-4F-BUTICA

4F-MDMB-BUTICA

4-Fluoro MDMB-BICA

4-Fluoro MDMB-BUTICA

4FBC

4FBCA

MDMB-073-F.

D. Trade names

(S)-Enantiomer (methyl(S)-2-(1-(4-fluorobutyl)-1*H*-indole-3-carboxamido)-3,3-dimethylbutanoate) is sold by Cayman Chemical as an analytical standard under the trade name 4-fluoro MDMB-BUTICA (5).

E. Street names

“Bika” (“bull” in Hungarian) (6). In one case, a seized smoking mixture branded as a “legal-high” product called “Pico Bello” was found to contain 4F-MDMB-BICA (7).

F. Physical appearance

Seized quantities of a street version were formulated as a white, off-white, brown or orange powder (8).

4F-MDMB-BICA has also been identified in herbal blends and vaping solutions and infused onto paper (8).

It is available as a crystalline solid from Cayman Chemicals (9).

G. WHO review history

4F-MDMB-BICA 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

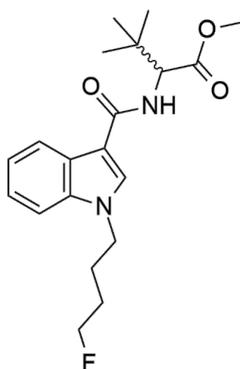
A. Chemical name

IUPAC name: Methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate

Chemical Abstracts Index Name: Valine, *N*-[[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl]-3-methyl-methyl ester

B. Chemical structure

Free base:

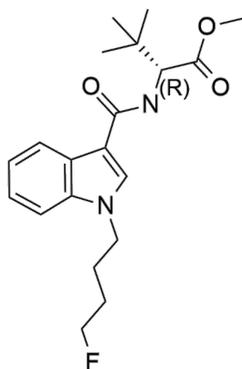


Molecular formula: C₂₀H₂₇FN₂O₃

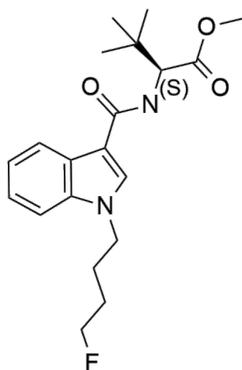
Molecular weight: 362.44 g/mol

C. Stereoisomers

The presence of an asymmetric carbon atom gives rise to the (*R*)- and (*S*)-enantiomers of 4F-MDMB-BICA. Although structurally related synthetic cannabinoid receptor agonists typically show the (*S*)-configuration, it could not be ruled out that the same substance with either the (*R*)-configuration or the racemic mixture is present in seized samples (7).



Methyl (R)-2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate ((*R*)-4F-MDMB-BICA).



Methyl (S)-2-({[1-(4-fluorobutyl)-1*H*-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate ((*S*)-4F-MDMB-BICA).

D. Methods and ease of illicit manufacture

No information was available on the manufacture of 4F-MDMB-BICA seized or collected from the market. Preparation of this substance is, however, straightforward, as it follows standard procedures with cheap, readily available reagents. One example is the synthesis procedure for (*S*)-4F-MDMB-BICA described by Annelies Cannart et al. (10), which comprises three steps, starting

from indole. The process, although simple, requires the equipment of a chemical synthetic laboratory and qualified personnel.

E. Chemical properties

Melting-point: The melting-point of the (S)-enantiomer has been reported to be 86–88 °C (10).

Boiling-point: No information was identified.

Solubility: No information was identified.

F. Identification and analysis

Synthetic 4F-MDMB-BICA was characterized, and ¹H-nuclear magnetic resonance (NMR), ¹³C-NMR and infrared (IR) spectroscopy properties (10) have been reported. (S)-4F-MDMB-BICA is available as a reference material from commercial suppliers for use in routine analysis in forensic and clinical investigations (5, 11).

Analytical methods for the identification and quantification of 4F-MDMB-BICA in seized and biological sample matrices have been published. They include various chromatographic, spectroscopic and mass spectrometric (MS) methods (12).

4F-MDMB-BICA was identified in powders by gas chromatography–mass spectrometry (GC–MS), IR spectroscopy, liquid chromatography–mass spectrometry (LC–MS), ion chromatography and NMR (13, 14) and in seized paper-impregnated samples by ion mobility spectrometry (15).

Analysis for identification and quantification of 4F-MDMB-BICA and its major metabolites was conducted in zebrafish exposed to 4F-MDMB-BICA, human liver microsome, human urine and blood samples by LC coupled with quadrupole time-of-flight (LC-QTOF) MS, ultra-high performance LC coupled to quadrupole-Orbitrap ultra-high-resolution MS (UHPLC–HRMS) or LC coupled to triple-quadrupole mass spectrometry (QqQ-MS) (16–18).

No information on the enantiomeric composition of 4F-MDMB-BICA has been reported, as stereochemical analysis is not usually undertaken, but it would seem likely that the 4F-MDMB-BICA on the market exists as the (S)-enantiomer, like most other closely related synthetic cannabinoids. Explicit identification of the (S)-enantiomer has not been confirmed with identification of 4F-MDMB-BICA. Until reference material for the (S)-enantiomer becomes available, the existence of the (R)-enantiomer (including its presence as an impurity) cannot be excluded (12).

3. Ease of convertibility into controlled substances

No information was available on whether 4F-MDMB-BICA can be converted into a controlled substance.

4. General pharmacology

A. Routes of administration and dosage

Postings on online user forums indicate that 4F-MDMB-BICA is usually inhaled by smoking or vaping after the chemical has been sprayed onto herbal material or solubilized in a vehicle for vaping, respectively (19, 20). The presence of 4F-MDMB-BICA has been confirmed in seizures of various products: herbal mixtures designed for smoking, liquids formulated for vaping, paper infused with the chemical (primarily used to smuggle material into controlled environments such as prisons) and powders for formulation by the user and for making products (21). The dose required for intoxication is uncertain.

B. Pharmacokinetics

No information was available on the absorption and distribution of 4F-MDMB-BICA. A few studies have specifically addressed its phase-I metabolism for identification of biomarker(s) to be used in forensic investigations as indicators of use. One study investigated the effects of 4F-MDMB-BICA in a pooled human liver microsome assay, with follow-up analysis of five authentic urine samples and two blood samples from people who had used 4F-MDMB-BICA (17), whereas another examined the metabolism of 4F-MDMB-BICA in zebrafish (18). A third study mentioned detection of the parent compound and hydrolysis metabolite(s) in serum or urine samples (16). While the authors of this study noted that the presence of hydrolysis metabolites extended the opportunity for detection of 4F-MDMB-BICA in biological samples, they did not provide further information on metabolite identification. The first (and most comprehensive) study reported that, like many other synthetic cannabinoids, 4F-MDMB-BICA is extensively metabolized, with the parent compound identified in only one (of five) authentic urine samples evaluated (17). Thirty putative metabolites were observed in pooled human liver microsomes, 20 were identified in authentic urine samples, and 13 were identified in blood. Of these, the ester hydrolysis metabolite (identified in urine and blood) was suggested to be the primary biomarker for 4F-MDMB-BICA, and the mono-hydroxylation and ester hydrolysis + dehydrogenation metabolites products in the urine and blood, respectively, were suggested as secondary markers.

While no information on time course has been published in the scientific literature, one user reported that the effects of vaped 4F-MDMB-BICA lasted 40 min to 1 h, and another user reported the time course of a smoked blend containing 4F-MDMB-BICA of approximately 1 h and 45 min (20). This information should be considered anecdotal, as the identify of the chemicals contained in the products was not verified.

C. Pharmacodynamics

Very little information is available on the pharmacodynamics of 4F-MDMB-BICA. Given the subjective cannabinoid effects reported in online user forums (20), CB₁ receptor binding would be suspected, but this has not been confirmed by empirical studies. Examination of 4F-MDMB-BICA in a β -arrestin-2 recruitment assay showed that it activates this signalling pathway (which has been associated with the CB₁ receptor), with a half maximal effective concentration (EC_{50}) = 121 nM and E_{max} = 253% (10). In the same assay and laboratory, the potency of 4F-MDMB-BICA was five or six times lower than that of JWH-018 (EC_{50} = 21.4 nM), with higher efficacy (253% of JWH-018 as standard), although 4F-MDMB-BICA was reported to have similar potency and efficacy (EC_{50} = 37.7 nM, Ema x= 129%) to that of JWH-018 at the CB₁ receptor, expressed in CHO cells in an aequorin-based assay of calcium flow (21, 22). The relation between activation of these non-canonical pathways, activation of the canonical pathway of the CB₁ receptor and in vivo potency has not been fully established. At the time of this report, the effects of 4F-MDMB-BICA on the canonical pathway have not been investigated, and its CB₁ receptor binding affinity had not been reported.

5. Toxicology

No preclinical studies have been conducted of the toxicology of 4F-MDMB-BICA.

6. Adverse reactions in humans

Between May and August 2020, 21 deaths related to confirmed use of 4F-MDMB-BICA were reported (23). The causes of death included cardiac arrest or failure (14 cases), traumatic shock (2 cases), strangulation (1 case), brain oedema (1 case) and asphyxiation after aspiration of vomit (1 case). The ante-mortem symptoms, when known, were similar to those reported in overdose with other synthetic cannabinoids, including loss of consciousness, chest pain, respiratory difficulty, seizures and somnolence (21, 23). A causal relation between exposure to 4F-MDMB-BICA and mortality cannot, however, be firmly established, as in most cases additional substances (e.g., other synthetic cannabinoids, benzodiazepines, stimulants, THC) were detected at post-mortem toxicological screening of femoral blood or urine (23).

Other fatal cases involving use of 4F-MDMB-BICA have been implied in the published literature; however, details were not available. For example, in an analysis of biological samples provided by law enforcement agencies in Germany, exposure to 4F-MDMB-BICA was confirmed in femoral blood (a typical medium for autopsy samples) (16). In New Zealand, 4F-MDMB-BICA was associated with two deaths (24). In the USA, 4F-MDMB-BICA was identified

in 26 blood samples from autopsies or DUID cases (25). Nonfatal cases requiring hospitalization with life-threatening symptoms similar to those reported with other synthetic cannabinoids were reported in the United Kingdom (21); however, other substances were also detected in all cases. One serious case requiring hospitalization was also reported in New Zealand (24).

While information on 4F-MDMB-BICA on user forums is scant, several posts on sub-Reddit sites (r/noids) reported adverse effects of 4F-MDMB-BICA use. For example, one user stated that he had smoked “pure chemical” placed in a cigar and on plant material and had passed out after each incident (19). Another user reported considerable anxiety after inhaling a “normal hit” and holding it in, while a third reported observing seizures in companions who used the substance (20). Other subjective effects following purported use of 4F-MDMB-BICA included dissociation, followed by “feeling stoned”, blurred vision, sleepiness and random muscle twitches (20). These user posts should be considered anecdotal, as there was no analytical confirmation of sole use of 4F-MDMB-BICA.

7. Dependence potential

A. Animal studies

No studies of the dependence potential of 4F-MDMB-BICA have been conducted in animals.

B. Human studies

No studies of the dependence potential of 4F-MDMB-BICA have been conducted in humans.

8. Abuse potential

A. Animal studies

No studies of the abuse potential of 4F-MDMB-BICA have been conducted in animals.

B. Human studies

No studies have been conducted to evaluate the abuse potential of 4F-MDMB-BICA in humans.

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

4F-MDMB-BICA has no known therapeutic applications and is not used medically.

10. Listing on the WHO Model List of Essential Medicines

4F-MDMB-BICA is not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

There is no known marketing authorization.

12. Industrial use

There is no known industrial use.

13. Non-medical use, abuse and dependence

4F-MDMB-BICA was first identified on the European drug market in March 2020 in a seizure by Belgian authorities (21). The substance was identified in the USA in May 2020 and was listed in toxicology trend reports issued by the Center for Forensic Science, Research and Education from the third quarter of 2020 to the latest report in the second quarter of 2021 (26). By November 2020, 111 seizures had been made in 12 Member States of the European Union, the bulk of the total amount being confiscated in Belgium (21). In Europe, law enforcement or customs authorities made seizures in the following Member States (number of seizures in parentheses): Hungary (72), the United Kingdom (17), Belgium (4), Slovenia (4), Cyprus (3), Finland (3), Germany (2), Lithuania (2), Croatia (1), Italy (1), Poland (1) and Sweden (1). The products seized included pure powder as well as e-liquids, plant material mixtures and paper blotters infused with the chemical. Toxicology showed that other synthetic cannabinoids were frequently used in conjunction with 4F-MDMB-BICA (21, 26).

The prevalence of chronic use and dependence of 4F-MDMB-BICA has not been reported.

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

At least 21 deaths in which 4F-MDMB-BICA was present post mortem have occurred in Hungary (23). While deaths are likely to have also occurred elsewhere (see section 6), no detailed information was available on the number of deaths or their circumstances. Five hospitalizations for acute poisoning with 4F-MDMB-BICA combined with other substances were reported in the United Kingdom (21), and one hospitalization for serious symptoms was reported in New Zealand (24). Driving under the influence of 4F-MDMB-BICA has also been documented in the USA (26). Eleven seizures of 4F-MDMB-BICA infused on paper blotters have been made in prisons, suggesting that the chemical has infiltrated to the incarcerated population (21, 23).

15. Licit production, consumption and international trade

There is no licit production.

16. Illicit manufacture and traffic and related information

The number and quantity of seizures indicate that early distribution appears to have been focused on Hungary and northern Europe (e.g., Belgium, Finland, the Netherlands) (21). The first documented seizure of the drug in Europe was in March 2020 in Belgium. The chemical quickly moved to the USA, being cited in at least 26 toxicology reports by July 2020 (26).

17. Current international controls and their impact

There are no international controls specific to 4F-MDMB-BICA.

18. Current and past national controls

Thirteen Member States of the European Union have issued regulations for the control of 4F-MDMB-BICA, under drug control or medicines legislation (21). The countries are Austria, Belgium, Croatia, Cyprus, France, Germany, Hungary, Italy, Latvia, Luxembourg, Norway, Poland, Turkey and the United Kingdom. The presence of 4F-MDMB-BICA has also been confirmed in New Zealand (24). The USA has not yet scheduled 4F-MDMB-BICA but recently issued a notice and request for comments on the substance in the Federal Register as a prelude to possible scheduling (27).

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

There were no other relevant medical or scientific matters.

3.1.2 Biorphine

1. Substance identification

A. International Nonproprietary Name (INN)

No information was identified.

B. Chemical Abstracts Services Registry Number

2244737-98-0 (base)

2707204-49-5 (HCl)

C. Other chemical names

1-(1-(1-(4-Bromophenyl)ethyl)piperidin-4-yl)-1*H*-benzo[d]imidazol-2(3*H*)-one

1-(1-(1-(4-Bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one

3-[1-[1-(4-Bromophenyl)ethyl]-4-piperidyl]-1*H*-benzimidazol-2-one

D. Trade names

No information was identified.

E. Street names

Brorphine; purple heroin.

F. Physical appearance

Brorphine freebase has been described as a white solid (28) and the hydrochloride salt as a neat solid (29). A collected sample identified as the free base has also been described as white-off-white (30). Seized brorphine samples have been reported as white and yellowish powders (30). Brorphine has also been found as a grey, purple or white powder or in crystal form (31).

G. WHO review history

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

2. Chemistry

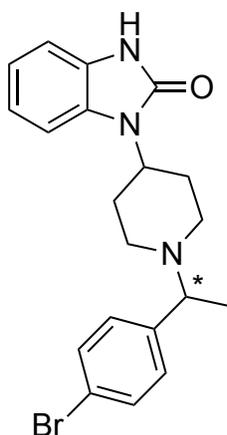
A. Chemical name

IUPAC name: 3- {1- [1- (4-bromophenyl) ethyl] piperidin-4-yl} -1*H*-benzimidazol-2-one

CA Index name: 1-[1-[1-(4-Bromophenyl)ethyl]-4-piperidiny]-1,3-dihydro-2*H*-benzimidazol-2-one

B. Chemical structure

Free base:



Note: Asterisk (*) refers to a chiral centre

Molecular formula: $C_{20}H_{22}BrN_3O$

Molecular weight: 400.32 g/mol

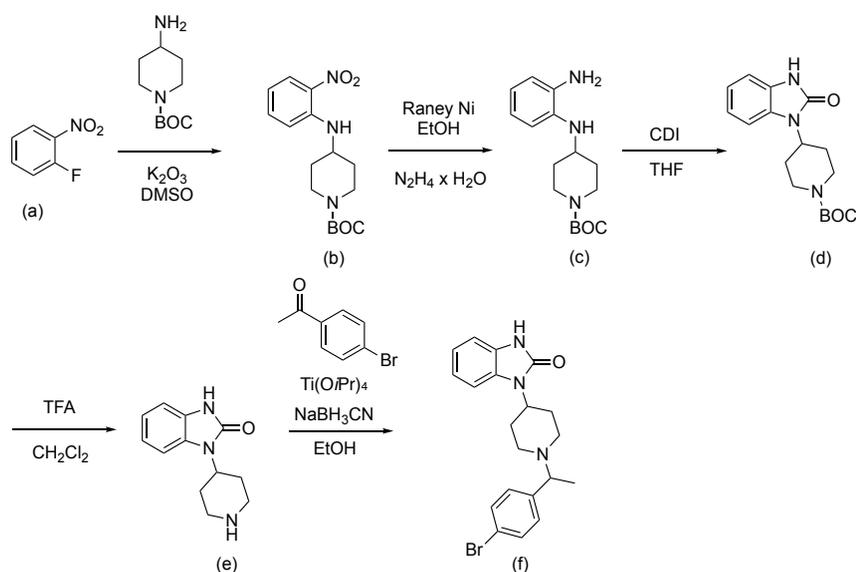
C. Stereoisomers

The presence of a chiral centre gives rise to the enantiomeric pair of (*S*)-bropirine and (*R*)-bropirine. Bropirine is probably available as the racemic mixture, although the appearance of individual stereoisomers cannot be excluded.

D. Methods and ease of illicit manufacturing

No information was found on the specific routes of synthesis used for bropirine products circulating on the market, but there are straightforward methods for its preparation by standard procedures that do not require access to internationally controlled precursors. One approach is shown in Fig. 1. 1-Fluoro-2-nitrobenzene (a) undergoes nucleophilic substitution with *tert*-butyl 4-aminopiperidine-1-carboxylate to give *tert*-butyl 4-((2-nitrophenyl)amino)piperidine-1-carboxylate (b). The nitro group is reduced to the amino group (intermediate c) and then converted into the cyclic urea intermediate (d). Deprotection with trifluoroacetic acid gives 1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one (e), followed by reductive amination with 1-(4-bromophenyl)ethanone, which results in the formation of bropirine (f) (32). Although not mentioned explicitly, bropirine and closely related compounds were included in a patent by Janssen Pharmaceutica N.V., which also includes a description of straightforward synthesis procedures (33).

Fig. 1. Synthesis of bropirine



Modified from reference 32.

E. Chemical properties

Melting-point: No information was available.

Boiling-point: No information was available.

Solubility: Brorphine base was reported to be partially soluble in dichloromethane and methanol but poorly soluble in water (34).

F. Identification and analysis

Identification is straightforward, especially when the product is available in larger quantities than are usually encountered in forensic toxicology. Analytical data reported in scientific publications include those obtained by chromatographic and spectroscopic methods (32, 35, 36), while information available in the public domain includes chromatographic, mass spectral and spectroscopic data (34, 37, 38). Certified reference material is available commercially for developing and validating analytical methods. The high potency of many synthetic opioids requires use of sensitive methods of detection that include suitable methods of separation and systems such as mass spectrometry (single or multi-stage analysis).

3. Ease of Convertibility into controlled substances

Bezitramide (IUPAC name: 4-[4-(2-oxo-3-propanoyl-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]-2,2-diphenylbutanenitrile), which also contains a piperidine 4-benzimidazolone template, is listed in Schedule I of the 1961 Convention (as amended by the Protocol of 25 March 1972) (39). No information on the convertibility of brorphine to bezitramide was identified. Published reports describe *N*-debenzylation of substituted piperidines under reductive conditions (e.g., 40, 41). If this is applicable to brorphine, the product of *N*-debenzylation would be the 1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one intermediate (e) shown in Fig. 1. In patents of the Research Laboratorium Dr C. Janssen NV (Belgium) on preparation of bezitramide-type compounds, benzyl group-containing intermediates were subjected to similar reductive *N*-debenzylation conditions, which showed that the 1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one intermediate can be converted into bezitramide, which is straightforward (33, 42, 43).

4. General pharmacology

A. Routes of administration and dosage

Descriptions on online forums suggest that brorphine is administered preferably orally as a powder (presumably also in capsules or tablets) or inhaled by smoking or vaporizing (e.g., 44–47). The solubility of brorphine base in acidified water (48, 49) and the preparation of emulsions in medium-chain triglyceride–water mixtures (50) have also been described. The extent to which such formulations are used for injection is unclear. Some information is available on the dose

and dose regimens of bupropion (e.g., 44) (Table 1). “Typical” doses depend on factors such as the route of administration, the opioid tolerance of people who use bupropion, use of other drugs and the desired effects. Higher single oral doses have also been described (e.g., 51). Bupropion was estimated to be 10 times more potent than morphine or three to five times more potent than morphine by oral administration (52). Given the difficulty of collecting such data, the doses shown below should be interpreted with caution.

Table 1. Doses of bupropion suggested in Internet forums

Route	“Average beginner”	“Veteran” dosage
Oral	1–2 mg: light 3–5 mg: medium > 6 mg: strong/danger	2–5 mg: light 6–9 mg: medium 10–13: strong
Smoked	1 mg: light 2 mg: medium 3 mg: strong/danger	1–2 mg: light 3–5 mg: medium > 6 mg: strong

Source: references 44 and 52

B. Pharmacokinetics

No clinical studies were identified in which pharmacokinetics was reported. Transformation of bupropion in pooled human liver microsomes *in vitro* resulted in six metabolites (35). The detected species represented *N*-debenzylation (plus hydroxylation of this metabolite), hydroxylations at the benzimidazol-2-one and piperidine rings, *O*-methylation of the hydroxylated benzimidazol-2-one metabolite, and oxidation of the piperidine moiety to the 1,2,3,4-tetrahydropyridine analogue of bupropion. The *N*-debenzylated and hydroxylated benzimidazol-2-one metabolites have also been detected in blood and urine samples taken from post-mortem samples (35). A bupropion metabolite hydroxylated at the benzimidazol-2-one moiety was detected in a serum sample from person who had used the substance (36). Grafinger and colleagues (53) subsequently reported detection of phase-I and phase-II biotransformation products in samples obtained *in vitro* and *in vivo* (case work), which also included detection of previously unreported metabolites. Information on Internet forums suggests that the effects last 3–8 h after oral administration (46, 54) and sometimes longer (45). In a published case report, a person who started taking bupropion orally four times a day reported that the effects lasted “quite long”. Bupropion was still detected in a serum sample analysed 60 h after admission of the person to an emergency department (36).

C. Pharmacodynamics

Brorphine is a potent agonist at the MOR (Table 2). In an in-vitro GTP γ S binding assay, brorphine was 7–13 times more potent than [D-Ala², N-mePhe⁴, Gly-ol]-enkephalin (DAMGO) or morphine. All three compounds acted as full agonists under the same assay conditions. Assessment of β -arrestin2 recruitment profiles in the same study showed that brorphine was equipotent to DAMGO and twice as potent as morphine, although the latter had very low efficacy (Table 2) (55).

Table 2. GTP γ S binding and β -arrestin2 recruitment activity

Compound	[³⁵ S]-GTP γ S (EC ₅₀ /nM)	E _{max} (%)	β -Arrestin2 (EC ₅₀ /nM)	E _{max} (%)
DAMGO	33	100	220	100
Morphine	64	83	379	24
Brorphine	4.8	91	182	92

Source: reference 55

MOR-stimulated GTP γ S binding, membranes prepared from CHO-hMOR cells; β -arrestin2 interactions with MOR, USOS- β arrestin-hMOR-PathHunter cells used in an enzyme fragment complementation assay.

The results of another study on the recruitment of either β -arrestin2 or mini-Gi to activated MOR in vitro confirmed that brorphine leads to MOR activation, like other synthetic opioids such as hydromorphone, fentanyl and isotonitazene (Table 3) (56). In the mini-Gi assay, brorphine was about 2.5 times less potent than hydromorphone but almost four times more effective. Isotonitazene was 6.5 times more potent than brorphine and was also more effective. Fentanyl was three times more potent than brorphine but was less effective, although both were more effective than hydromorphone. In the β -arrestin2 recruitment assay, brorphine was 4.7 times less potent than isotonitazene and 2.2 times less potent than fentanyl but was slightly more efficient. Brorphine was 1.6 times more potent than hydromorphone, with doubled efficacy. Results in the β -arrestin2 assay under similar conditions were reported subsequently for brorphine (EC₅₀ = 30.9 nM; E_{max} = 209%) and hydromorphone (EC₅₀ = 26.0 nM; E_{max} = 97.5%) (36).

Table 3. Mini-G_i- and β -arrestin2 recruitment

Compound	Mini-G _i (EC ₅₀ / nM)	E _{max} (%)	β arrestin2 (EC ₅₀ / nM)	E _{max} (%)
Brorphine	106	385	31.1	226
Hydromorphone	44	100	51.0	100
Fentanyl	32.7	284	14.3	163

Source: reference 57

HEK293T stably expressing either MOR- β arr2-GRK2 (or MOR-mini-G_i system; mini-G_i: GTPase domain of G_{ai} subunit)

In the three-factor analysis documentation for temporary control of brorphine published by the US Drug Enforcement Administration (DEA), it was also reported that brorphine binds to and activates MOR. In the functional ³⁵S-GTP γ S binding assay, brorphine (EC₅₀ = 16.3 nM; E_{max} = 117.6% relative to DAMGO) was stated to be equipotent to fentanyl (EC₅₀ = 19 nM; E_{max} = 88.5% relative to DAMGO) with slightly higher efficacy (58).

5. Toxicology

No information was found on the acute or chronic preclinical toxicology of brorphine.

6. Adverse reactions in humans

Detection of brorphine in biological samples collected during case work reported in the literature are summarized in tables 4 and 5. In a non-fatal case of intoxication, the combination of brorphine with chronic serotonergic therapy was considered to account for unconsciousness and severe rhabdomyolysis with acute kidney failure due to serotonergic toxicity (59). It is not known whether brorphine has serotonergic effects in vivo. Verougstraete et al. (36) described a patient who presented at an emergency department for detoxification, with confusion, bradyphrenia, generalized weakness and cramping and complaining of generalized pain, mainly in the chest, abdomen and muscles. Serum analyses confirmed the presence of brorphine and prescription medicines. Vohra et al. (59) presented an accidental fatal case involving poly-substance use (Table 4).

Table 4. Cases in which bupropion was detected in biological fluids

Age, sex	Comments	Reference
45, M	<p><i>Non-fatal intoxication:</i> severe rhabdomyolysis and acute kidney failure after ingestion of four crushed “M30” tablets bought as oxycodone on the Internet. Patient had a history of depression, which was treated with 25 mg sertraline daily for 6 months; arrived at emergency department 12 h after ingestion.</p> <p>Had become euphoric and dizzy and lost consciousness 30 min after ingesting crushed tablets. Was shivering and drooling while unconscious; woke up after 6 h and was somnolent, confused and nauseous. He was unable to walk due to diffuse myalgia; reported a small volume of dark urine.</p> <p>On arrival at the emergency department, the patient was conscious, confused, diaphoretic and agitated, with diffuse myalgia, ocular clonus, tremor and hyperreflexia. Initial laboratory results revealed severe rhabdomyolysis (serum creatine kinase > 100 000 μkat/L and myoglobin > 20 000 μg/L) and acute kidney failure (serum urea, 16.5 mmol/L and creatinine, 220 μmol/L). Patient became hypervolemic due to deterioration of renal function with oliguria. Diuretic therapy with furosemide was initiated on the third day, and polyuria developed on day 4. Serum myoglobin and creatine kinase normalized within 2 weeks and serum creatinine level within 3 weeks. Bupropion was detected in blood 12 h after ingestion and in the tablet (not quantified).</p>	60
24, M	<p><i>Non-fatal intoxication:</i> Patient presented at an emergency department for admission for detoxification. He had normal blood pressure with tachycardia (114 bpm), oxygen saturation of 98% and temperature of 37.3 °C. His prescribed medications were sertraline, mirtazapine, methylphenidate and enoxaparin.</p> <p>Two serum samples taken about 60 h apart were available; the first was collected at the emergency department (69.4 ng/mL) and the second during hospitalization in a psychiatric ward (7.9 ng/mL). Sertraline and mirtazapine (prescribed) and risperidone were detected at subtherapeutic levels. Trazodone and nordiazepam (administered in the hospital context) were detected in the second sample. A powdered sample provided by the patient was identified as bupropion.</p>	36
61, F	<p><i>Fatal intoxication:</i> accidental death due to combined drug toxicity.</p> <p>A woman with a history of obesity, tobacco use, hypertension, chronic obstructive pulmonary disease, schizophrenia and hyperlipidaemia, with no documented history of substance use was found dead at home. Analysis of cardiac blood showed: ethanol (27 mg/dL), 4-anilino-N-phenethyl piperidine (4-ANPP) (positive), bupropion (2.0 ng/mL), gabapentin (6.8 μg/mL), chlorpromazine (82 ng/mL), fentanyl (0.32 ng/mL), benzodiazepines (presumptive positive) and amphetamines (presumptive positive). Urine analysis showed: benzodiazepines (presumptive positive) and amphetamines (presumptive positive).</p>	59, 61
NA	Detection of bupropion was described (urine or serum), but no further details were reported.	62
NA	Clinical admission after oral administration of the substance. Ante-mortem serum concentration of bupropion, 69 μ g/L.	63

One country in the European Union Early Warning System Network reported a serious adverse event to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), in which exposure to bupropion was confirmed analytically in a biological sample. A non-fatal poisoning in 2021 was linked to use of falsified oxycodone tablets containing bupropion that had been purchased on the Internet (64), which may be the same case reported by Razinger et al. (60) (Table 4).

A series of 20 cases in which a number of substances were found post mortem in June–July 2020 was published by Krotulski et al. (35) (Table 5). Fentanyl was confirmed in all cases and flunitrazepam in 80%. The average concentration of bupropion reported in blood was 2.5 ± 3.1 ng/mL (median, 1.1 ng/mL; range, 0.1–10 ng/mL), and the average concentration of bupropion in urine was 4.6 ± 7.6 ng/mL (median, 1.6 ng/mL; range, 0.2–23 ng/mL). Thirteen of the decedents were male and seven female, with an average age of 48 ± 9 years (median, 49 years; range, 29–61 years). The cases originated from Illinois (n = 13), Minnesota (n = 5), Wisconsin (n = 1) and Arizona (n = 1).

Table 5. Presence of bupropion and other substances in post-mortem samples

Age, sex	Bupropion ^a (ng/mL)	Comments
53, M	Blood: 10 Urine: 23	Suspected overdose; history of opioid use; “heroin” present at scene Analytical results: flunitrazepam (50 ng/mL), 4-ANPP, caffeine, cotinine, quinidine, codeine (6.6 ng/mL), morphine (66 ng/mL), 6-monoacetylmorphine (1.5 ng/mL), citalopram/escitalopram (76 ng/mL), fentanyl (3.4 ng/mL), norfentanyl (0.36 ng/mL), isotonitazene
60, M	Blood: 0.9 Urine: 0.4	No case history available Analytical results: 4-ANPP, caffeine, methadone (160 ng/mL), EDDP (45 ng/mL), morphine (42 ng/mL), bupropion (18 ng/mL), hydroxybupropion (380 ng/mL), duloxetine (520 ng/mL), lamotrigine (6.8 µg/mL), gabapentin (15 µg/mL), fentanyl (14 ng/mL), norfentanyl (11 ng/mL), flunitrazepam
45, M	Blood: 1.0 Urine: 1.9	Suspected overdose; accidental death; cause of death: toxic effects of multiple drugs Analytical results: flunitrazepam (2.5 ng/mL), 4-ANPP, caffeine, cotinine, tramadol (33 ng/mL), Δ^9 -THC (0.62 ng/mL), fentanyl (5.0 ng/mL)
57, F	Blood: positive	Suspected overdose; drug paraphernalia recovered from scene Analytical results: 4-ANPP, caffeine, cotinine, naloxone, cocaine (110 ng/mL), benzoylecgonine (1300 ng/mL), Δ^9 -THC (0.88 ng/mL), diphenhydramine (61 ng/mL), fentanyl (31 ng/mL), norfentanyl (5.5 ng/mL), acetylfentanyl (0.13 ng/mL)

Age, sex	Brorphine ^a (ng/mL)	Comments
42, M	Blood: 1.1 Urine: 3.3	Suspected overdose; accidental death; cause of death: combined drug toxicity Analytical results: 4-ANPP, caffeine, cotinine, naloxone, diphenhydramine (620 ng/mL), fentanyl (36 ng/mL), norfentanyl (1.4 ng/mL), morphine (110 ng/mL), 6-monoacetylmorphine (7.3 ng/mL), flualprazolam
60, M	Blood: 8.1 Urine: 21	Suspected overdose; accidental death; cause of death: combined drug toxicity Analytical results: cotinine, sertraline (26 ng/mL), desmethylertraline (110 ng/mL), verapamil (42 ng/mL), diphenhydramine (960 ng/mL), fentanyl (3.1 ng/mL), morphine (79 ng/mL), 6-monoacetylmorphine (2.5 ng/mL), flualprazolam
47, M	Blood: 2.5	Suspected overdose; sudden death; counterfeit oxycodone pills tested positive for brorphine. Analytical results: 4-ANPP, naloxone, oxycodone (22 ng/mL), sildenafil (35 ng/mL), N-desmethyilsildenafil (10 ng/mL), fentanyl (16 ng/mL), norfentanyl (1.1 ng/mL)
39, M	Blood: 6.7 Urine: 7.3	Suspected overdose; accidental death; cause of death: combined drug toxicity Analytical results: 4-ANPP (positive), caffeine (positive), cotinine (positive), nicotine (positive), alprazolam (14 ng/mL), tramadol (70 ng/mL), gabapentin (10 µg/mL), diphenhydramine (1200 ng/mL), fentanyl (45 ng/mL), norfentanyl (2.1 ng/mL), codeine (6.5 ng/mL), morphine (290 ng/mL), hydromorphone (4.7 ng/mL), flualprazolam
37, F	Blood: 0.7	Suspected overdose; accidental death; cause of death: combined drug toxicity Analytical results: ethanol (138 mg/dL), 4-ANPP (positive), cotinine (positive), naloxone (positive), Δ ⁹ -carboxy-THC (85 ng/mL), Δ ⁹ -THC (18 ng/mL), diphenhydramine (110 ng/mL), fentanyl (22 ng/mL), flualprazolam
48, M	Ante-mortem blood: 0.6 Post-mortem blood: 0.1 Urine: 0.2	Suspected overdose; puncture marks found at autopsy; cause of death: intoxication by brorphine and other drugs Analytical results: flualprazolam (5.4 ng/mL), 4-ANPP (positive), caffeine (positive), naloxone (positive), morphine (8.0 ng/mL), diphenhydramine (190 ng/mL), fentanyl (4.7 ng/mL), norfentanyl (1.6 ng/mL), acetylfentanyl (1.2 ng/mL), clonazepam
47, F	Blood: 6.7 Urine: 2.1	Suspected "heroin" overdose; cause of death: toxic effects of multiple drugs, including brorphine Analytical results: flualprazolam (13 ng/mL), 4-ANPP (positive), cotinine (positive), naloxone (positive), codeine (7.0 ng/mL), morphine (85 ng/mL), 6-monoacetylmorphine (12 ng/mL), xylazine (170 ng/mL), amphetamine (55 ng/mL), methamphetamine (580 ng/mL), fentanyl (190 ng/mL), norfentanyl (5.4 ng/mL), acetylfentanyl (0.15 ng/mL)

Age, sex	Brorphine ^a (ng/mL)	Comments
30, F	Blood: 0.3 Urine: 1.4	Suspected overdose; death occurred at hospital; COVID-19 negative Analytical results: caffeine (positive), naloxone (positive), midazolam (20 ng/mL), amphetamine (110 ng/mL), methamphetamine (1900 ng/mL), 3,4-methylenedioxyamphetamine (9.8 ng/mL), MDMA (75 ng/mL), fentanyl (0.37 ng/mL), norfentanyl (0.97 ng/mL)
53, M	Blood: negative Urine: 0.2	Suspected overdose; cause of death: toxic effects of multiple drugs Analytical results: flualprazolam (20 ng/mL), 4-ANPP (positive), caffeine (positive), naloxone (positive), morphine (15 ng/mL), xylazine (30 ng/mL), fentanyl (19 ng/mL), norfentanyl (4.2 ng/mL)
57, M	Blood: 0.5	Suspected overdose; accidental death; cause of death: combined drug toxicity Analytical results: 4-ANPP (positive), cotinine (positive), naloxone (positive), tramadol (48 ng/mL), diphenhydramine (950 ng/mL), fentanyl (130 ng/mL), norfentanyl (20 ng/mL), acetylfentanyl (0.10 ng/mL), morphine (21 ng/mL), flualprazolam, isotonitazene
54, F	Blood: Urine:	Suspected overdose; pulmonary and cerebral oedema Analytical results: ethanol (19 mg/dL), codeine (21 ng/mL), morphine (290 ng/mL), 6-monoacetylmorphine (34 ng/mL), lamotrigine (0.60 µg/mL), topiramate (9400 ng/mL), cyclobenzaprine (38 ng/mL), amphetamine (140 ng/mL), methamphetamine (730 ng/mL), fentanyl (17 ng/mL), flualprazolam
NA	Blood: 0.7 Urine: negative	Suspected overdose; accidental death; cause of death: combined drug toxicity Analytical results: ethanol (100 mg/dL), 4-ANPP (positive), caffeine (positive), cotinine (positive), naloxone (positive), nicotine (positive), nordiazepam (130 ng/mL), chlordiazepoxide (66 ng/mL), lorazepam (9.4 ng/mL), 9-THC (0.70 ng/mL), diphenhydramine (53 ng/mL), fentanyl (32 ng/mL), flualprazolam
51, M	Blood: 1.1 Urine: 0.4	Suspected overdose; accidental death; cause of death: combined drug toxicity Analytical results: ethanol (60 mg/dL), 4-ANPP (positive), caffeine (positive), cotinine (positive), naloxone (positive), nicotine (positive), cocaine (71 ng/mL), benzoylecgonine (1600 ng/mL), diphenhydramine (98 ng/mL), fentanyl (9.3 ng/mL), norfentanyl, flualprazolam

Age, sex	Brorphine ^a (ng/mL)	Comments
49, F	Blood: 3.8 Urine: 1.8	Suspected overdose; cause of death: combined drug toxicity, including brorphine Analytical results: 4-ANPP (positive), caffeine (positive), naloxone (positive), diphenhydramine (260 ng/mL), fentanyl (21 ng/mL), norfentanyl (12 ng/mL), acetylfentanyl (2.0 ng/mL), morphine (70 ng/mL), flualprazolam
29, M	Blood: 1.1 Urine: 0.8	Suspected overdose; illicit drugs found at scene; history of drug use; cause of death: adverse effects of drugs Analytical results: flualprazolam (3.6 ng/mL), 4-ANPP (positive), caffeine (positive), cotinine (positive), naloxone (positive), nicotine (positive), quinine (positive), acetaminophen (16 µg/mL), 7-aminoclonazepam (5.2 ng/mL), tramadol (70 ng/mL), diphenhydramine (490 ng/mL), amphetamine (10 ng/mL), methamphetamine (42 ng/mL), fentanyl (37 ng/mL), norfentanyl (1.3 ng/mL)
61, F	Blood: 0.4 Urine: 0.2	Suspected overdose; cause of death: multiple drug intoxication Analytical results: ethanol (57 mg/dL), 4-ANPP (positive), cotinine (positive), naloxone (positive), nicotine (positive), alprazolam (65 ng/mL), benzoylecgonine (330 ng/mL), morphine (33 ng/mL), 6-monoacetylmorphine (2.3 ng/mL), gabapentin (9.9 µg/mL), fentanyl (21 ng/mL), norfentanyl (1.9 ng/mL)

Modified from reference 35

^a Femoral, peripheral, iliac or hospital blood

Aggregated data on 58 brorphine detections in various types of forensic cases were published by the US Center for Forensic Science Research and Education (CFSRE) covering the period between the third quarter of 2020 and the second quarter of 2021. The detections included other substances (Table 6), for a total of over 60 detections.¹ Brorphine was found in 3.7% (third quarter 2020), 1.25% (fourth quarter 2020) and 0.9% (first quarter 2021) of cases (64). At the time of writing, brorphine had been identified in about 200 cases overall, although all may not have been analytically confirmed.¹ This represented an increase in the number of the detections reported up to the fourth quarter of 2020 (56) and the results (120 cases) reported between June and October 2020 (31). The actual number of confirmed identifications may be lower than those identified during screening.

¹ A.J. Krotuski, personal communication

Table 6. New psychoactive substance (NPS) opioids in the USA, 2020–2021

Quarter	Brorphine	Fentanyl	Combinations b	Frequency	Reference
Third 2020	44	361	Brorphine + fentanyl Brorphine + flualprazolam Brorphine + stimulant (cocaine and/or methamphetamine) Brorphine + tramadol Brorphine + isotonitazene	39 39 18 9 6	65
Fourth 2020	9	392	Brorphine + fentanyl Brorphine + flualprazolam Brorphine + stimulant (cocaine and/or methamphetamine)	8 8 7	66
First 2021	4	249	–	–	67
Second 2021	1	306	–	–	68

From Center for Forensic Science Research and Education

The forensic cases included illicit drug investigations, medicolegal death investigations and DUID investigations. Identifications at CFSRE include those from sample-mining, data-mining and/or esoteric testing.

7. Dependence potential

A. Animal studies

Information could not be identified.

B. Human studies

No clinical studies on withdrawal or physical dependence were identified. Self-reports from people who used brorphine suggested that regular consumption was associated with the development of tolerance (36, 47, 49) and withdrawal symptoms (69).

8. Abuse potential

A. Animal studies

Drug discrimination studies: In a two-lever discrimination task, 10 male Sprague-Dawley rats were given a training dose of morphine sulfate at 3.2 mg/kg under a fixed-ratio schedule of reinforcement, brorphine at 0.1–0.32 mg/kg fully substituted (median effective dose [ED_{50}] = 0.16 mg/kg) for the discriminative stimulus effects of morphine (ED_{50} = 1.46 mg/kg). The ED_{50} for a fentanyl standard was 0.0090 mg/kg. The peak morphine-appropriate response (E_{max}) was $99 \pm 1\%$. The response rate decreased to 74% of vehicle control after 0.32 mg/

kg brrorphine. Naltrexone (1 mg/kg) blocked the morphine-like discriminative stimulus effects of brrorphine, reducing the morphine-appropriate response to $26 \pm 12\%$. Brrorphine was nine times more potent than morphine according to the differences in ED_{50} values (70).

Warm-water tail flick assay: The analgesic effects of brrorphine were tested in 10 Swiss-Webster mice for baseline tail withdrawal latency in water at 50° C. Brrorphine was administered subcutaneously at doses of 0.01–3.2 mg/kg. Brrorphine ($ED_{50} = 0.11$ mg/kg) dose-dependently increased the tail-flick latency to a maximum peak effect. The ED_{50} was 1.31 mg/kg ($E_{max} = 98\%$ peak effect) for the morphine standard and 0.084 mg/kg ($E_{max} = 100\%$ peak effect) for the fentanyl standard. The peak analgesic effect of brrorphine lasted 75 min and returned to baseline within 120 min. Naltrexone (1 mg/kg) blocked the analgesic effects of brrorphine, reducing the tail-flick latency to $14.9 \pm 3.3\%$ of the peak effect. The ED_{50} values indicate that brrorphine was 12 times more potent than morphine, and fentanyl was 1.3 times more potent than brrorphine (71).

B. Human studies

No clinical studies were available.

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

No information on therapeutic use was identified.

10. Listing on the WHO Model List of Essential Medicines

Brrorphine is not listed on the 21st WHO Essential Medicines List or the 7th WHO Essential Medicines List for Children.

11. Marketing authorization (as a medicinal product)

No information was found on marketing authorization of brrorphine as a medicinal product.

12. Industrial use

No recorded industrial use was identified.

13. Non-medical use, abuse and dependence

No epidemiological evidence on the use of brrorphine was identified. Detection of brrorphine in biological fluids confirms that this substance is used recreationally. Information from Internet forums suggests that this substance might be used by individuals who use heroin, prescription opioid analgesics and other synthetic opioids. It may be used in combination (intentionally or unintentionally) with other drugs, and people using the substance may be unaware of the exact dose or compound they are taking. Brrorphine is available as a product and is

advertised for sale by some Internet retailers, including on the “dark web” (72). The information available suggests that buprenorphine shows abuse liability and that it extends to dependence-producing properties. Discussions on buprenorphine on online forums appear to have been available since at least early 2019 (56, 73, 74).

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

No epidemiological data were found on harm associated with buprenorphine use. The information on fatal and non-fatal intoxications (section 6) suggests poly-substance use. No data were identified on the effects of buprenorphine on the ability to drive and operate machines; however, it is well established that opioid analgesics reduce the mental and physical ability required for these activities. It has been suggested that buprenorphine was introduced onto the US market to replace isotonitazene, another synthetic opioid (56).

Marginalized and vulnerable people who use opioids, including those who inject such substances, might also use synthetic opioid “research chemicals” but may not be aware of using them, and the high potency of some synthetic opioids might increase their risk of life-threatening overdose. Buprenorphine has been detected in falsified oxycodone tablets and implicated in fatal and non-fatal intoxications (35, 60, 75), and there is evidence that these falsified products may be purchased via the Internet (75). The EMCDDA has noted that falsified medicines are commonly visually indistinguishable from legitimate products, and people using these products will be unaware of what and how much of the drug they contain, posing inherent individual risks. The risk of poisoning may be greater with unintentionally high doses, especially when combined with other substances. Like other opioid analgesics, buprenorphine combined with other central nervous system depressants can increase the risk of life-threatening respiratory depression and arrest. Both people with current high-risk opioid use and groups who may have no or limited tolerance to opioids, including people who use recreational drugs, may be at risk of poisoning. People who use drugs recreationally are less likely to be aware of the risk of overdose and might be less likely to have access to community opioid overdose prevention programmes, including naloxone programmes (30, 75). Buprenorphine was reported to be one of the constituents of poly-substance mixtures called “purple heroin”, which have also been found to include benzodiazepines, acetaminophen, antidepressants and fentanyl (31).

15. Licit production, consumption and international trade

Buprenorphine is used as a reference material in scientific research. It is not known to have any agricultural, industrial or cosmetic use.

16. Illicit manufacture, traffic and related information

Brorphine was formally notified to the European Union Early Warning System Network by the EMCDDA on behalf of Sweden on 4 June 2020 after a sample was seized in March 2020. Brorphine has been available on the drug market in Europe since at least March 2020. As of 15 July 2021, three countries in the Early Warning System network had reported five detections of brorphine to the EMCDDA, two of which were seizures. The most recent detection was reported in January 2021. In the detections reported to the EMCDDA, brorphine was found in powders (6 g), in capsules (4 units) and in tablets (2 units). The detections included seizures and collected samples (test purchases and one collection associated with a serious adverse event). The limited data indicate that brorphine can be purchased under its own name. In at least one case, brorphine was mis-sold as oxycodone tablets (75).

As of 25 July 2021, two countries had reported brorphine detections to the UNODC in 2019, two in 2020 and two in 2021 (76).

The National Forensic Laboratory Information System (NFLIS) in the USA, which collects drug cases submitted by state and local laboratories, has registered reports of the detection of brorphine. Three-factor analysis documentation for temporary control of brorphine published by the DEA in August 2020 showed that 20 reports had been received, one of which reported 12 533 g of brorphine. At the time of the query (18 August 2020), the DEA was aware of 11 more seizures of brorphine that had not yet been reported to the NFLIS, some in 2019 (58) and 20 between June 2019 and August 2020 (77). The numbers were not reported in the NFLIS annual drug report in 2019 (78) nor in the 2020 mid-year report (79). Brorphine was, however, included in the NFLIS “snapshot” report of March 2021 (80; Table 7). It was also reported that brorphine was included in an NFLIS snapshot report in December 2019 (35).

Table 7. National Forensic Laboratory Information System (USA) reports on the first five drugs in the category “selected narcotic analgesics” received between 1 January and 31 March 2021

Compound	No. of reports
Phenylfentanyl	151
Fluorofentanyl	77
Brorphine	28
Isotonitazene	26
Metonitazene	23

Source: reference 80

a All positional and unspecified isomers reported by participating laboratories

Some cases were reported in which bupropion was found in combination with heroin and fentanyl, while some reports on suspected heroin–fentanyl powders reported detection of bupropion in combination with flunitrazepam and diphenhydramine (77).

Bupropion was not included in the 2019 annual report on emerging threats in reports from the DEA laboratory system (81). The 2020 annual report included 4862 identifications of fentanyl, fentanyl-related compounds and other new synthetic opioids. Fentanyl accounted for approximately 89% of the identifications (4323). Bupropion was reported twice and was indicated as being reported for the first time in 2020 (82). A DEA bulletin published in July 2021 contains updated NFLIS drug data of 131 reports received between June 2019 and June 2021, showing an increase in mid-2020 (31). The numbers covered in this section are likely to change because of delays in reporting related to the COVID-19 pandemic.

17. Current international controls and their impact

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

18. Current and past national controls

See Annex 1, the report on the WHO questionnaire for review of psychoactive substances.

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

Detections of bupropion may be under-reported if it is not routinely screened for in all laboratories that receive samples for analysis.

3.1.3 Metonitazene

1. Substance identification

A. International Nonproprietary Name (INN)

No information was found.

B. Chemical Abstract Services Registry Number

14680-51-4 free base

3983-24-2 hydrochloride salt

C. Other chemical names

Benzimidazole

1-[2-(Diethylamino)ethyl]-2-(*p*-methoxybenzyl)-5-nitro- (6CI, 7CI, 8CI)

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

D. Trade names

Metonitazene is also known as NIH 7606.

E. Street names

Not available

F. Physical appearance

Metonitazene has been described as a white, off-white or beige powder, sometimes referred to as crystalline in consistency (83–85). The free base and the hydrochloride salt occur as white or coloured powders. The citrate salt is described as a crystalline solid (86).

Images on Reddit, an online discussion forum (87), and on a website offering metonitazene for sale (88) depict metonitazene as white, off-white or beige powder.

G. WHO review history

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

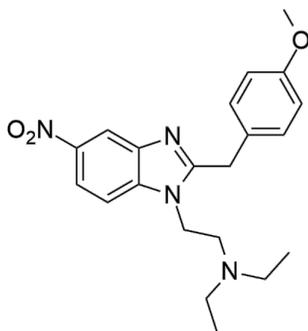
2. Chemistry**A. Chemical name**

IUPAC name: *N,N*-Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-benzo[d]imidazol-1-yl)ethan-1-amine

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

B. Chemical structure

Free base:



Molecular formula: $C_{21}H_{26}N_4O_3$
Molecular weight: 382.46 g/mol

C. Stereoisomers

No stereoisomers of metonitazene have been described.

D. Methods and ease of illicit manufacturing

Metonitazene is a 5-nitro-2-benzylbenzimidazole belonging to the series of 2-benzylbenzimidazole compounds developed in the late 1950s as opioid analgesics (89). Etonitazene, isonitazene, protonitazene and butonitazene are homologues of metonitazene. Substitution at the C-4 position of the benzyl moiety with a methoxy, ethoxy, isopropoxy and n-propoxy group differentiates metonitazene, etonitazene, protonitazene and butonitazene, respectively. 2-Benzylbenzimidazole compounds can be synthesized via several pathways described in the literature (90–99). Although the reagents are readily available on the market and cheap, all syntheses must be conducted by specialized personnel in well-equipped synthetic chemistry laboratories.

No information was available on the method and scale of manufacture of recently detected 2-benzylbenzimidazoles, although there are several simple, cost-efficient methods that do not require regulated precursors (89).

E. Chemical properties

Melting-point: The melting-point of metonitazene is 76–78 °C as free base and 197–198 °C as the hydrochloride salt (89, 91).

Boiling-point: No information was found.

Solubility: Metonitazene is lipophilic, as are its homologues etonitazene and isonitazene. The calculated octanol:water distribution coefficient for metonitazene is $\log P = 3.734 \pm 0.936$ at 25 °C (100).

Metonitazene free base is soluble in DMF at 25 mg/mL and in dimethylsulfoxide (DMSO) at 20 mg/mL. In a mixture of DMF and phosphate-buffered saline (pH 7.2) (1:1), the free base is soluble at 0.5 mg/mL and at 10 mg/mL in ethanol (100).

Metonitazene citrate is soluble in DMF and DMSO at 10 mg/mL and at 1 mg/mL in phosphate-buffered saline (pH 7.2) (100).

F. Identification and analysis

Synthetic metonitazene was characterized by nuclear magnetic resonance spectroscopy (¹H-NMR), high-performance liquid chromatography coupled to diode-array detection (HPLC-DAD), GC-MS and liquid chromatography coupled to time-of-flight MS (LC-QTOF-MS) (89). Metonitazene free base, citrate salt and metonitazene-d₃ citrate are available as reference materials from commercial suppliers for routine methods of analysis in forensic and clinical investigations (86).

Analytical methods for the identification and quantification of metonitazene in seized and biological samples have been published, which include various chromatographic, spectroscopic and mass spectrometric methods (99). Analyses

for identification of metonitazene in powders were conducted with GC–MS, infrared spectroscopy (IR), LC–MS, ion chromatography, NMR (101). Analyses for identification and quantification of metonitazene have been conducted in forensic post-mortem cases, showing average concentrations at 6.3 ± 7.5 ng/mL (median, 3.8 ng/mL; range, 0.5–33 ng/mL, $n=18$) in blood and 15 ± 13 ng/mL (median, 11 ng/mL; range, 0.6–46 ng/mL, $n=14$) in urine by LC-QTOF-MS for qualitative analysis and by LC coupled to triple-quadrupole MS (LC-QqQ-MS) for quantitative analysis (84).

3. Ease of convertibility into controlled substances

No information was found.

4. General pharmacology

A. Routes of administration and dosage

In the few clinical studies available, metonitazene was administered subcutaneously or intramuscularly to assess its analgesic effects (89). Anecdotal reports on discussion forums suggest that the powder can be insufflated directly (although it was reported to cause significant nasal irritation and burning) or used intranasally when dissolved in solution (101–103). For intranasal administration, forums recommend 10–40 mg per occasion. People who used metonitazene also expressed interest in vaping metonitazene solutions (103, 104).

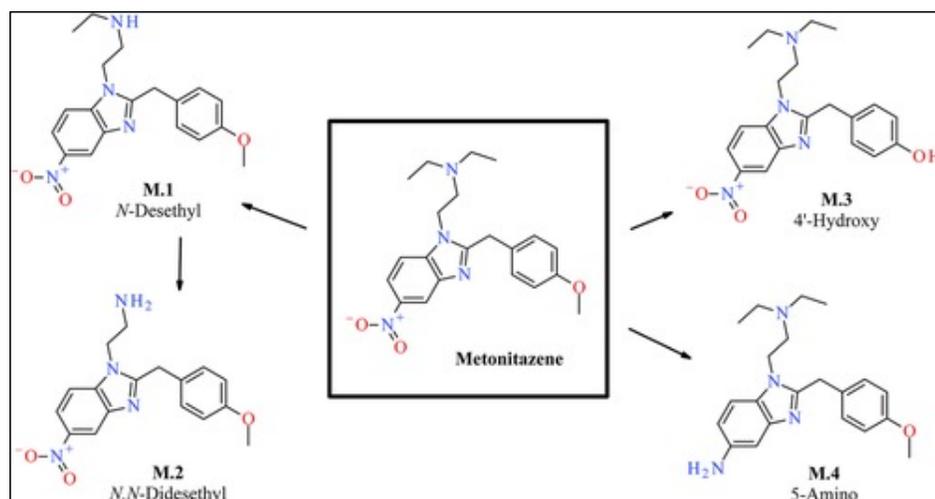
Reports of iv use after dissolving the powder in water or saline solution were also found (105), for which 5–10 mg was recommended as a “smaller” dose and 75–100 mg was recommended for those experienced with opioid use or opioid-dependent individuals. Because of its acidity, people on forums often recommend mixing metonitazene with sodium bicarbonate for iv use (106). People who use metonitazene also report or recommend smoking metonitazene through a glass pipe or foil at a recommended dose of 30 mg for people who are experienced with opioid use and people who are opioid-dependent (103).

B. Pharmacokinetics

Few published reports on the pharmacokinetics of metonitazene or metabolite identification were found, including in a recent narrative review (89). Krotulski and colleagues (84) investigated metonitazene metabolites in 20 forensic post-mortem samples with LCQTOF MS and quantitative confirmation with LCQ-MS-MS. Fig. 2 shows the metabolic pathway they proposed. Metonitazene is considered to undergo *N*-dealkylation and *O*-dealkylation. *N*-Desethyl metonitazene (M.1, $C_{19}H_{22}N_4O_3$) was produced via *N*-deethylation and was found to be a prominent metabolite in the urine and vitreous samples tested. M.1 is further metabolized by subsequent *N*-deethylation to form *N,N*-didesethyl

metonitazene (M.2, $C_{17}H_{18}N_4O_3$). 4'-Hydroxynitazene (M.3, $C_{20}H_{24}N_4O_3$) is then produced by *O*-demethylation. 5-Amino metonitazene (M.4, $C_{21}H_{28}N_4O$) is produced via reduction of the nitro moiety (84).

Fig. 2. Proposed metabolic pathway for metonitazene



Source: reference 84. Reproduced with permission.

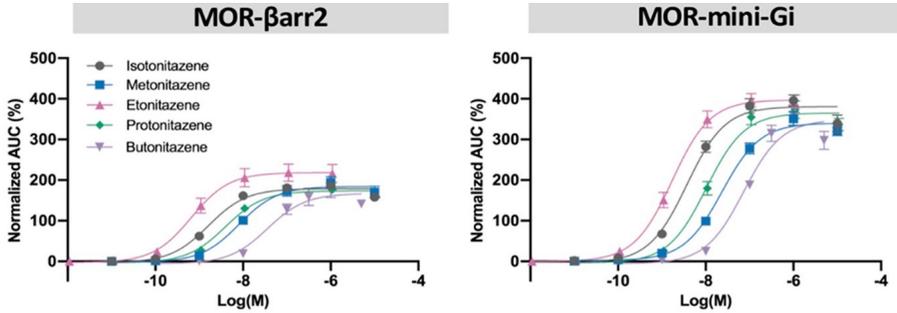
C. Pharmacodynamics

As metonitazene is an opioid, investigations of its pharmacodynamics have focused on its affinity for the MOR and subsequent characterization of analgesia or antinociception, abuse potential and respiratory depression. Ujváry et al. (89) reviewed the pharmacodynamics of metonitazene and other benzimidazoles, and the relevant studies described are cited in this document. The pharmacodynamics indicate the pharmacokinetics required to penetrate the blood–brain barrier (i.e., lipophilicity) and for abuse potential (i.e., rapid onset of effects).

Opioid receptor activity

Vandeputte and colleagues (99) characterized the MOR activation profiles of five benzimidazole opioids in in-vitro recruitment assays (MOR- β arr2 and MOR-mini- Gi). Fig. 3 shows the mean receptor activation (\pm standard error) normalized to the maximum response of hydromorphone, a potent opioid analgesic with strong abuse potential (107).

Fig. 3. Activation profiles of metonitazene, etonitazene, protonitazene and butonitazene



Reproduced from reference 99, with permission.

The left and right panels show data from the μ -opioid receptor (MOR) β -arrestin 2 and mini-Gi recruitment assays, respectively. Data are presented as the mean receptor activation \pm standard error of the mean and are normalized to the maximum response of hydromorphone.

The investigators calculated the potency (EC_{50}) and efficacy (E_{max}) of metonitazene relative to fentanyl and hydromorphone. Metonitazene was highly active in both assays of μ -opioid receptor activation, with a potency and efficacy slightly greater than those of fentanyl (113–121%) and significantly greater than those of hydromorphone (184–340%) (Table 8).

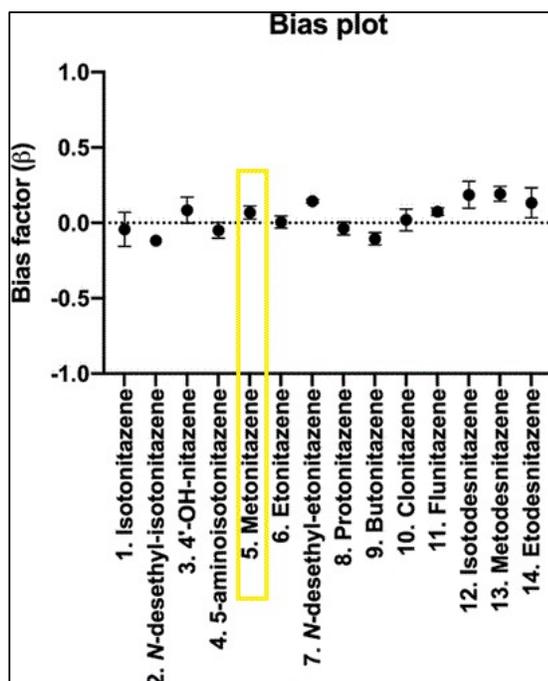
Table 8. Relative potency of metonitazene, fentanyl and hydromorphone, with 95% confidence intervals

	MOR- β arr2			MOR-mini-Gi		
	EC_{50}	% fentanyl E_{max}	% hydromorphone E_{max}	EC_{50}	% fentanyl E_{max}	% hydromorphone E_{max}
Metonitazene	8.14 nM (5.12 ; 12.8)	113 (106 ; 121)	184 (172 ; 197)	23.5 nM (17.7 ; 31.4)	121 (115 ; 126)	340 (326 ; 355)

Source: reference 99

The authors found no evidence of significantly biased agonism (i.e., a preference for β_{arr2} or mini-Gi recruitment) in the effects of metonitazene at the MOR as compared with hydromorphone (Fig. 4).

Fig. 4. Quantitative bias plot for μ -opioid receptors



Reproduced from reference 99, with permission. Bias factors \pm SEM are plotted for all the tested compounds, calculated from five independent experiments. Hydromorphone was used as the unbiased reference agonist ($\beta = 0$, not shown). Positive and negative bias factors imply a preference towards β_{arr2} and mini-Gi recruitment, respectively. None of the evaluated compounds showed statistically significant biased agonism at MOR as compared with hydromorphone.

The activity of metonitazene was compared with that of the typical opioid, morphine, in early ex-vivo experiments (108, 109). Metonitazene inhibited provoked contractions in isolated guinea-pig ileum and mouse vas deferens in a dose-dependent manner. The potency of metonitazene was 50 times greater than that of morphine in guinea-pig ileum preparations and 100 times greater in mouse vas deferens. These effects were reversed by nalorphine, a MOR antagonist, κ -opioid receptor partial agonist (110). No data were available on the action of metonitazene on the κ and δ opioid receptor subtypes.

Analgesia and antinociception

The relative antinociceptive potency of metonitazene in mice is estimated to be 100 times that of 5 mg/kg morphine (subcutaneous) (90, 111). In the preclinical studies found (in mice, rats and rabbits), the potency of metonitazene was

estimated to be 30–100 times (subcutaneous), 15 times (oral) and 200 times (iv) that of morphine (112).

In a more recent preclinical investigation, the analgesic effects of subcutaneous metonitazene (0.001–0.1 mg/kg) were tested in the rodent tail withdrawal paradigm with fentanyl and morphine (113). All three opioids increased the tail withdrawal latency (i.e., induced antinociception) in a dose-dependent manner. The calculated ED₅₀ values were 0.20 mg/kg for metonitazene, 0.025 mg/kg for fentanyl and 4.8 mg/kg for morphine, suggesting that the antinociceptive effects of fentanyl were eight times greater than that of metonitazene, while metonitazene was 24 times as potent as morphine. The opioid receptor antagonist naltrexone caused a 10-fold rightward shift in the effects of metonitazene and a 24-fold shift for fentanyl.

Metonitazene hydrochloride was studied in a clinical trial of 363 patients with post-operative or injury-related pain (114). The results of the study were described by Ujváry and colleagues (89). Metonitazene at 1 mg (subcutaneous or intramuscular) produced analgesia accompanied by sedation, drowsiness, vertigo, confusion, nausea and vomiting. Depressed respiration with cyanosis was observed in one fifth of the patients, requiring emergency intervention with nalorphine in one case. The patient recovered, but the pain returned. It was concluded that metonitazene has 10 times the analgesic potency of morphine; however, because of the high risk of adverse effects, clinical exploration was not pursued.

5. Toxicology

Metonitazene was a potent respiratory depressant in rabbits (115). An iv dose of 10 µg/kg resulted in a 50% decrease in respiration frequency, equivalent to that caused by 0.5 mg/kg of morphine. In mice, the acute toxicity (LD₅₀) of metonitazene was estimated to be 50 mg/kg after iv administration and 100 mg/kg orally (90, 111).

In both preclinical (108, 109, 113) and human studies (114), the effects of metonitazene could be antagonized by administration of nalorphine or naltrexone. This implies that the commonly available emergency intervention for opioid overdose, naloxone, should be effective in cases of over-intoxication in which metonitazene is a contributing drug. It has not been established whether metonitazene produces skeletal muscle rigidity of the chest wall, “wooden chest syndrome”, which is a distinguishing characteristic of fentanyl over-intoxication, attributed to an increase in noradrenergic outflow (116, 117); however, the syndrome has been observed in preclinical studies of the structurally related etonitazene (118). Thus, naloxone may be able to antagonize only the adverse effects of metonitazene that are attributable to its actions at opioid receptors.

6. Adverse reactions in humans

In the USA, metonitazene was first identified in eight blood specimens obtained during post-mortem investigations (119) and was confirmed in 20 further forensic post-mortem cases. Krotulski and colleagues (84) described these cases in detail and summarized them as shown in Table 9. Metonitazene was found most often with fentanyl (55% of cases). It was the sole opioid identified in 30% of cases and was identified as the cause of death in 15% of these cases. Most of the decedents had a history of opioid use disorder and were using or seeking heroin or fentanyl at the time of death. The drug product was usually described as white, off-white or beige. Witnesses described the overdose events as typical of opioid over-intoxication, with few uncharacteristic symptoms.

Table 9. Case histories and toxicological results of post-mortem cases involving metonitazene in the USA

Synopsis and date	Metonitazene (ng/mL)	4'-Hydroxynitazene (ng/mL)	Additional toxicological findings (ng/mL, unless otherwise noted)
A 42-year-old man was found dead in bed with purge fluid coming from the nose and mouth. A glass container with beige powder was found. (2021)	Femoral blood: 33 Serum: 18 Urine: 8.4	Femoral blood: negative Serum: positive Urine: 9.8	Butonitazene (femoral blood: 3.2, serum: 2.4, urine 10), N-ethyl pentedrone
A 26-year-old man with a history of heroin use was found unresponsive at his residence, with "bloody purge" coming from his nose. (2021)	IVC blood: 1.6 Urine: positive	IVC blood: Negative Urine: Positive	Fentanyl (12), norfentanyl (0.66), para-fluorofentanyl, 4-ANPP, 6-monoacetylmorphine (2.7), morphine (43), Δ^9 -carboxy THC (20), diphenhydramine (460), caffeine, quinine, ethanol (16 mg/dl)

Synopsis and date	Metonitazene (ng/mL)	4'-Hydroxynitazene (ng/mL)	Additional toxicological findings (ng/mL, unless otherwise noted)
A 52-year-old man with a history of drug and alcohol use collapsed at his residence. His roommate noted that the decedent was struggling to breathe and become unresponsive; he attempted chest compressions and called EMS. Upon EMS arrival, the decedent was found to be in asystole. The mouth and nares contained vomitus. (2021)	Femoral blood: 3.1	Femoral blood: negative	Caffeine, ethanol (199 mg/dl)
A 63-year-old man with a history of heroin use was found dead in bed with an empty plastic bag next to him. (2021)	IVC blood: positive (< 0.5) Urine: 0.58 Vitreous: positive (estimated 1.1)	IVC blood: negative Urine: positive Vitreous: positive	Flunitazene (positive), 8-aminoclonazepam, 4-ANPP, fentanyl (7.5), norfentanyl (0.85), naloxone, gabapentin (6.8 µg/mL), caffeine, diphenhydramine (220), quinine
A 34-year-old man with a history of alcoholism, anxiety and drug use was found dead in his bed by his roommate. A bottle of clonazepam was on the nightstand. The decedent had complained of stomach pain and vomiting the previous day. (2021)	Femoral blood: 0.52	Femoral blood: negative	Methamphetamine (1400), amphetamine (96), alprazolam (5.0), 7-amino clonazepam (11), diphenhydramine (53), citalopram/escitalopram (420), ethanol (15 mg/dL)

Synopsis and date	Metonitazene (ng/mL)	4'-Hydroxynitazene (ng/mL)	Additional toxicological findings (ng/mL, unless otherwise noted)
A 42-year-old homeless man was found at a friend's residence to be unresponsive, kneeling in a slumped forward position with blood coming from his nose and mouth. He was holding a syringe and nylon wrap. A white–yellow powder was recovered from the scene. (2021)	Femoral blood: 8.9 Urine: 14 Vitreous: positive	Femoral blood: negative Urine: 8.0 Vitreous: negative	Fentanyl (17), norfentanyl (3.8), 4-ANPP, caffeine, quinine
A 40-year-old man with a history of drug use, HIV/AIDS and hepatitis C was found unresponsive at his residence in a frog-like position, with a loaded syringe in the upper left thigh. A bag with pieces of cotton and a metal cap were found in the bathroom. The nares were congested with pink-tinged fluid.	Femoral blood: 2.3 Urine: 4.6 Vitreous: positive	Femoral blood: Positive Urine: 1.2 Vitreous: negative	Fentanyl (5.8), norfentanyl (1.2), acetylfentanyl (0.49), 4-ANPP, methamphetamine (29), caffeine, cotinine, venlafaxine (1300), O-desmethylvenlafaxine (390), quinine
A 44-year-old man was found unresponsive at his parents' residence. On arrival earlier in the day, he informed his stepfather that he had used heroin and went outside. A few minutes later, the stepfather found the decedent snoring. Approximately 1 h later, the decedent was found unresponsive and slumped in the chair. EMS was called but resuscitative measures were unsuccessful. (2021)	Femoral blood: 1.5 Urine: 4.7 Vitreous: positive	Femoral blood: negative Urine: 2.7 Vitreous: negative	Fentanyl (16), norfentanyl (1.2), 4-ANPP, methamphetamine (18), amphetamine (6.6), caffeine, cotinine, xylazine, quinine, ethanol (85 mg/dL)

Synopsis and date	Metonitazene (ng/mL)	4'-Hydroxynitazene (ng/mL)	Additional toxicological findings (ng/mL, unless otherwise noted)
<p>A 59-year-old man with a history of hypertension, atrial fibrillation, status post unknown cardiac procedure, prior stroke, smoking and drug use (cocaine and oxycodone) had been complaining of vomiting. He was found dead in bed 2 days later with evidence of vomiting. No drug paraphernalia was found. (2021)</p>	<p>Peripheral blood: 2.4 Urine: 46 Vitreous: positive (estimated 1.8)</p>	<p>Peripheral blood: 1.4 Urine: 5.3 Vitreous: negative</p>	<p>Fentanyl (33), norfentanyl (10), 4-ANPP, morphine (41), caffeine, cotinine, gabapentin (31 µg/mL), fluoxetine (85), norfluoxetine (46), quinine</p>
<p>A 19-year-old man with a history of mescaline, lysergic acid diethylamide (LSD) and molly use was found unresponsive at a friend's residence, snoring and with froth in the mouth. Multiple unidentified powders, capsules and pills were recovered from the scene, including <i>N,N</i>-dimethyltryptamine. (2021)</p>	<p>Femoral blood (P): 8.7 Femoral blood (P): 7.6</p>	<p>Femoral blood: positive Femoral blood: positive</p>	<p><i>N</i>-Ethyl deschloroketamine, etizolam (6.3), <i>O</i>-hydroxyetizolam (2.3), tramadol (1100), <i>O</i>-desmethyltramadol (270), 11-hydroxy Δ^9-THC (32), Δ^9-carboxy THC (200), Δ^9-THC (48), caffeine, naloxone</p>
<p>A 43-year-old man with a history of hepatitis C, heroin use and overdose was found unresponsive in the bathroom of his residence by his father. The decedent had completed a 3-month rehabilitation programme 1 week previously. A syringe, orange cap, clear plastic bag with a white powder and a belt were found near the body. (2020)</p>	<p>Femoral blood: 6.9 Urine: 35 Vitreous: positive (est. 1.4)</p>	<p>Femoral blood: positive Urine: 3.5 Vitreous: positive</p>	<p>Caffeine, cotinine</p>

Synopsis and date	Metonitazene (ng/mL)	4'-Hydroxynitazene (ng/mL)	Additional toxicological findings (ng/mL, unless otherwise noted)
A 58-year-old man with a history of “heroin” use was found dead at his residence in a hunched-over position on the floor with a yellow–brown bloody purge coming from the nose. A white powder and two cut straws with residue were located near the decedent. (2021)	Peripheral blood: positive Urine: 16	Peripheral blood: negative Urine: 18	Flunitazene (peripheral blood: 0.58, urine: 9.1), 8-aminoclonazepam, flualprazolam, fentanyl (13), norfentanyl (1.5), 4-ANPP, caffeine, diphenhydramine (300), quinine
A 47-year-old man with a history of chronic pain, hepatitis C and drug and alcohol use was found unresponsive in the bathroom of his residence by his girlfriend, who called EMS and administered two doses of naloxone. Upon EMS arrival, the decedent was in asystole. A small amount of vomit was noted on the floor. (2021)	Femoral blood: 4.0 Vitreous: positive (est. 0.76)	Femoral blood: negative Vitreous: positive	Fentanyl (41), norfentanyl (2.4), acetylfentanyl (25), 4-ANPP, caffeine, naloxone, diphenhydramine (72), quinine, ethanol (21 mg/dL)
A 27-year-old man was found dead in his apartment. He had a history of heroin use but had reportedly been abstinent for many years. No known significant medical history or trauma was found at autopsy. (2021)	Femoral blood: 3.5 Urine: 19 Vitreous: positive (est. 1.6)	Femoral blood: Positive Urine: 4.6 Vitreous: positive	8-Aminoclonazepam, pyrazolam (14), quinine, caffeine, ethanol (13 mg/dL)

Synopsis and date	Metonitazene (ng/mL)	4'-Hydroxynitazene (ng/mL)	Additional toxicological findings (ng/mL, unless otherwise noted)
<p>A 35-year-old man was found dead in his room having not being seen since the night before, when he reported no complaints. The body was found fully clothed on the floor, in full rigor with lividity. He held an uncapped syringe containing an unknown pink liquid. The roommate stated that the decedent was depressed and had a heroin use disorder. (2021)</p>	<p>Iliac blood: 5.8 Urine: 4.0 Vitreous: positive (estimated 0.71)</p>	<p>Iliac blood: Negative Urine: 28 Vitreous: Positive</p>	<p>Caffeine, cotinine, mirtazapine (37)</p>
<p>A 29-year-old woman with a history of drug and alcohol use, cardiomyopathy and hepatitis C was found unresponsive in a vehicle outside of her boyfriend's residence. She had recently been released from incarceration for drug charges. She had purchased "heroin" and "fentanyl", but her boyfriend had told her that he did not want her to bring drugs into his residence, so she remained in the vehicle. After the boyfriend found her unresponsive, he called EMS, naloxone was administered, and cardiopulmonary resuscitation was performed. The decedent was pronounced dead on arrival. (2021)</p>	<p>Femoral blood: 13 Urine: 10 Vitreous: positive (estimated 1.0)</p>	<p>Femoral blood: Positive Urine: 2.1 Vitreous: positive</p>	<p>Methamphetamine (150), amphetamine (32), caffeine, cotinine, naloxone, nicotine, mirtazapine (160)</p>

Synopsis and date	Metonitazene (ng/mL)	4'-Hydroxynitazene (ng/mL)	Additional toxicological findings (ng/mL, unless otherwise noted)
A 47-year-old man with a history of heroin use was found dead in his bed at his residence. (2021)	Femoral blood (P): 5.0 Heart blood (C): 12 Urine: 2.1	Femoral blood: positive Heart blood: negative Urine: 0.5	Flunitazene (femoral blood: 2.1, heart blood: 4.8, urine: 0.5), 8-aminoclonazepam, flualprazolam, fentanyl (3.0), norfentanyl (0.44), 4-ANPP, Δ^9 -THC (0.52), Δ^9 -carboxy THC (12), caffeine, cotinine, nicotine, bupropion (300), hydroxybupropion (290), 10-hydroxycarbazepine (9.5 µg/ml), quetiapine (590), gabapentin (34 µg/ml)
A 32-year-old man was found unresponsive in an abandoned building. Numerous empty bags of suspected "heroin" and several used syringes were recovered from the scene. (2021)	IVC blood: 2.5 Urine: 2.0	IVC blood: negative Urine: negative	Flunitazene (IVC blood: 0.6, urine: positive), fentanyl (6.6), 4-ANPP, caffeine, lorazepam (24), trazodone (0.083 µg/mL), ziprasidone (10), diphenhydramine (110), quinine, ethanol (170 mg/dL)

Synopsis and date	Metonitazene (ng/mL)	4'-Hydroxynitazene (ng/mL)	Additional toxicological findings (ng/mL, unless otherwise noted)
A 32-year-old man with a history of drug and alcohol use and endocarditis of the tricuspid valve with regurgitation was found unresponsive at a motel by a friend with whom he had been residing. EMS was called, and the decedent was confirmed to be asystolic on arrival. Multiple drug paraphernalia, including syringes, glass pipes, a small bag of an unspecified white powder and naloxone were found on the scene. Both nares emitted a red-tinged fluid. (2021)	Femoral blood: 10 Urine: 28 Vitreous: positive (est. 3.7)	Femoral blood: negative Urine: 10 Vitreous: negative	Fentanyl (3.2), norfentanyl (1.1), 4-ANPP, methamphetamine (3900), amphetamine (160), caffeine, cotinine, quinine
A 53-year-old woman with a history of heroin use was found unresponsive by her family at her residence and was transferred to hospital. Cardiac arrest and an anoxic brain injury were diagnosed, and admission urine was positive for amphetamines, benzodiazepines and opiates. Brain death was ruled 5 days after admission. A burnt spoon and a bag containing an illicit substance were found at the decedent's residence. (2021)	Blood: 1.4	Blood: Positive	Etizolam (54), <i>para</i> -fluorofentanyl (28), 4-ANPP, methadone (130), morphine (36), caffeine, naloxone, mirtazapine (52)

Adapted from reference 84

EMS, emergency medical services; IVC, inferior vena cava

7. Dependence potential

A. Animal studies

In morphine-dependent rhesus monkeys, metonitazene was 100 times more potent than morphine sulfate in suppressing the symptomology of opioid withdrawal (120, 121).

B. Human studies

No studies have been reported on the ability of metonitazene to produce physiological dependence in humans; however, given its pharmacological profile, metonitazene can probably produce physiological dependence like most opioids. Reports from forums from people who use drugs support this conclusion (105).

8. Abuse potential

A. Animal studies

No preclinical studies on the abuse potential of metonitazene were identified.

B. Human studies

No studies have been conducted on human abuse liability. As metonitazene can be synthesized as a free base or as a hydrochloride salt (111), however, it could be administered by routes with faster pharmacokinetics associated with greater abuse potential of opioids, such as smoking, insufflation and injection. Anecdotal reports from user forums such as Reddit and Bluelight (section 4A) and forensic evidence obtained at the scene of overdose events (i.e., the presence of injection-related paraphernalia and pipes) support this conclusion (84).

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

Metonitazene has no approved therapeutic application.

10. Listing on the WHO Model List of Essential Medicines

Metonitazene is not on the WHO List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

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

12. Industrial use

Metonitazene has no reported industrial uses.

13. Non-medical use, abuse and dependence

No population surveys or data on human abuse liability were found. Data from post-mortem reports suggest that, because of its potency, metonitazene may be used as an adulterant to increase the potency of heroin (in a similar manner to fentanyl) (84). Metonitazene use does not appear to be intentional, as, in most cases, decedents had purchased heroin or fentanyl. Internet forums for people who use drugs suggest, however, that there is interest in metonitazene among people who are experienced with opioid use (e.g., queries about its potency, subjective pharmacodynamic profile). The frequency of use could not be estimated.

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

Metonitazene is offered for sale by numerous Internet retailers. As people who use drugs are likely to obtain metonitazene from unregulated sources, its purity and quantity are not assured, thus presenting an additional risk of adverse reactions. Currently, metonitazene has a small impact on public health, as its presence on the drug market is minimal; however, given its pharmacodynamics, metonitazene appears to have a high risk for recreational use, physiological dependence and overdose.

15. Licit production, consumption and international trade

Metonitazene is available for sale by pharmaceutical retailers for research and forensic applications only.

16. Illicit manufacture and traffic and related information

In March 2019, metonitazene was identified during testing of drug paraphernalia and seizures in Alberta, Canada (122), and later in Ontario (123).

In Europe, the first reports of metonitazene appeared in Germany in 2020 (124, 125). In the USA, metonitazene was first reported by NPS Discovery after detection in a seized drug powder in July 2020 (126), and the National Forensic Laboratory Information System identified 23 cases of metonitazene from federal, state and local laboratories between 1 January and 31 March 2021 (127).

Metonitazene is offered for sale on numerous Internet sites, which do not appear to be reputable pharmaceutical retailers. Some are self-reported as based in China and state that their metonitazene product can be shipped worldwide (88).

17. Current international controls and their impact

Metonitazene is not currently under international control. In response to concern from the WHO, the US Department of Health and Human Services published a

request for comments in the Federal Register about the abuse potential, actual abuse, medical usefulness, trafficking and impact of scheduling changes of several drugs, including metonitazene (128).

18. Current and past national controls

Metonitazene does not appear to be subject to restrictive measures in the Member States of the European Union (125).

In the USA, metonitazene is not explicitly a scheduled substance at federal level; however, the structurally related etonitazene and isotonitazene have been placed under the most restrictive controls (129). It is unclear whether the structure of metonitazene is sufficiently similar to that of these drugs to fall under the same scheduling restrictions as an “analogue” of either drug. Some states have used emergency scheduling to place the drug under the most restrictive controls (130, 131).

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

No further comments.

3.1.3 Eutylone

1. Substance identification

A. International Nonproprietary Name (INN)

Not available.

B. Chemical Abstracts Services Registry Number

Free base: 802855-66-9

Hydrochloride salt: 17764-18-0

C. Other chemical names

1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)-1-butanone (ACI)

Butyrophenone, 2-(ethylamino)-3',4'-(methylenedioxy)-(8CI)

1-(2*H*-1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one

β -keto-Ethylbenzodioxolylbutanamine

β -keto-1,3-Benzodioxolyl-N-ethylbutanamine

D. Trade names

Not available.

E. Street names

Eutylone, bk-EBDB, MDEBP, β -keto-ethylbenzodioxolylbutanamine, N-ethylbutylone. In New Zealand in 2021, eutylone was found in “Red Bull” and “Blue Playboys” tablets (132). Eutylone has also been detected in cases of suspected use of “Ecstasy,” “Molly” or MDMA” (133).

F. Physical appearance

The hydrochloride salt of eutylone has been described as a crystalline solid (134). No reports on its odour have been identified, but its structure indicates that its pure form is expected to be odourless.

Eutylone for recreational use is distributed mainly as powder, crystals, capsules or tablets. Pink, yellow and blue tablets containing eutylone have been detected (132).

G. WHO review history

Eutylone 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

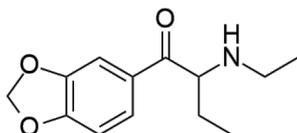
A. Chemical name

IUPAC Name: 1-(Benzo[d][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one

Chemical Abstracts Index Name: 1-Butanone, 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)-(ACI)

B. Chemical structure

Free base:

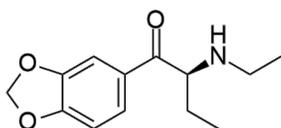


Molecular formula: $C_{13}H_{17}NO_3$

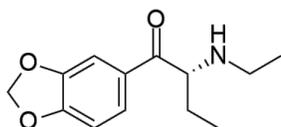
Molecular weight: 235.28 g/mol

C. Stereoisomers

The presence of a chiral centre at the α -carbon of the side-chain gives rise to the enantiomeric pair of (2S)-1-(1,3-benzodioxol-5-yl)-2-(ethylamino)butan-1-one and (2R)-1-(1,3-benzodioxol-5-yl)-2-(ethylamino)butan-1-one. Eutylone is most likely to be available as a racemic mixture.



(2S)-1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one



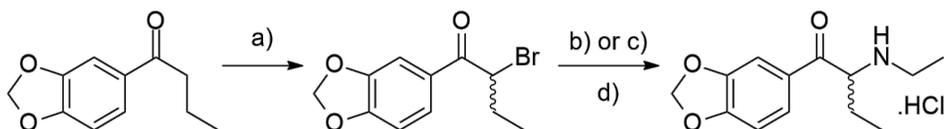
(2R)-1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one

D. Methods and ease of illicit manufacturing

No information was available on the routes of synthesis used for the eutylone products circulating on the market. The first synthesis of eutylone was described in a patent in the 1960s by a German pharmaceutical company, C.H. Boehringer Sohn AG & Co. KG (135). The chemical synthesis of cathinones is facile and usually follows a two-step process. The initial synthesis is of an α -bromoketone from the appropriate arylketone, followed by a nucleophilic substitution with an appropriate amine to give the corresponding free base of the cathinone.

Cathinones are generally isolated as their salts because of the instability of the free base (136). For eutylone (scheme 1), the procedure includes α -bromination (a) of the 1-(2*H*-1,3-benzodioxol-5-yl)butan-1-one precursor and formation of the 1-(2*H*-1,3-benzodioxol-5-yl)-2-bromobutan-1-one intermediate (b). Reaction with *N*-ethylamine gives eutylone (c), which may then be converted into its hydrochloride salt. This procedure has been also used for preparation of eutylone analogues. The ketone species (a) is accessible by various routes.

Scheme 1. Reagents and conditions: a) $\text{Br}_2/\text{HBr}/\text{CH}_2\text{Cl}_2/\text{rt}/1 \text{ h}$; b) $\text{EtNH}_2 \cdot \text{HCl}/\text{NET}_3/\text{CH}_2\text{Cl}_2/\text{rt}/24 \text{ h}$ or c) $\text{EtNH}_2 \cdot \text{HCl}/\text{NET}_3/\text{CHCl}_3/\text{reflux}/24 \text{ h}$; d) $\text{HCl-dioxane}/\text{propan-2-ol}/\text{rt}/1 \text{ h}$.

**E. Chemical properties**

Melting-point: 238–239 °C (hydrochloride salt) (137)

Boiling-point: No information was available.

Solubility: The hydrochloride salt is soluble in water, methanol, ethanol, DMF and DMSO (138, 139).

F. Identification and analysis

Eutylone hydrochloride salt and eutylone-d5 hydrochloride salt are available as reference materials from commercial suppliers for use in routine methods of analysis for forensic and clinical investigations (134).

Analytical methods for the identification and quantification of eutylone in seized and biological sample matrices have been published. They include various chromatographic, spectroscopic and mass spectrometric methods. Eutylone was analysed in seized sample by GC-MS, IR spectroscopy, LC-MS and ion chromatography (138).

Eutylone has been identified and quantified in post-mortem and DUID cases (140). Although the majority (75%) of cases corresponded to polydrug abuse involving methamphetamine or amphetamine (n=2), cocaine (n=2), THC (n=2) and/or buprenorphine (n=1), eutylone was the only drug detected in two DUID cases, other than caffeine. The matrix types included blood, urine and tissue. Eutylone was identified in a comprehensive drug screening protocol with LC-TOF-MS under non-targeted acquisition parameters. Quantitative analysis of eutylone was performed by LC-MS/MS. The blood concentration of eutylone in the forensic cases ranged from 1.2 to 11 000 ng/mL.

3. Ease of convertibility into controlled substances

No information was available.

4. General pharmacology

A. Routes of administration and dosage

A patent issued by Boehringer Sohn AG and Co KG Boehringer Ingelheim GmbH (141) included the synthesis of eutylone and other analogues. Eutylone was claimed to be suitable for formulation in pharmaceutical compositions such as tablets, capsules, pills, injectable solutions and suppositories, in accordance with the observation that synthetic cathinones can be administered by oral, parenteral and rectal routes. Reports on seized materials indicate the presence of eutylone in tablets, capsules, crystals and pills, suggesting oral administration as the intended route. Nasal administration has also been reported on online user forums (142–144). People who use eutylone have reported experiencing effects at 35 mg, with the average dose reported as 60–100 mg. Eutylone has also been found in “Red Bull” tablets (containing no MDMA) at 300–350 mg (132). Information published on online user forums suggest administration of 50 mg eutylone by snorting (143) or 100–200 mg orally (142, 143).

B. Pharmacokinetics

No detailed information was found on the pharmacokinetics of eutylone. Its chemical structure and its structural similarities to pentylone indicate that the β -ketone moiety of eutylone is first reduced to hydroxyl metabolites. In 3',4'-methylenedioxyphenyl cathinone derivatives, like eutylone, demethylenation of the 3',4'-methylenedioxy moiety to a dihydroxy metabolite (mediated by cytochrome P450 [CYP]2D6 and CYP2C19) followed by its O-methylation

(mediated by catechol O-methyl transferase) are the major metabolic pathways. Both hydroxyl, 4'-methoxy-3'-hydroxyl, and 3'-methoxy-4'-hydroxyl metabolites are usually then metabolized by phase-II metabolism such as glucuronidation and/or sulfation (145).

The stability of 22 synthetic cathinones, including eutylone, was studied in urine and blood by LC-Q/TOF-MS (146). The stability was evaluated in preserved blood (pH 7) and urine (pH 4 and 8) at 100 and 1000 ng/mL and four storage temperatures (-20°C , 4°C , 20°C and 32°C). It was concluded that methylenedioxy-substituted cathinones like eutylone are significantly more stable than other structural classes of cathinones, denoting the stabilizing effect of the methylenedioxy group. Eutylone had a half-life of 31 and 4.8 days in blood at 20°C and 32°C , respectively, a half-life of 13 days in urine (pH 4.0) at 32°C and 6.2, 11 and 3 days in urine (pH 8.0) at -4°C , 20°C , and 32°C , respectively. No degradation of eutylone was observed at lower temperatures.

Between January 2019 and April 2020, eutylone was identified quantitatively in 83 forensic investigations, including post-mortem and DUID cases, in the USA. The mean concentration of eutylone in post-mortem blood was 1020 ± 2242 ng/mL (range = 1.2–11 000 ng/mL, $n=67$). The mean concentration of eutylone in blood from DUID cases was 942 ± 1407 ng/mL (range = 17–3600 ng/mL, $n=7$). Further analysis of authentic human specimens revealed the presence of three eutylone metabolites, including one unique biomarker and one metabolite in common with butylone (133).

C. Pharmacodynamics

In vitro

The interaction of eutylone with monoamine transporters was determined by testing the effects of eutylone on radioligand ($[^{125}\text{I}]\text{RTI-55}$) binding and $[^3\text{H}]$ neurotransmitter (i.e., dopamine, serotonin, norepinephrine) uptake by HEK cells expressing cDNA for the human dopamine transporter (DAT) (HEK-hDAT cells), the human serotonin transporter (HEK-hSERT cells) and the human norepinephrine transporter (HEK-hNET cells). Eutylone had greater affinity for DAT ($K_i = 640$ nM) than NET (inhibitory constant $[K_i] = 1,870$ nM) or SERT ($K_i = 8500$ nM) and was shown to inhibit monoamine neurotransmitter uptake with a potency rank order of DAT (half maximal inhibitory concentration $[\text{IC}_{50}] = 281$ nM) > SERT ($\text{IC}_{50} = 640$ nM) > NET ($\text{IC}_{50} = 700$ nM) (Table 10). As also shown in Table 10, comparison of the effects of eutylone on binding and uptake with that of other stimulants indicated that the affinity of eutylone for DAT was more similar to that of cocaine than that of methamphetamine or methcathinone. Eutylone was also a more potent inhibitor of serotonin uptake than methamphetamine or methcathinone (about 14 and 56 times higher, respectively) but a less potent inhibitor of norepinephrine uptake (about 30 and 18 times relative to methamphetamine and methcathinone, respectively).

Table 10. Effects of eutylone, cocaine, methamphetamine and methcathinone on [¹²⁵I]RTI-55 binding and [³H]neurotransmitter uptake by HEK-hDAT, HEK-hSERT and HEK-hNET cells (mean ± SEM)

HEK-hDAT	Eutylone	Cocaine	Methamphetamine	Methcathinone
[¹²⁵ I]RTI-55 binding: K _i (nM)	640 ± 71	750 ± 130	4660 ± 660	6600 ± 130
[¹²⁵ I]RTI-55 binding: IC50 (nM)	651 ± 72	–	–	–
Hill slope	-0.94 ± 0.02	-1.04 ± 0.08	-0.97 ± 0.08	-0.99 ± 0.09
[³ H]DA uptake: IC50 (nM)	281 ± 80	366 ± 51	177 ± 30	450 ± 130
HEK-hSERT				
[¹²⁵ I]RTI-55 binding: K _i (nM)	8500 ± 2500	734 ± 60	14 000 ± 44 000	237 000 ± 61 00
[¹²⁵ I]RTI-55 binding: IC50 (nM)	8800 ± 2700	–	–	–
Hill Slope	-1.38 ± 0.22	-0.97 ± 0.09	-1.12 ± 0.08	-1.09 ± 0.10
[³ H]5-HT uptake: IC50 (nM)	640 ± 160	270 ± 47	9200 ± 2400	36 000 ± 3900
HEK-hNET				
[¹²⁵ I]RTI-55 binding: K _i (nM)	1,870 ± 550	1560 ± 340	1340 ± 270	3110 ± 190
[¹²⁵ I]RTI-55 binding: IC50 (nM)	1,880 ± 560	–	–	–
Hill Slope	-0.55 ± 0.17	-0.80 ± 0.18	-0.89 ± 0.10	-1.08 ± 0.19
[³ H]NE uptake: IC50 (nM)	700 ± 100	390 ± 100	23.1 ± 5.4	38.3 ± 7.7

Adapted from reference 147
5-HT, 5-hydroxytryptamine

These findings were supported by other studies of monoamine transporters performed in rat brain synaptosomes, which showed that eutylone is a hybrid transporter with uptake inhibition properties at DAT and NET (the effects at DAT being 10 times more potent than those at NET) but substrate activity at SERT. Consistent with its isomer pentylone, but in contrast to dibutylone (another eutylone isomer), eutylone was found to inhibit serotonin uptake. The authors observed that eutylone had weak partial releasing action at serotonin transporters, which reached 50% of maximal response (135).

In vivo

Treatment with eutylone ($ED_{50} = 4.87$ mg/kg) resulted in time- and dose-dependent stimulation of locomotor activity in male Swiss-Webster mice (Hsd:ND4, aged 2–3 months) after ip administration of 1–25 mg/kg (in assays conducted according to the DEA locomotor activity studies time-course protocol). At 10 and 25 mg/kg, the stimulating effects of eutylone occurred within 10 min of administration and lasted for 70 min (148).

These findings were supported by studies showing that eutylone stimulated locomotion in a dose-dependent manner after subcutaneous administration to mice ($ED_{50} = 2$ mg/kg). Eutylone showed higher potency and efficacy in stimulating locomotor activity than its isomers pentylone and dibutylone (135).

5. Toxicology

No reports were found on the toxic doses of eutylone. A retrospective chart review was conducted of emergency department cases involving eutylone use in Taiwan, China between January 2019 and July 2020 (149). Urine concentrations of eutylone were documented in 11 cases, including one fatal case, at concentrations of 210–18 364 ng/ml, with no apparent correlation with the severity of clinical manifestations.

The UNOCD Early Warning Advisory (150) included one incident in which eutylone was found to have contributed to a clinical admission in Australia in 2020. No details were available.

6. Adverse reactions in humans

In a retrospective review of 11 emergency department cases, including a fatal case, involving eutylone use in Taiwan, China between January 2019 and July 2020, all the patients presented pronounced sympathomimetic effects (149). All, except one who had cardiac arrest out of hospital, had tachycardia (pulse rate > 100/min), four presented with hyperthermia (body temperature > 38 °C), and three had hypertension (systolic blood pressure > 140 mm Hg). Other common clinical manifestations were delirium (5 cases), agitation (5 cases) and visual hallucinations (2 cases). Five patients developed leukocytosis (white cell count > 11 K/L), and one patient presented with rhabdomyolysis (CK > 1500 U/L). Nausea and vomiting were reported in one case. Although other substances (e.g., 7-aminonitrazepam, acetaminophen, aminonitrazepam, lorazepam, midazolam and nitrazepam) were also found in biological samples, eutylone was the only psychostimulant detected. Of note, eutylone was the only substance detected in two cases. Effects such as agitation, hypertension, tachycardia and death are consistent with those generally reported with synthetic cathinones (151).

Reports found on online user forums also included euphoria and social disinhibition (152) and tingling sensations (144). Unverified adverse events

reported on online forums include bruxism, irritation of the mucous membranes after nasal administration (142, 144), insomnia, anxiety, paranoia and seizures (132). Most of the effects induced by eutylone appeared to occur almost immediately after administration and to disappear within a few hours.

The presence of eutylone in several post-mortem cases suggests that it may also cause or contribute to death (133, 149). Of the 22 post-mortem cases in which eutylone was identified quantitatively between January 2019 and April 2020, 5 cases involved only eutylone (blood concentration, 1.2–4400 ng/mL). Moreover, the medical examiner identified eutylone as the cause of death in 4 cases on the basis of autopsy findings and toxicological results. In 2020, acute eutylone intoxication was listed as the official cause of death of a man after an accidental drug overdose (153).

7. Dependence potential

A. Animal studies

No studies were identified.

B. Human studies

No studies were identified.

8. Abuse potential

A. Animal studies

In drug discrimination studies (two-lever choice method), eutylone fully substituted for the discriminative stimulus effects of a training dose of 1 mg/kg methamphetamine ($ED_{50} = 2.83$ mg/kg) after ip administration to Sprague-Dawley rats at a dose of 1–10 mg/kg. The response rate to eutylone increased to 139% of vehicle control after administration of 5 mg/kg. The potency ratio of eutylone to methamphetamine (ED_{50} test compound:reference) was 10.89. Eutylone and methamphetamine were found to be equally effective: $[(E_{\max} \text{ test compound}/E_{\max} \text{ reference compound}) \times 100] = 113\%$ (154).

B. Human studies

No studies on the abuse potential of eutylone in humans were identified. On the basis of its structure, however, eutylone is expected to cause stimulant-related psychological and somatic effects similar to those of Schedule I (under the Controlled Substances Act in the USA) synthetic cathinones (e.g., methylone, pentylone) and other Schedule I and II (under the Controlled Substances Act in the USA) substances (e.g., cocaine, methamphetamine, MDMA), which have high potential for abuse (155).

Potential nonmedical use of eutylone is described on online user forums (143, 156).

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

Eutylone appears to have been explored for use in pharmacological formulations (141), but it is not known to have any therapeutic use.

10. Listing on the WHO Model List of Essential Medicines

Eutylone is not on the WHO Essential Medicines List or the WHO Essential Medicines List for Children

11. Marketing authorizations (as a medicinal product)

Eutylone is not known to have any marketing authorizations.

12. Industrial use

Eutylone is not known to have any industrial use.

13. Non-medical use, abuse and dependence

Since 2019, eutylone has become highly prevalent in seizures in Australia, Europe, New Zealand and the USA. For example, between 2019 and 2020, eutylone was identified in about 23 000 seizures in the USA or at US points of entry.

In New Zealand, eutylone has been found in a large number of products sold as MDMA or Ecstasy. It is therefore possible that some people who use drugs may be unaware that they have consumed eutylone or the dose, which could contribute to adverse effects, especially if consumed in combination with other substances. A review of case reports in Taiwan, China suggested that people who used eutylone self-medicated with benzodiazepines, as these drugs were detected with eutylone in biological fluids of people admitted to hospital emergency rooms after eutylone use (149).

Abuse and dependence potential in humans have not been studied, and there are only a few self-reports of intentional eutylone use on online user forums (e.g., Erowid, Bluelight). Nevertheless, two people reported features of craving (143, 156), needing to take more eutylone over a few days. It has been suggested that the mild euphoric effects (in contrast with MDMA) may lead consumers to take additional doses after a short time, leading to insomnia, which may last 48 h (132).

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

No specific information was found on the nature or magnitude of public health problems associated with the use of eutylone. Detection of eutylone in biological fluids has been described mainly post mortem and in DUID cases.

Eutylone has frequently been detected in products thought to be MDMA, Ecstasy, mephredrone, methylone, alprazolam or Spice, suggesting that most people who use eutylone may be unaware that they are using it (132, 157). Some products tested were found to contain very high doses (i.e., 300–350 mg) (132). Adverse effects experienced by people who have taken eutylone are detailed in section 6.

15. Licit production, consumption and international trade

Eutylone is used as a reference material for scientific research, for “research use only”.

16. Illicit manufacture and traffic and related information

Eutylone was first detected in Europe in March 2014, in Poland (158) and has been listed as an NPS under intensive monitoring by EMCDDA since 23 March 2021. Reports from the NFLIS indicate that eutylone emerged on the US illicit drug market in 2014, with 29, 182 and 3958 reports for eutylone in 2017, 2018 and 2019, respectively (155).

Eutylone was detected in wastewater in Australia collected bimonthly between October 2017–June 2018 and October 2019–February 2020 (159).

Drug checking by KnowYourStuffNZ also identified the presence of eutylone at festivals in New Zealand in 2021. The substance was present in about 40% of tested tablets, of which 45% had been bought as MDMA (132).

Since 2019, eutylone has also been one of the most prevalent NPS identified in the USA by the Office of National Drug Control Policy in leading law enforcement datasets. Preliminary and projected data suggest the involvement of eutylone in about 23 000 independent seizure events domestically and/or at US points of entry in 2019 and 2020 (160). Trend reports from the CFSRE showed 63 instances of eutylone since 2018 (161). The CFSRE has issued a public health alert on the increasing prevalence of eutylone in forensic casework in the USA and its contribution to mortality, after scheduling of N-ethylpentylone in the USA in August 2019 (161).

17. Current international controls and their impact

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

18. Current and past national controls

Eutylone is controlled under Schedule I of the Controlled Drugs and Substances Act in Canada. In Germany, eutylone is classified as “Neue-psychoaktive-Stoffe-Gesetz”, which authorizes its use only for industrial and scientific purposes. In

2019, eutylone was listed in Sweden as a product that is harmful to health in accordance with the Ordinance banning certain products that are harmful to health (162). Eutylone is controlled as Class B under the United Kingdom Misuse of Drugs Act. As a positional isomer of pentylone, eutylone is controlled under Schedule I of the Controlled Substances Act in the USA (155).

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

As eutylone has been identified in products sold as MDMA or Ecstasy (132), it is reasonable to expect that the prevalence of eutylone and eutylone-related intoxications may be under-reported. In some cases, samples sold as MDMA contained potentially harmful amounts of eutylone (132).

3.1.4 Benzylone

1. Substance identification

A. International Nonproprietary Name (INN)

No information was available.

B. Chemical Abstracts Services Registry Number

1387636-19-2 (base)

1823274-68-5 (HCl salt)

C. Other chemical names

1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one

3,4-Methylenedioxy-*N*-benzylcathinone

N-Benzyl-3,4-methylenedioxycathinone

Methylenedioxybenzedrone [sic]

1-(3,4-Methylenedioxyphenyl)-2-(benzylamino)-1-propanone

1-(1,3-Benzodioxol-5-yl)-2-(benzylamino)propan-1-one

1-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-1-propanone

2-Benzylamino-1-(3,4-methylenedioxyphenyl)propan-1-one

N-Benzylmethylone [sic]

N-Benzylnormethylone

D. Trade names

No information was available.

E. Street names

The chemical names listed above may be used as street names. Other code names include bk-MDBZ and 3,4-MDBC.

F. Physical appearance

The hydrochloride salt of benzylone has been described as crystalline solid (163). In its pure form, benzylone hydrochloride is expected to be odourless and white,

like many other ring-substituted synthetic cathinones. Benzylone hydrochloride has also been described as a white powder (164).

G. WHO review history

Benzylone 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

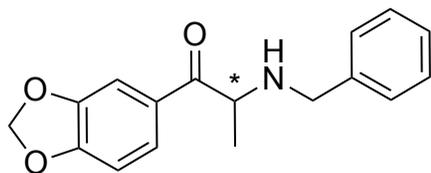
IUPAC name:

1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(benzylamino)propan-1-one

Chemical Abstracts Index Name: 1-(1,3-Benzodioxol-5-yl)-2-[(phenylmethyl)amino]-1-propanone

B. Chemical structure

Free base:



* a chiral centre

Molecular formula: C₁₇H₁₇NO₃

Molecular weight: 283.33 g/mol

C. Stereoisomers

The presence of a chiral centre at the α -carbon of the side-chain gives rise to the enantiomeric pair of (*S*)-benzylone and (*R*)-benzylone. Benzylone on the streets is probably 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 used for benzylone products circulating on the market. The chemistry of ring-substituted synthetic cathinones is, however, well established and straightforward. A common approach involves bromination of the 3,4-methylenedioxypropiofenone precursor (a) to yield the α -brominated intermediate (b). This is then followed by amination with phenylmethanamine to give benzylone (c), similar to procedures used for related cathinones investigated by pharmaceutical companies since the 1960s (e.g. 165).

E. Chemical properties

Melting-point: No information was available

Boiling-point: No information was available

Solubility: Benzylone hydrochloride was reported to be soluble in ethanol (~3 mg/mL), DMSO and DMF (5 mg/mL) but only sparingly soluble in aqueous buffers. If dissolved in DMF first, the solubility of benzylone hydrochloride was approximately 0.13 mg/mL in a 1:7 solution of DMF:phosphate-buffered saline (pH 7.2) (163). A seized sample of benzylone hydrochloride was described as being partially soluble in water and dichloromethane and soluble in methanol (166).

F. Identification and analysis

Identification of benzylone, especially when it is available in larger quantities than are usually available for forensic toxicology, is straightforward. Analytical results reported in scientific publications include those from photodiode array detection (167), electron ionization MS (167–169), electrospray ionization single and tandem MS (169–177), direct analysis in real time (DART) ionization MS (178, 179), NMR spectroscopy (167, 169, 172, 180), Fourier transform IR spectroscopy (169) and GC (181). Analysis of biological samples requires sensitive analytical methods, e.g., GC or LC coupled with (tandem) MS (high and low resolution). Analytical information available in the public domain includes chromatographic, MS and spectroscopic data (164, 166, 182, 183). Certified reference material is commercially available for analytical method development and validation. Results from presumptive colour tests have also been disseminated in the public domain (184–186).

3. Ease of convertibility into controlled substances

No information was available on conversion of benzylone to substances under international control. Subjecting benzylone to conditions resulting in N-debenzylation and reduction of the ketone group could, however, give 3,4-methylenedioxyamphetamine (tenamfetamine; IUPAC name: 1-(2*H*-1,3-benzodioxol-5-yl)propan-2-amine), which is listed in Schedule I of the United Nations Convention on Psychotropic Substances 1971.

4. General pharmacology

A. Routes of administration and dosage

No clinical studies on benzylone were identified, and the information in Internet discussion forums appears to be limited with regard to dosages and routes of administration. It has been suggested that benzylone is inactive (187–190), although, in one case, nasal administration of 70–100 mg was reported to induce a “decent rush” (189); another report noted that the effects were “very light and short lived”. The route of administration was not described, but the dosage

tested was 500 mg, starting with 200 mg, followed by two 150-mg doses, with no “increase in results” (191). A report of several trials of oral doses of 550 mg and > 1.4 g noted some mild effects, including “wobble eyes, chills, stretching, sweaty palms, mild grind”. Although some comparisons were made with methylone (3,4-methylenedioxymethcathinone, 1-(2*H*-1,3-benzodioxol-5-yl)-2-(methylamino)propan-1-one), the psychoactive effects associated with these doses were not considered favourable (192). It is difficult to assess such reports, not least because people who use these substances might not be able 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. One self-report after oral administration of 1 g of what was believed to be benzylone suggested a short duration of a “methylone rush” of 2 h (192), although other reports suggested that benzylone is inactive (see above). Exposure of pooled human liver microsomes to benzylone resulted in the three metabolites 2-(benzylamino)-1-(3,4-dihydroxyphenyl)propan-1-one, 1-(2*H*-1,3-benzodioxol-5-yl)-2-(benzylamino)propan-1-ol and 2-amino-1-(2*H*-1,3-benzodioxol-5-yl)propan-1-one, reflecting desmethylenation, reduction of the keto group and *N*-debenzylation. The *N*-debenzylated metabolite (3,4-methylenedioxycathinone) may be biologically active (193–197), although it is unknown whether the concentrations – if formed in vivo – would be sufficient to induce bioactive effects.

C. Pharmacodynamics

The results of assays of binding affinity to monoamine transporters and inhibition of uptake in vitro are summarized in Table 11 (198). The binding affinities determined for benzylone in HEK293 cells expressing human recombinant monoamine transporters were found to be very low, with K_i values close to 2.5 μM at the dopamine (DAT) and norepinephrine (NET) transporters, and that at the serotonin transporter (SERT) was even lower, at $K_i = 11.5 \mu\text{M}$ (Table 11). Cocaine, methamphetamine and methcathinone were tested for comparison. At DAT, the binding affinity of cocaine was three times higher and those of methamphetamine and methcathinone were 2 and 2.5 times less potent. At SERT, the binding affinity of cocaine was 20 times higher, while those of methamphetamine and methcathinone were 15 and 25 times less potent. At NET, the binding affinity of cocaine was comparable, whereas that of methamphetamine was equivalent and that methcathinone two times less potent. In an investigation of inhibition of the uptake of radiolabelled neurotransmitters, benzylone showed submicromolar K_i values at DAT ($K_i = 764 \text{ nM}$) and NET ($K_i = 469 \text{ nM}$), while cocaine, methamphetamine and methcathinone inhibited uptake at higher potencies. Cocaine was also more potent than benzylone at SERT, and methamphetamine and methcathinone were significantly potent than benzylone.

Table 11. Effects of benzylone on binding and uptake in HEK-hDAT, HEK-hSERT and HEK-hNET cells

	Benzylone	Cocaine	Methamphetamine	Methcathinone
HEK-hDAT				
[¹²⁵ I]RTI-55 binding; IC ₅₀ (nM)	2300	–	–	–
[¹²⁵ I]RTI-55 binding; K _i (nM)	2240	710	4 610	5500
[³ H]DA uptake; IC ₅₀ (nM)	764	376	61.7	186
HEK-hSERT				
[¹²⁵ I]RTI-55 binding; IC ₅₀ (nM)	11 900	–	–	–
[¹²⁵ I]RTI-55 binding; K _i (nM)	11 500	580	174 000	285 000
[³ H]5-HT uptake; IC ₅₀ (nM)	7 500	265	9 200	45 000
HEK-hNET				
[¹²⁵ I]RTI-55 binding; IC ₅₀ (nM)	2480	–	–	–
[¹²⁵ I]RTI-55 binding; K _i (nM)	2460	1960	2580	5560
[³ H]NE uptake; IC ₅₀ (nM)	469	301	24.3	36.5

Source: reference 198

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

Uptake experiments with benzylone were also conducted within the US National Institute of Mental Health Psychoactive Drug Screening Program (199). At SERT, no inhibition was observed below 10 µM, whereas the K_i values at NET and DAT were 1629 nM and 637 nM. In comparison, the uptake inhibition values for cocaine were NET (K_i = 1275 nM), DAT (K_i = 249 nM) and SERT (K_i = 818 nM).

Benzylone was also screened for binding affinity against 49 targets. The results below K_i = 10 µM are summarized in Table 12, with results for mephedrone (4-methylmethcathinone; 2-(methylamino)-1-(4-methylphenyl)propan-1-one) included for comparison. For benzylone, the only submicromolar K_i values were determined for σ₁ receptors and NET (980 nM) and DAT (40 nM). In this study, the radioligands used for NET and DAT binding were [³H]nisoxetine and [³H]WIN-35428 ([³H]citalopram for SERT), whereas [¹²⁵I]RTI-55 was used for all three transporters (see Table 11) (198).

Table 12. Binding affinities of benzylone and mephedrone to receptor and transporters (K_i, nM)

Compound	5-HT1A	5-HT1B	5-HT2B	α2B	α2C	D4	σ1	σ2	NET	DAT	DOR	KOR
Benzylone	1140	-	1660	3775	3775	1969	155	2841	980	40	4300	3030
Mephedrone	-	1630	739	-	4476	-	-	-	-	-	-	-

From reference 199

Results only for K_i < 10 μM. NET: norepinephrine transporter; DAT: dopamine transporter; DOR: delta opioid receptor; KOR: kappa opioid receptor

5. Toxicology

No information was available on the acute or chronic preclinical toxicology of benzylone.

6. Adverse reactions in humans

No information was found on benzylone-induced adverse reactions in humans. Correspondence received by the ECDD secretariat from the US Office of National Drug Control Policy claimed that “at least 9 post mortem overdose event has involved BMDP, specifically, in the United States since 2012”, citing “private correspondence between ONDCP and key partners in state public health departments, March 15–22, 2021”. No further data were available. As summarized in Table 13, benzylone has been detected with other substances in post-mortem cases involving poly-substance use. A causative role of benzylone can be considered unlikely. The UNODC Early Warning Advisory (Tox-Portal) database lists one case in Australia in which etizolam and benzylone were identified in femoral blood from a post-mortem case. The relative or probable contribution of both substances was listed as “contributory (medium)” (200).

Table 13. Detections of benzylone and other substances in post-mortem cases suggesting poly-substance use

Date submitted	Age, gender	Case history	Findings
June 2019	50, M	Suspected overdose; history of iv drug use; found dead face down on floor of bathroom; unknown powder found on floor nearby	Benzylone, etizolam, morphine, naloxone, hydrocodone, THC
August 2019	22, M	Not available	Benzylone, methamphetamine, xylazine, 4-ANPP, quinine, fentanyl, etizolam
August 2019	24, M	Suspected overdose; history of "heroin" overdose	Benzylone, fentanyl, morphine, naloxone, THC
August 2020	28, M	Suspected overdose; history of cocaine and "heroin" use	Benzylone, eutylone, cocaine, lidocaine, fentanyl, etizolam, aripiprazole, ethanol
Not available	Not available	Not available	Benzylone, eutylone

Sources: A.J. Krotulski, personal communication and references 202 and 203
4-ANPP, 4-anilino-*N*-phenethyl piperidine (*N*-phenyl-1-(2-phenylethyl)piperidin-4-amine)

One country in the European Union Early Warning System Network reported a serious adverse event to the EMCDDA, in which benzylone was analytically confirmed in a biological sample from a fatal case in 2019, but further details were not available (201).

7. Dependence potential

A. Animal studies

No information was found.

B. Human studies

No information was found.

8. Abuse potential

A. Animal studies

Time-course (6 h) locomotor activity tests in mice were conducted to compare the effects of benzylone and methamphetamine. Groups of eight non-habituated male Swiss-Webster mice (Hsd:ND4, aged 2–3 months) received benzylone HCl

by ip injection at a concentration of 1, 2.5, 5, 10, 25, 50 or 100 mg/kg. Horizontal activity (interruption of photocell beams) was measured in one mouse per activity chamber for 6 h for 10-min periods. The period 0–30 min was selected for analysis of dose–response (maximal effects for benzylone). Stimulant effects occurred within 10 min of injection and lasted for 30 min (204). The results (Table 14) suggested that benzylone has little effect, even at high doses. Modest stimulant effects at 50 mg/kg occurred within 10 min of injection and lasted 30 min. Depressant effects were also noted after administration of 2.5 and 100 mg/kg. Significant effects were modest increases or random decreases, suggesting that they were not dose-dependent. The benzylone ED₅₀ value (117.07 μ mol/kg) was determined by linear regression against log₁₀ doses of 25–50 mg/kg benzylone.

Table 14. Results of tests for locomotor activity in mice

Compound	ED ₅₀ [mg/kg (μ mol/kg)]	95% Confidence Interval [mg/kg (μ mol/kg)]
(S)-(+)-Methamphetamine HCl	0.62 (3.34)	0.19–2.06 (1.02–11.09)
Benzylone HCl	37.44 (117.07)	12.99–107.88 (40.60–337.33)

Source: reference 204

Benzylone did not significantly substitute for the discriminative stimulus effects of MDMA. In a two-lever discrimination task, 10 male Sprague-Dawley rats received an MDMA training dose of 1.5 mg/kg under a fixed-ratio schedule of reinforcement. Benzylone at 5–50 mg/kg increased the MDMA-appropriate lever response, with a response of $33 \pm 33\%$ at 50 mg/kg. The response rate decreased to 34% of vehicle control after administration of 50 mg/kg, while full substitution requires $\geq 80\%$ MDMA-appropriate response. No unusual effects were observed at any dose of benzylone (205).

Tests for substitution of methamphetamine (training dose, 1 mg/kg) showed that benzylone at 10–50 mg/kg increased the methamphetamine lever response, with a maximum methamphetamine-appropriate response of $67 \pm 20\%$ at 50 mg/kg. The response rate to benzylone increased to 139% of vehicle control after 10 mg/kg and decreased to 26% of vehicle control after 50 mg/kg benzylone. Decreased muscle tone was observed in 8 of 10 rats after 50 mg/kg, and 5/10 rats failed to complete the first fixed ratio at that dose (206). These findings suggest that benzylone tended to be perceived as methamphetamine-like, but the trend was not significant and occurred only at doses that significantly impaired response. The data suggest that benzylone is unlikely to cause abuse liability.

B. Human studies

No information was identified.

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

Information about therapeutic use could not be identified.

No information was available.

10. Listing on the WHO Model List of Essential Medicines

Benzylone is not on the 21st WHO Essential Medicines List or the 7th WHO Essential Medicines List for Children updated in June 2019.

11. Marketing authorizations (as a medicinal product)

No information was available.

12. Industrial use

No information was available.

13. Non-medical use, abuse and dependence

No epidemiological evidence was found on use of benzylone. Its use is likely to be limited to people who use drugs recreationally rather than by the general population. The mode of use may involve combination (intentionally or unintentionally) with other drugs, and people who use this substance may be unaware of the exact dose or compound they are taking. Benzylone is available in its own right and is advertised for sale by some Internet retailers. The available information (sections 4 and 8) suggests that benzylone is unlikely to show abuse liability and that it might not show significant psychostimulant properties comparable to those of other synthetic cathinones under international control.

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

No epidemiological study on harm associated with benzylone use was identified. The information on six post-mortem cases (section 6) involved poly-substance use and included detection of benzylone among other substances. Information available from the EMCDDA and drug-testing services in Switzerland and the USA suggests the presence of benzylone in products acquired or sold as MDMA and ketamine (184–186, 201), which suggest that people who use certain types of recreational drugs might be exposed unintentionally to benzylone. EMCDDA reported that an e-liquid used for vaping found on a poisoned patient contained the synthetic cannabinoid receptor agonist MDMB-4en-PINACA (methyl 3,3-dimethyl-2-{{[1-(pent-4-en-1-yl)-1H-indazole-3-carbonyl]amino}}

butanoate), five other synthetic cannabinoid receptor agonists and benzylone. The case occurred in July 2020 (207).

15. Licit production, consumption and international trade

Benzylone is used as a 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

Detection of benzylone was first reported by the EMCDDA in December 2010 in a sample collected in October 2010 (201, 208). As of 15 July 2021, 17 countries in the European Union Early Warning System Network and the United Kingdom had reported detection of benzylone to the EMCDDA (201). The EMCDDA has since received reports of 173 seizures of benzylone, with 33 seizures between 2011 and 2018, 89 in 2019 and 51 in 2020 (data for 2020 not final). Most seizures (52%) occurred in 2019.

In the reported seizures, benzylone was usually found as a powder (86%), while tablets (9% of cases) and herbal material (3%) were less frequently reported (201). About 25 kg of powders containing benzylone were reported, with 2.7 kg between 2011 and 2018, 21.8 kg in 2019 and just under 0.5 kg in 2020 (not final). Most powders (87%) were seized in 2019 (201).

The EMCDDA has also received reports of 1657 tablets containing benzylone, all of which were seized in 2020. In one sample, benzylone was found in a blue tablet also containing eutylone, which had been purchased as MDMA. Benzylone was found in bags labelled RTI-11, 3-methylmethcathinone, 3F-phenmetrazine, 5-DBFPV and diclazepam (201).

The numbers of countries that reported benzylone detections to the UNODC were four each in 2010, 2011 and 2012; two each in 2013 and 2014; none in 2015 and 2016; one in 2017; eight in 2018; 19 in 2019; and two each in 2020 and 2021 (209). Benzylone was identified in 17 reports from the NPS Monitoring Programme in China for June 2018–June 2019. Eutylone was counted 15 times, and *N*-ethylnorpentylone (1-(2*H*-1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one) was identified 58 times. Benzylone ranked sixth on a list of the main 10 synthetic cathinones (210). In an UNODC report on synthetic drugs in East and South-East Asia in 2021, eutylone was still featured but not benzylone (211). The Brazilian Federal Police first reported detection of benzylone in 2018 (212).

The US NFLIS has registered relatively few reports of the detection of benzylone since 2019, when it was first reported (Table 15). According to the currently available collection of mid-year and annual reports, the number of reports of benzylone submitted to NFLIS decreased in 2020.

Table 15. Numbers of reports (and proportions under the phenethylamine classification) received by the US National Forensic Laboratory Information System on detections of benzylone in law enforcement operations

Year ^a	Benzylone (%)	Eutylone (%)	MDMA (%)	Methamphetamine (%)	Reference
2018 (annual report)	Not reported	260 (0.06)	6616 (1.56)	386 272 (91)	213
2019 (mid-year report)	390 (0.17)	2800 (1.23)	3558 (1.56)	209 439 (92.03)	214
2019 (annual report)	681 (0.15)	5787 (1.28)	7238 (1.60)	417 867 (92.43)	215
2020 (mid-year report)	246 (0.13)	5118 (2.64)	2672 (1.38)	177 794 (91.69)	216

A summary of “snapshot” drug reports received by NFLIS-Drug is presented in Table 16, in which benzylone is initially one of the first five synthetic cathinones, while the number (and proportion) of reports fell in January–March 2021 (81 reports, 3.40%) from that in 2020. The 2020 National Drug Threat assessment document published by the DEA in March 2021 stated that 9575 reports of synthetic cathinones had been submitted to NFLIS-Drug in 2019, which represented a 28% decrease from 2018 (13 226 reports). Eutylone was the most frequently reported synthetic cathinone (58%), while the proportion was 8% for benzylone (217). The snapshot shown in Table 16 indicates that the mean proportion of benzylone submissions dropped to 4.34% in the period January 2020–March 2021, whereas the mean number of eutylone reports increased to 78.42% in the same period. The snapshot data are only for the first five synthetic cathinones.

Table 16. US National Forensic Laboratory Information System (NFLIS) snapshot reports for the first five drugs in the category “selected synthetic cathinones”

Period	Benzylone (%)	Eutylone (%)	Total	Reference
January–March 2020 ^a	91 (4.90)	1221 (65.86)	1 854	218
April–June 2020 ^b	135 (4.79)	2116 (75.04)	2 820	219
October–December 2020 ^c	161 (4.87)	2745 (82.96)	3 309	220
January–March 2021 ^d	81 (3.40)	2381 (84.76)	2 809	221
Total	468 (4.34)	8463 (78.42)	10 792	–

- ^a Reports received by NFLIS-Drug submitted to a NFLIS participating laboratory on or after 1 January 2019. The three other synthetic cathinones were: *N*-ethylpentylone [sic] (185); *a*-PiHP (4-methyl-1-phenyl-2-(pyrrolidin-1-yl)pentan-1-one) (86) and *N*-butylpentylone [sic] (1-(2*H*-1,3-benzodioxol-5-yl)-2-(butylamino)pentan-1-one) (56).
- ^b Reports received by NFLIS-Drug submitted to a NFLIS participating laboratory on or after 1 April 2019. The three other synthetic cathinones were: *N*-ethylpentylone [sic] (135), butylpentylone [sic] (99) and *a*-PiHP (83).
- ^c Reports received by NFLIS-Drug submitted between 1 October 2020 and 31 December 2020. The three other synthetic cathinones were: *N*-ethylpentylone [sic] (90), *a*-PHP (1-phenyl-2-(pyrrolidin-1-yl)hexan-1-one) (48) and *a*-PiHP (32).
- ^d Reports received by NFLIS-Drug between 1 January 2021 and 31 March 2021. The three other synthetic cathinones were: *N*-ethylpentylone [sic] (54), 3,4-methylenedioxy PV8 (1-(2*H*-1,3-benzodioxol-5-yl)-2-(1-pyrrolidinyl)-1-heptanone) (45) and “fluoro-methyl- α -PVP” [sic] – isomer not specified (17).

Benzylone was not included in the 2018 annual DEA Emerging Threat report covering drug reports collected from the DEA laboratory system, which presented 327 detections of synthetic cathinones (21 compounds listed). *N*-Ethylpentylone represented 62% (204/327) of the identifications, and eutylone was also not listed (222). Benzylone was reported for the first time in the 2019 report, with 12/184 (6.5%; 19 cathinones listed) identifications. In comparison, eutylone was identified 67/184 times (36%) (223). The 2020 annual report listed 13 synthetic cathinones (200 identifications in total); benzylone was identified 5 times (2.5%) and eutylone 154 times (77%) (224).

17. Current international controls and their impact

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

18. Current and past national controls

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

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

Detections of benzylone may be under-reported if there is no routine screening for this substance in all laboratories that receive samples for analysis.

3.2 Pre-review reports

3.2.1 Kratom (*Mitragyna speciosa*), mitragynine and 7-hydroxymitragynine

1. Substance identification

A. International Nonproprietary Name (INN)

Kratom: No information was available.

Mitragynine: No information was available.

7-Hydroxymitragynine: No information was available.

B. Chemical Abstracts Services Registry Number

Kratom: Not applicable.

Mitragynine:

4098-40-2 (-)-Mitragynine free base

1908497-94-8 (+)-Mitragynine free base

36455-45-5 Mitragynine hydrochloride

58375-35-2 Mitragynine hydriodide

11047-38-4 Mitragynine hydrobromide

11047-42-0 Mitragynine perchlorate

11047-41-9 Mitragynine oxalate

11047-35-1 Mitragynine cinnamate

11047-36-2 Mitragynine trichloroacetate

36455-46-6 Mitragynine ethanedisulfonate

11047-37-3 Mitragynine, compd. with 1,3,5-trinitrobenzene (1:1)

7-Hydroxymitragynine:

174418-82-7 7-Hydroxymitragynine

C. Other chemical names

Kratom: Not applicable

Mitragynine:

Corynan-16-carboxylic acid, 16,17-didehydro-9,17-dimethoxy-, methyl ester, (16E,20β)- (ZCI)

Corynantheidine, 9-methoxy- (7CI)

Mitragynine (6CI)

(-)-Mitragynine

9-Methoxycorynantheidine

Indolo[2,3-a]quinolizine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy- α -(methoxymethylene)-, methyl ester, [2S-[2 α (E),3 α ,12b β]]-

Mitragynin

7-Hydroxymitragynine:

Corynan-16-carboxylic acid, 1,2,16,17-tetrahydro-2,7-dihydro-7-hydroxy-9,17-dimethoxy-, methyl ester, (7 α ,16E,20 β)- (ZCI)

7-Hydroxymitragynine

7 α -Hydroxy-7*H*-mitragynine

9-Methoxycorynantheidine hydroxyindolenine

Mitragynine hydroxyindolenine

D. Trade names

Kratom:

M. speciosa is available online and in shops that sell equipment for smoking cannabis and tobacco (“head shops”). The derived products are often distinguished according to vein colour, “provenance” (origin) and potency. Three types of kratom with different leaves and potency have been described, such as red-veined (*kan daeng* in Thai), white-veined (*tang gua*) and yak yai, which has two small teeth-like formations near the apex of the leaf (225, 226).

Several other types of kratom are available online with the following names (227):

- Premium kratom

- Commercial grade kratom

- Bali kratom

- Enhanced Bali kratom

- Ultra enhanced Indo (U.E.I.) kratom

- Indo red vein, Malaysian kratom

- Red-vein Thai kratom

- Green- or white-vein Thai kratom

- Maeng Da kratom

- White-veined Borneo kratom

- New Guinea kratom

- Java kratom

- Sumatra red

- The Rifat strain

- The bumblebee strain

- Red Riau

- Green Riau.

The “strain” of kratom designated by the vein colour actually corresponds to the leaf age (228). For example, the red-vein “strain” is younger and more potent than the mature green vein “strain”, grows more abundantly in South-East Asia and is slightly more persistent than other *M. speciosa* trees. The red-vein “strain” is

marketed with several names including (Kratomgardens):

- Borneo Red
- Red Vein Sumatra
- Pontianak Red Horn
- Red Thai.

White-vein kratom is known as (Kratomgardens):

- White Vein Sumatra
- Borneo White
- Pontianak White Horn.

The green vein is described as a mix of the red and the white types and is called Malaysian Green or Pontianak Green Horn (Kratomgardens).

Todd et al. (229) investigated the chemical composition of over 50 commercial kratom products with different names.

E. Street names

Kratom is the common term used for the *M. speciosa* leaf and derived products. Street names in South-East Asia include *krathom*, *kakuam*, *ithang* and *thom* (Thailand), *biak-biak* and *ketum* (Malaysia) and *mambog* (Philippines). Kratom “cocktail” refers to a decoction of kratom leaves mixed with another beverage. In Germany, “krypton” refers to a mixture of kratom and *O*-demethyltramadol (230).

F. Physical appearance

Kratom

Marketed kratom products usually consist of light to dark-green crushed or powdered dried leaves (231). Vendors also offer powdered, greenish or beige-brown preparations fortified with extracts of other leaves. An aqueous decoction of kratom leaves can be used to make paste-like extracts and dark-brown kratom resin by partially or fully boiling down the water. Tinctures and capsules filled with powdered kratom are also available.

Botanical description: Kratom, *Mitragyna speciosa* (Korth.) Havil., is a tropical tree that grows in Thailand, Myanmar, Malaysia, Borneo, Sumatra, the Philippines and New Guinea (227). *Mitragyna* Korth. is a small genus of the Rubiaceae family. The genus *Mitragyna* belongs to the tribe Naucleaeae of the subfamily Cinchonoideae (232).

The genus *Mitragyna* comprises 10 species, of which four occur in Africa (*M. inermis*, *M. ledermannii*, *M. rubrostipulata* and *M. stipulosa*) and six in South and South-East Asia, between India and New Guinea (*M. speciosa*, *M. tubulosa*, *M. rotundifolia*, *M. parvifolia*, *M. hirsuta* and *M. diversifolia*). The nomenclature of *M. speciosa* has been changed over the years. First described by the Dutch botanist Pieter Willem Korthals (1807–1892) (233), the genus was reclassified several times, until George Darby Haviland gave the final name and classification in 1897 (234).

M. speciosa is an evergreen tree that reaches 25 m in height and 0.6–0.9 m in diameter. It generally has a straight trunk, a smooth, grey outer bark and a pinkish inner bark (227). The petiolate leaves are generally dark glossy green and elliptical and can reach 14–20 cm in length and 7–12 cm in width. They typically present 12–17 pairs of veins. The flowers are arranged in groups of three heads, one with a short peduncle between two heads with a longer peduncle. The heads are 1.5–2.5 cm in diameter with light, hairy interfloral bracts 4–6 mm long. The flower calyx is about 2 mm long, with five lobes. The corolla is funnel-shaped, with an intense yellow colour. The corolla tube measures 3.5–5 mm, while the corolla lobes are 2.5–3 mm long and hairless with a revolute margin and a distinct ring of hairs within the base of the lobes. The fruiting heads are 2–3 cm wide, with 10 ribbed fruits of 7–9 mm length and 4–5 mm width. They contain numerous flat seeds, which are about 1 mm long with a 1–2-mm paper wing at each end (227, 233, 234).

Synonyms for *M. speciosa* Korth. (Havil.) (227):

Nauclea korthalsii Steud.; *Nauclea luzoniensis* Blanco; *Nauclea speciosa* (Korth.) Miq.; *Stephegyne speciosa* Korth.

Common names used for *Mitragyna speciosa* Korth. (Havil.) (227):

Indonesia: *kadamba* (Kelantan), *puri* (Batak Toba, Sumatra), *keton*

Malaysia: *biak*, *biak-biak*, *ketum*, *kutum*, *pokok biak*, *pokok ketum*, *sepat* (Sabah)

Myanmar: *beinsa*, *bein-sa-ywat*

Philippines: *mambog* (Tagalog), *lugub* (Mandaya), *polapupot* (Ibanag)

Thailand: *ithang* (central), *thom* (peninsular), *bai krathom*, *gratom*, *kakaum*, *katawn*, *krathawm*, *kratom*, *kraton*

Viet Nam: *giam d[ef]p*, *giam l[as] nh[or]*.

Marketed kratom products:

A mix of kratom extract combined with codeine or diphenhydramine containing cough syrup, soda, ice and potentially other pharmaceuticals, drugs or chemicals is referred to as “4x100” (235–237).

Kratom is sold for recreational use either whole or as crushed leaves, leaf powder, encapsulated powder, concentrated extracts (5–100x times), solid resin or tinctures. Kratom extracts or raw material are also used in dietary supplements (238). Live plants and seeds are available online (227).

Mitragynine

White, amorphous crystals (231)

7-Hydroxymitragynine

Amorphous powder (239)

G. WHO review history

Kratom has not been formally reviewed by WHO and is not currently under international control. Kratom has been under ECDD surveillance since national reports of the abuse liability of its main psychoactive ingredient, mitragynine, and reports from international organizations on fatalities. A pre-review was initiated after a proposal from an international organization that provided information about fatalities due to kratom use.

2. Chemistry

A. Chemical Name

IUPAC name:

Kratom: Not applicable

Mitragynine: Methyl (E)-2-[(2S,3S,12bS)-3-ethyl-8-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate

7-Hydroxymitragynine: Methyl (2E)-2-[(2S,3S,7aS,12bS)-3-ethyl-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate

Chemical Abstracts Index Name:

Kratom: Not applicable

Mitragynine: Indolo[2,3-a]quinolizidine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy- α -(methoxymethylene)-, methyl ester, (α E,2S,3S,12bS)-(9CI, ACI)

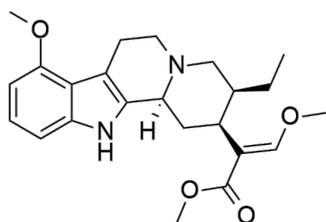
7-Hydroxymitragynine: Indolo[2,3-a]quinolizidine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,7a,12b-octahydro-7a-hydroxy-8-methoxy- α -(methoxymethylene)-, methyl ester, (α E,2S,3S,7aS,12bS)-(9CI, ACI)

B. Chemical structure

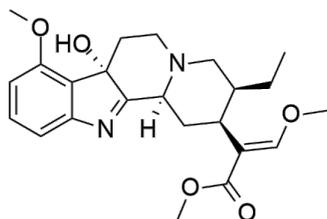
Free base:

Kratom: Not applicable

Mitragynine:



7-Hydroxymitragynine:

**Molecular formula:**

Kratom: Not applicable

Mitragynine: $C_{23}H_{30}N_2O_4$ 7-Hydroxymitragynine: $C_{23}H_{30}N_2O_5$ **Molecular weight:**

Kratom: Not applicable

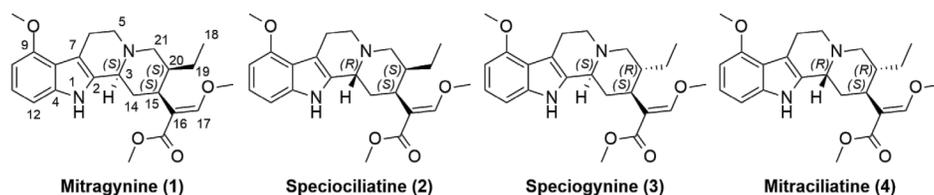
Mitragynine: 398.50 g/mol

7-Hydroxymitragynine: 414.50 g/mol

C. Stereoisomers

Kratom: Not applicable

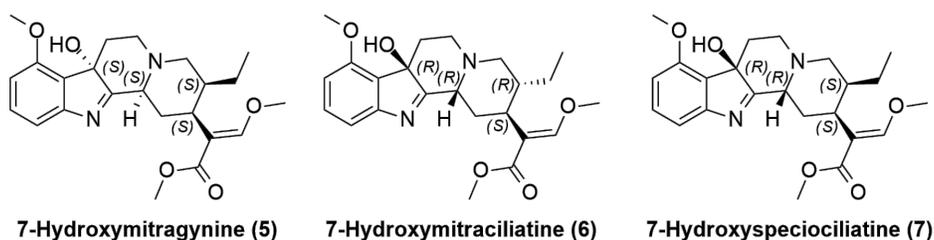
Mitragynine: The presence of three stereogenic centres and an *E-Z* isomerism in the double bond on the methoxy acrylate group indicate the possibility of 16 stereoisomers; however, only four stereoisomers occur naturally in *M. speciosa*: mitragynine, which has the 3*S*,15*S*,20*S* configuration (1); speciociliatine 3*R*,15*S*,20*S* (2), speciogynine 3*S*,15*S*,20*R* (3) and mitraciliatine 3*R*,15*S*,20*R* (4) (Fig. 4). The *E*- stereochemistry is always present in the double bond on the C-15 methoxy acrylate group in mitragynine stereoisomers isolated from *M. speciosa* (240). Of the four stereoisomers, mitragynine (1) is the most abundant, accounting for up to 66% of the total alkaloid content in kratom leaves, while speciociliatine (2) and speciogynine (3) combined account for an average of 8–9%. Mitraciliatine (4) is the least abundant, accounting for < 1% of the total alkaloid content (240).

Fig. 4. Naturally occurring stereoisomers of mitragynine

Atom numbering is shown in the main component (1). Absolute configurations are indicated.

7-Hydroxymitragynine: The presence of four stereogenic centres and an *E-Z* isomerism in the double bond on the methoxy acrylate group generate 32 potential stereoisomers, but only three are found in *M. speciosa*: 7-hydroxymitragynine, which has the configuration 3*S*,7*S*,15*S*,20*S* (5), 7-hydroxyspeciociatine 3*R*,7*R*,15*S*,20*S* (6) and 7-hydroxymitraciliatine 3*R*,7*R*,15*S*,20*R* (7), all presenting the *S*- configuration and *E*- stereochemistry in the double bond on the C-15 methoxy acrylate group (Fig. 5) (240).

Fig. 5. Naturally occurring stereoisomers of 7-hydroxymitragynine



Absolute configurations are indicated.

D. Methods and ease of illicit manufacture

Kratom

Chemical composition

Most studies of the chemical composition of kratom have addressed the alkaloids, resulting in isolation of at least 54 alkaloids from the plant (241). Secondary metabolites, like flavonoids, terpenoid saponins, polyphenols and glycosides, have also been isolated or identified. The main psychoactive components, which are exclusive to *M. speciosa*, are mitragynine and 7-hydroxymitragynine and are found in the leaves. The total alkaloid content in dried leaves is 0.5–1.5%. The most abundant compounds are indoles, mainly of the corynanthe type, which are found in tetra- or penta-cyclic rings. A hydroxy or methoxy group at C-9, unsaturation at C-3, C-5 or C-18, hydroxylation at C-7 and various configurations at C-3, C-7 and/or C-20 are found in indole and oxindole alkaloids (241).

Mitragynine is the major alkaloid in the kratom plant, representing up to 66% of the total alkaloid content. It was initially isolated by Field in 1921 (242), but its structure was definitely elucidated only in 1965 (240, 243) and the absolute stereochemistry confirmed by X-ray crystallographic analysis. Its concentration depends on the plant organ and origin and also to genetic and morphogenetic factors, the plant defence system against pathogenic attacks, light, ultraviolet (UV) light, moisture, temperature, soil microorganisms, soil fertility, salinity and storage conditions (244, 245).

Mitragynine has a corynanthe-type skeleton, with a tetracyclic tetrahydro- β -carboline, four cycles with a methoxyl substitution at C-9, an ethyl group at C-20 and a β -methoxy acrylate moiety at C-15 (246). Paynantheine is described as the second major alkaloid, accounting for 10% of the total alkaloid content. On average, 7 α -hydroxymitragynine (5) (Fig. 5) accounts for < 2% of the alkaloid content (247). Oxindole alkaloids are biosynthesized from indole alkaloids through an oxidative rearrangement (248) and are found in *Mitragyna* and other Rubiaceae species, such as *Uncaria* (249).

The presence of fungi or bacteria can affect the presence and concentration of alkaloids in the plant. For example, *M. speciosa* root cultures infected with *Agrobacterium rhizogenes* generated more mitragynine than uninfected plants (250). Another reported spirocyclic oxindole is mitragynine pseudoindoxyl, which is a major transformation product when fungal *Helminthosporium* spp. feed on mitragynine (251).

Flavonoids and flavonols have been identified in *M. speciosa* leaves, including apigenin and its 7-glycosides, with quercetin and its glycosides (quercitrin, rutin, isoquercitrin, hyperoside and quercetin-3-galactoside-7-rhamnoside, kaempferol and its 3-glucoside derivative and epicatechin). Other phenolic compounds include caffeic acid and chlorogenic acid, 1-*O*-feruloyl- β -D-glucopyranoside and benzyl- β -D-glucopyranoside (227, 252). The phytosterols sitosterol, stigmasterol and daucosterol have been reported in *M. speciosa* (250). The leaves of *M. speciosa* also contain the monoterpenes 3-oxo- α -ionyl-*O*- β -D-glucopyranoside and roseoside and secoiridoid glycosides such as vogeloside and epivogeloside (227).

Adulteration

Preparation of kratom products intended for sale can involve adulteration of the original material. In 2011, it was reported that products sold in Germany and Sweden under the name “Krypton” were “enhanced” kratom preparations containing caffeine and synthetic *O*-desmethyltramadol (231, 253, 245). In 2016, concentrations of 7-hydroxymitragynine suspiciously higher than those found in raw *M. speciosa* leaves were reported in several commercial kratom products, suggesting artificial addition (255).

Alkaloid extraction

Alkaloids from *Mitragyna* are generally extracted from raw material with methanol, ethanol (or 2-propanol), an alcohol–chloroform or an alcohol–water mixture by maceration, sonication or the Soxhlet technique. The crude extract is subjected to acid–base purification to yield the alkaloid fraction (227, 256). Other techniques used are ultrasound-assisted extraction, microwave-assisted extraction and supercritical carbon-dioxide extraction, which increase the yield of alkaloids over that of other techniques (257).

Mitragynine

Several methods for total synthesis of mitragynine (1) (Fig. 4) have been developed (258–262), but they are too complex, with too many steps, for economic production of this alkaloid (231) and provide the final product in very low yields. Moreover, they can be performed only in well-equipped chemical laboratories by well-trained personnel. Extraction of the compound appears to be more convenient.

7-Hydroxymitragynine

7-Hydroxymitragynine can be obtained from mitragynine by a single-step chemical reaction. Takayama et al. (263) reported in 2002 that treatment of mitragynine with lead tetraacetate and subsequent alkaline hydrolysis led to 7-hydroxy-7*H*-mitragynine in good yield.

In 2016, Kruegel et al. (262) reported that mitragynine was easily oxidized to 7-hydroxymitragynine with the hypervalent iodine species [bis(trifluoroacetoxy)iodo]benzene or by irradiation with visible light in the presence of rose bengal under air or pure oxygen. Interestingly, they also found that room temperature and sunlight alone cause conversion of mitragynine into its 7-hydroxy derivative, albeit in low yield (8% by NMR). A similar process may occur naturally or, more likely, in dry leaf material exposed to air for a long time, with strongly coloured phytochemicals (e.g., porphyrins) playing the role of rose bengal. This phenomenon may account for the observation of 7-hydroxymitragynine in some samples of *M. speciosa*. In 2019, Kruegel et al. (249) reported that singlet oxygen and potassium peroxymonosulfate (oxone) were also effective oxidants for the conversion of mitragynine into 7-hydroxymitragynine.

E. Chemical properties

Melting-point:

Kratom: Not applicable.

Mitragynine: Forms white, amorphous crystals that melt at 102–106 °C. The melting-point of mitragynine hydrochloric acid salt is 243 °C; the picrate melts at 223–224 °C and the acetate at 142 °C (253).

Amorphous crystals of mitragynine show optical rotation $[\alpha]_D = -126$ (c. 0.66, CHCl₃) (or -128 (c. 1.2, CHCl₃)) (261).

7-Hydroxymitragynine: No information was available.

An amorphous powder of 7-hydroxymitragynine showed optical rotation $[\alpha]_D = +47.9$ (c. 0.55, CHCl₃) (239).

Boiling-point:

Kratom: Not applicable.

Mitragynine: Mitragynine distils at 230–240 °C at 5 mm Hg (231).

7-Hydroxymitragynine: No information was available.

Solubility:

Kratom: Not applicable.

Mitragynine: Mitragynine is insoluble in water; it is soluble in conventional organic solvents such as acetone, acetic acid, alcohols, chloroform and diethyl ether, forming fluorescent solutions. The solubility limit of mitragynine was measured in aqueous solution at pH 4 and pH 7 to be 130 and 83 μM , respectively (264). Mitragynine has a logP (partition coefficient) of 1.73 and a pKa of 8.11 ± 0.11 (265).

7-Hydroxymitragynine: No information was available.

Stability of kratom alkaloids

Basilieri and Kerrigan (266) reported the short-term stability of mitragynine, 7-hydroxymitragynine, speciociliatine, speciogynine and paynantheine over pH 2–10 and temperatures of 4–80 °C over 8 h. All the *Mitragyna* alkaloids studied were acid labile. The methyl ester is hydrolysed under alkaline conditions to produce 16-carboxymitragynine. 7-Hydroxymitragynine is reported to be the most unstable alkaloid, with significant drug loss after 8 h at ≥ 40 °C. No significant drug losses were observed in aqueous solution (pH 2–10) at 4, 20 or 40 °C. Diastereoisomers of mitragynine (speciociliatine and speciogynine) were even more stable (267, 268).

*F. Identification and analysis***Kratom****Botanical identification**

M. speciosa can be identified macroscopically by examining the leaf, which is elliptic to ovate, with the apex shortly pointed and the base rounded to cordate (240). Macroscopic identification can, however, be misleading, as the leaves from plants of the same tribe or genus such as *Uncaria homomalla* and *M. diversifolia* are similar (240, 244, 267), and chemical analysis can be resolute.

Microscopic identification of eight *Mitragyna* species (but not *M. speciosa*) was reported by examination of calcium oxalate crystal concretions, but the studies were based on limited samples (268).

Sukrong et al. (226) showed that sequences from the nuclear internal transcribed spacer region can be used to differentiate *M. speciosa* from related species by the polymerase chain reaction–restriction fragment length polymorphism method.

A highly specific, selective assay based on DNA bar-coding was reported for the detection of kratom products, in which the matK nucleotide signature site is used as a marker to discriminate *M. speciosa* from other *Mitragyna* species (269). DNA bar-coding with high-resolution melting analysis was proposed as a simple method for use in routine forensic analysis (270).

Chemical analysis

Numerous analytical methods have been reported for the identification and quantification of kratom alkaloids, particularly mitragynine, in a wide range of samples, including commercial samples, raw plant material and biological specimens. Commercial standards are available for mitragynine and its stereoisomers speciogynine, mitraciliatine and speciociliatine, its hydroxylate derivative 7-hydroxymitragynine and deuterated mitragynine and 7-hydroxymitragynine. Other indole and oxindole kratom alkaloids are sold as analytical standards, although Flores-Bocanegra et al. (241) reported that some “pure” commercial standards were either mixtures or even completely different compounds.

Chromatographic methods, and particularly LC, are most commonly used for analysis of *M. speciosa* alkaloids.

- Thin-layer chromatography (TLC)

Kratom alkaloids can be separated by TLC on silica gel plates and detected under a UV lamp (254 nm). A mobile phase composed of hexane:ethyl acetate:25% ammonia solution (30:15:1, v/v/v) provides an R_f value of mitragynine of 0.49 (271). After spraying with either modified Ehrlich’s reagent or ferric chloride–perchloric acid reagent, mitragynine can be detected as purple or grey-to-brown spots, respectively (255).

- Gas chromatography (GC)

The first GC method for the analysis of mitragynine in kratom was published in 2005 (257), but identification of mitragynine was given only by comparison of experimental mass spectra with library spectra. Philipp et al. (272) developed a GC–MS method for the analysis of kratom and/or krypton in urine by trimethylsilylation to increase the volatility of the alkaloids. Cornara et al. (273) described a GC–MS method for the analysis of underivatized mitragynine and other alkaloids in kratom.

Wang et al. (274) compared three chromatographic methods coupled to two detection systems, GC with MS, supercritical fluid chromatography with diode array detection (DAD) and HPLC with MS and DAD, for the analysis of mitragynine and structurally related alkaloids in *M. speciosa* plants. They concluded that the GC method could not resolve the two diastereoisomers mitragynine and speciociliatine, which also give identical electron impact mass spectra. This could be overcome only by derivatization. Moreover, the temperature range available for method optimization is limited.

A GC–MS method for the determination of mitragynine in three Malaysian *M. speciosa* samples includes ultrasonic-assisted extraction (275). Basiliere et al. (276) suggested that GC methods lack overall sensitivity (limit of detection, about 50 ng/mL) and therefore cannot be used to quantify the alkaloids in biological specimens.

- Liquid chromatography (LC)

- LC-UV

HPLC and UHPLC (ultrahigh) methods provide the most accurate discrimination of structurally similar kratom alkaloids (240).

An HPLC-DAD method was developed to identify and quantify mitragynine, caffeine, codeine, chlorpheniramine and phenylephrine in a “kratom cocktail” prepared by mixing boiled kratom leaves, carbonated cola beverages, antitussive syrup, coffee and codeine (277). Parthasarathy et al. (278) reported a HPLC-DAD method for quantifying mitragynine from raw material. Mudge and Brown (279) reported a validated HPLC-UV method for qualitative and quantitative analysis of mitragynine and 7 α -hydroxymitragynine in solid and liquid commercial kratom products.

Parthasarathy et al. (280) reported a solid-phase extraction method for HPLC-UV determination of mitragynine in rat plasma, with a limit of quantification of 50 ng/mL. Neng et al. (281) developed a method for extraction of mitragynine from human urine by bar adsorptive microextraction, consisting of a modified N-vinylpyrrolidone polymer sorbent phase combined with liquid desorption, followed by analysis by HPLC-DAD.

- LC-MS

LC-based methods are the most widely used for determination of kratom alkaloids, as they allow good resolution of mitragynine isomers and are highly sensitive, a key factor for qualitative and quantitative determination of trace amounts in biological specimens. As metabolites of mitragynine are not yet commercially available, kratom in forensic toxicology specimens is currently evaluated by analysis for the parent drug and related alkaloids. The mitragynine concentrations in urine from 50 people who use kratom recreationally covered a broad dynamic range (1–50 000 ng/mL) (282).

LC-MS methods were developed for simultaneous determination of mitragynine, 7-hydroxymitragynine, speciogynine, speciociliatine and paynantheine in both raw material and commercial kratom products (283). Some methods are highly sensitive, with limits of detection and quantification of mitragynine of 0.02 ng/mL and 0.1 ng/mL, respectively (284).

LC has also been coupled to low- and high-resolution MS to identify phase-I and -II metabolites of speciogynine in rat urine after administration of a high dose of the pure alkaloid and in human urine after kratom use (285). The same method was used to determine paynantheine (286), speciociliatine (287), mitraciliatine and isopaynantheine (288) and their metabolites in rat urine after administration of the pure alkaloids, which showed that they matched the metabolites detected in the urine of people who use kratom.

An LC-MS/MS method was used to detect *O*-desmethyltramadol and kratom alkaloids in the urine of a woman who consumed “krypton”, a mixture of kratom and *O*-desmethyltramadol (253). Mitragynine was also detected in post-mortem urine and blood samples by LC-MS/MS (289) after hydrolysis with glucuronidase and sulfatase and extraction with *n*-butyl chloride before analysis. The method was also used for other specimens, including liver, vitreous humour, kidney, spleen, lung, bile and heart, the last being the only specimen in which mitragynine was not detected. Solid phase extraction and LC-MS/MS were used to detect and quantify mitragynine, 16-carboxy mitragynine and 9-*O*-demethyl mitragynine in human urine (290).

Simultaneous quantification in marketed products of 10 kratom alkaloids (corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine, isocorynantheidine, mitragynine, mitraphylline, paynantheine, speciociliatine and speciogynine) in a UHPLC tandem MS method has been reported (291). The limit of quantification was 1 ng/ml. The method was used to quantify kratom alkaloids in alkaloid-rich fractions, ethanolic extracts, lyophilized teas and commercial products. The most abundant alkaloids were mitragynine (0.7–38.7% w/w), paynantheine (0.3–12.8%), speciociliatine (0.4–12.3%) and speciogynine (0.1–5.3%). Minor kratom alkaloids like corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine and isocorynantheidine were found at 0.01–2.8% (w/w). Mitraphylline was below the limit of quantification in all analyses. An HPLC method for quantification of mitragynine in kratom leaf extracts and a multiple reaction mode ultra-performance LC-MS/MS method for the quantification of the same alkaloid in rat plasma have also been reported (292).

Speciociliatine and speciogynine were investigated as alternative biomarkers of kratom use in urine, as their levels often exceeded the concentration of mitragynine in unhydrolysed urine (293).

A method for the detection of mitragynine and 7-hydroxymitragynine by LC-MS/MS in hair samples has been reported, with limits of quantification of 4 pg/mg and 30 pg/mg, respectively (294).

- Supercritical fluid chromatography (SFC)

Three chromatographic techniques, GC-MS, SFC-DAD and LC, were compared for the analysis of the indole alkaloids paynantheine, 3-isopaynantheine, mitragynine, speciogynine and speciociliatine and the oxindole alkaloids corynoxine and corynoxine B in *M. speciosa* plants (274). LC and SFC resolved the major components with slightly different elution orders, but the GC method failed to resolve the diastereoisomers mitragynine and speciociliatine.

- Capillary electrophoresis (CE)

Non-aqueous capillary electrophoresis (NACE) interfaced to an MS detector was used to separate a large number of diastereomeric compounds in alkaloid mixtures from a plant extract of *M. speciosa* (295). In this technique, background electrolytes often consist of a mixture of methanol and acetonitrile, with soluble ammonium salts added as electrolyte. A mixture of glacial acetic acid and acetonitrile was used, creating an acidic background electrolyte with a very low dielectric constant. The addition of ammonium formate as electrolyte and variation of the solvent ratio significantly changed the selectivity and resolution necessary for separation of structurally closely related indole alkaloids, including diastereomers.

- DART

A direct analysis in real time (DART)–MS method was developed for rapid identification of *M. speciosa* plant material and discrimination from other plants (296) and also for analysis and classification of *M. speciosa* plant varieties according to their chemical profile. A DART-HRMS method for quantification of mitragynine and 7-hydroxymitragynine in 16 kratom products available commercially online was reported (297). The linear range was 5–100 µg/mL, the limit of quantification was 5 µg/mL, and the mitragynine concentrations in these samples were 2.76–20.05 mg/g dried plant material. The advantage of a DART system is that it allows straightforward analysis of raw plant material with no sample preparation (296, 297).

- Ion mobility spectrometry

An ion mobility spectrometry method was used for quantification of mitragynine in 15 commercial samples, and the results were compared with those obtained by an LC-MS/MS method (298). The limit of detection was 0.5 ng. Mitragynine was detected in 14 of 15 samples by LC-MS/MS and 13 of 15 samples by ion mobility spectrometry, as the compound was below the limit of detection in one sample.

- Raman and portable devices

Surface-enhanced Raman spectroscopy was used to detect mitragynine in *M. speciosa* samples (299). The advantage of the method is that it can be used by non-experts. Over 100 samples and blanks were examined in duplicate with five identical handheld Raman spectrometers, with a false-positive rate of 2.1% and a false-negative rate of 0.7%. The limit of detection for mitragynine was 342 ng/mL. The method is ideal for preliminary screening for mitragynine, which can be confirmed by more time-consuming laboratory techniques.

DART with thermal desorption MS, hand-held MS, portable ion mobility spectrometry and portable Fourier-transform IR spectroscopy were all tested as

field screening techniques for detection of mitragynine in food and drug products, and the results were compared with those obtained with laboratory techniques such as LC-MS, HPLC-UV and GC-MS (300). The methods were applied to 96 kratom products, including capsules, bulk powder and bulk plant material. The portable devices allowed rapid detection of mitragynine in chloroform extracts and in solid kratom matrices. DART-TD-MS and ion mobility spectrometry are useful for initial screening because of short analysis time and absence of sample preparation. Hand-held MS gave the highest false-negative rate (6%). Both FT-IR and the hand-held MS require extraction of samples.

Immunological methods

Although chromatographic techniques have the advantage of good sensitivity, the separation step limits their routine use, and other screening and detection methods have been developed. For example, immunoassays are used worldwide for rapid screening or detection drugs in kratom preparations and biological fluids, with the advantages of good sensitivity, simplicity and convenience (301). The antibody to a specific kratom alkaloid prepared for an immunological assay may, however, cross-react with other alkaloids present in a sample (302, 303).

An electrochemical immunosensor for sensitive, rapid detection of mitragynine has been reported, with a modifier for the sensor based on multiwalled carbon nanotubes or chitosan nanocomposite (304). Mitragynine was detected in an indirect competitive assay with 3,3',5,5'-tetramethylbenzidine, which is the substrate in the enzymatic reaction of horseradish peroxidase-modified secondary antibody. The electrochemical immunosensor was 10 times more sensitive than conventional ELISA, with a limit of detection of 0.018 µg/mL and a limit of quantification of 0.06 µg/mL.

Mitragynine

The pure synthetic compound was obtained and characterized by NMR (258–262), HRMS (260), $[\alpha]_D$ (258, 262) and elemental analysis (259).

7-Hydroxymitragynine

The pure synthetic compound was obtained and analysed by NMR (258, 262) and both EI-MS and HRMS (258).

3. Ease of convertibility into controlled substances

Kratom: No information was available.

Mitragynine: No information was available. As reported above (section 2D), mitragynine can be converted into the bioactive 7-hydroxymitragynine in only one step (247, 258, 262); however, 7-hydroxymitragynine is not listed as a controlled substance.

7-Hydroxymitragynine: No information was available.

4. General pharmacology

Kratom is the common term for *M. speciosa*, a tree native to South-East Asia. The indigenous population has used kratom leaves and derived products for centuries as a herbal medicine to treat pain, cough, diabetes, diarrhoea and fever and as a wound poultice, to enhance sociability and sexual desire and to increase energy and decrease fatigue (304). More recently, kratom has been used as an opioid substitute and to treat opioid withdrawal. Lower doses (1–5 g of plant material orally) reportedly have stimulant effects, while higher doses (concentrated products such as kratom extracts or > 5 g of plant material) have opioid-like effects (305). Use of kratom has spread to western Europe and the USA during the past two decades, chiefly to self-medicate pain and opioid withdrawal and as a substitute for opioids (304).

Kratom contains more than 50 alkaloids, but only two indole alkaloids, mitragynine and its active metabolite 7-hydroxymitragynine (247), have been well characterized pharmacologically (229, 306). A third alkaloid, mitragynine pseudoindoxyl, is not found in the plant but is a metabolite of 7-hydroxymitragynine and is active *in vitro* at the MOR (307). Mitragynine represents up to two thirds of the total alkaloid content of kratom and is considered to be primarily responsible for its pharmacological actions. 7-Hydroxymitragynine comprises $\leq 1\%$ of kratom alkaloids in the leaf but is often present at a higher concentration in processed kratom products sold commercially (255). Kratom grown experimentally in the USA may have a lower mitragynine content than kratom grown in Thailand (308).

A. Routes of administration and dosage

Kratom in several forms is almost always taken orally. In South-East Asia, typical usage includes chewing raw leaves, ingesting powdered leaves, brewing leaves or leaf extract in tea or boiling the leaves for several hours to make a decoction (304, 309). A kratom decoction is often mixed with another beverage (e.g., cola, cough syrup) to create a kratom “cocktail”, in part to hide its bitter taste (304, 309). In western Europe and the USA, kratom is commonly taken as a powder dissolved in a beverage or in a capsule or tablet (304, 310, 311). Mitragynine and 7-hydroxymitragynine have been found in resins and liquids sold online for use in electronic drug delivery devices (so-called “e-cigarettes”) (312).

If kratom products are not accurately labelled, the actual doses of kratom alkaloids ingested by people who use kratom are not known. Surveys of convenience samples of people who use kratom in South-East Asia suggest that a typical daily dose of liquid formulation (tea, decoction) is three to six glasses per day, containing an estimated 200–400 mg of mitragynine (236, 313). In the USA, surveys of people who use kratom suggest that a typical daily dose of powder formulations is 2–6 g/day, although people with heavy use may ingest up to 20 g/day (310, 311).

B. Pharmacokinetics

a. Animal studies

Orally administered mitragynine (20–50 mg/kg) in rats had a mean T_{\max} of 1.3–4.5 h, a mean C_{\max} of 400–700 ng/mL and a mean half-life of 3.3–9.4 h (280, 314, 315). The mean oral bioavailability was 17% and 3% (280, 292). Oral dosing of rats with lyophilized kratom tea or an organic extract of kratom tea (equivalent to 20 mg/kg mitragynine) showed T_{\max} of 0.3 and 1.0 h, C_{\max} of 0.55 and 0.66 ng/mL and oral bioavailability of 25.1% and 31.2%, respectively (as compared with 17.0% for pure mitragynine) (292).

Mitragynine administered orally (5 mg/kg) to beagle dogs had a T_{\max} of 0.3 (± 0.1) h, C_{\max} of 278 (± 47.4) ng/mL, a half-life of 8.7 (± 0.2) h and bioavailability of 69.6% (316).

In rats, iv mitragynine readily crossed the blood–brain barrier, with a T_{\max} and half-life comparable to those in plasma (317).

b. Human studies

Two published studies of the pharmacokinetics of oral kratom were conducted in young men in South-East Asia who had used kratom daily for at least 6 months at the time of the study. In a study in Thailand, 10 men (mean [SD] body weight 77.3 [14.8] kg) drank kratom tea (60 mL, containing 6.25–11.5 mg mitragynine) daily for 7 days (318). Blood and urine samples were collected for 24 h after a loading dose (equivalent to 6.25–23 mg mitragynine) given on the 8th day. The mean (SD) T_{\max} of mitragynine was 0.83 (0.35) h, and the elimination half-life was 23.24 (16.07) h. The C_{\max} varied linearly ($R^2 = 0.677$) with the loading dose, from 18–30 ng/mL after 6.25 mg to 50–100 ng/mL after 20–23 mg. In a study in Malaysia, 26 men were given a single dose of 1.6 mg/kg of mitragynine in a kratom decoction containing 0.4–0.5 mg/mL mitragynine. The mean (SD) T_{\max} was 2.0 (0.8) h (range, 1–3 h), and the C_{\max} was 1884 (1056) ng/mL (range, 829–5034 ng/mL) (319).²

No data were available on the oral bioavailability of mitragynine or 7-OH-mitragynine, either alone or in a kratom product. In view of the variation in oral bioavailability between rodents and dogs (see above), an accurate extrapolation cannot be made to humans.

The effect of mitragynine on human liver cytochrome P450 activity is unclear. Mitragynine inhibited three P450 enzymes (CYP2C9, CYP2D6, CYP3A) in human liver cells in vitro at 1 μM concentration (229) and 7-hydroxymitragynine more weakly. Mitragynine (1–25 μM) produced concentration-dependent increases in mRNA and protein expression and the activity of CYP1A2, CYP2D6 and CYP3A4 in human liver cells in vitro (320). These findings suggest the possibility of clinically significant interactions of kratom–drug pharmacokinetics with

² Dr Marek Chawarski, personal communication

commonly used medications that are metabolized by these liver cytochromes, such as warfarin (CYP2C9), desipramine and dextromethorphan (CYP2D6) and benzodiazepines (CYP3A) (321).

C. Pharmacodynamics

a. Animal studies

Mitragynine, 7-hydroxymitragynine, and mitragynine pseudoindoxyl are partial agonists at the human MOR, activating the G-protein-coupled intracellular signalling pathway but with little or no effect on the β -arrestin pathway (229, 262, 306, 322, 323). This so-called MOR agonist bias has been proposed to confer differential efficacy on MOR ligands. Ligands that preferentially activate the G-protein-coupled intracellular signalling pathway should be more effective in producing analgesia and less effective in producing respiratory depression and physical dependence than ligands that preferentially activate the β -arrestin pathway (324, 325). In mice, mitragynine pseudoindoxyl at subcutaneous doses equipotent with morphine for analgesia was significantly less potent than morphine in generating tolerance or withdrawal, slowing gastrointestinal transit, causing respiratory depression or rewarding behaviour (323).

7-Hydroxymitragynine has 5–23 times greater affinity than mitragynine at the MOR (depending on the binding assay used) (229, 323, 326, 327), and morphine has 8–10 times greater affinity than 7-OH-mitragynine (229, 323, 327). MOR activation is considered to be responsible for most of the pharmacodynamics of kratom and its alkaloids observed in rodents and humans. Mitragynine and 7-hydroxymitragynine are also competitive antagonists at the human κ - and δ -opioid receptors (262), with less affinity than at the MOR (327, 328).

7-Hydroxymitragynine is 5–20 times more effective than mitragynine in activating the β -arrestin pathway (i.e., intrinsic activity) at the MOR (229, 323, 327). Morphine has three times more intrinsic activity at the MOR than 7-hydroxymitragynine (229, 327).

Mitragynine, but not 7-hydroxymitragynine, binds to α 1- and α 2-adrenergic receptors and serotonin-1A and -2A receptors (326, 329). Mitragynine binds with low affinity to dopamine-D1 receptors on rat striatal membranes and not at all to dopamine-D2 receptors (330). The functional significance of this binding pattern remains unclear.

Kratom extracts, mitragynine and 7-hydroxymitragynine have various effects on the behaviour of rodents. Some are observed inconsistently among studies, perhaps because of differences in dose, type of kratom extract, route of administration and timing of data collection (e.g., on motor activity, see below). Few studies included a broad range of doses and might therefore have missed some effects or non-linear dose–response relations. The most consistently observed effects are opioid-like (331): analgesia (332), suppression of opioid withdrawal (333) and inhibition of gastrointestinal transit (292).

Kratom extracts, mitragynine, 7-hydroxymitragynine and mitragynine pseudoindoxyl significantly reduced acute mechanical or thermal pain in rats and mice when given by the intracerebroventricular, ip, subcutaneous or oral route (332, 334). The analgesic effect was blocked by pretreatment with MOR antagonists (332) and did not occur in knock-out mice lacking the MOR (330, 334, 335), suggesting a MOR mechanism of action. Repeated dosing generated tolerance to the analgesic effect, with cross-tolerance among mitragynine, 7-hydroxymitragynine and morphine (332). The relative analgesic potency of kratom alkaloids and conventional opioids is uncertain, as few studies have been conducted in which the two were compared after administration by the same route of a range of doses to establish equipotent doses. In rats, 100 mg/kg of mitragynine given orally had the same analgesic effect as 6 mg/kg oral oxycodone (336).

Kratom extracts, mitragynine and 7-hydroxymitragynine suppressed naloxone-precipitated opioid withdrawal in rodents when given ip or orally (333, 334, 337, 338).

Kratom extracts and mitragynine have inconsistent effects on motor activity in rodents. In mice, kratom extract decreased (mitragynine 0.5 mg/kg ip or orally) (330), increased (mitragynine 7.4 mg/kg orally) (334) or had no effect (50–200 mg/kg methanolic extract or 5–20 mg/kg alkaloid extract orally) (339) on motor activity. In another study, mitragynine (30 mg/kg ip) had no effect (340). In three studies of motor activity in rats, kratom alkaloid extract (60 mg/kg orally) had no effect (341), and mitragynine had no effect (1–10 mg/kg ip) (342) or increased (30 mg/kg ip) motor activity (343). 7-Hydroxymitragynine (3 mg/kg ip) increased motor activity in male and female mice (322).

Kratom extracts and mitragynine have various non-opioid-like behavioural effects in rodents (331). They reduce immobility in the forced swim test and tail suspension test, which are considered models of anti-depressant action (344, 345). Kratom extract significantly influenced behaviour in several mouse models of anti-psychotic action, including apomorphine-induced climbing, haloperidol-induced catalepsy and ketamine-induced social withdrawal (346). Kratom extracts reduced alcohol self-administration, alcohol reinforcement (conditioned place preference), alcohol-induced increase in dopamine concentration in the nucleus accumbens and alcohol withdrawal in mice and rats (322, 347, 348). In rats, mitragynine (10–30 mg/kg ip) attenuated the acquisition and expression of morphine-conditioned place preference (349) and reduced self-administration of heroin but not of methamphetamine (0.1–3.0 mg/kg ip) (328).

b. Human studies

In an observational study in the United Kingdom in the early 1930s, five men given mitragynine acetate orally (50 mg once or twice separated by 2 h) or kratom (0.65 g or 1.3 g of powdered leaves) showed reduced heat sensitivity, dermal electrical

resistance and dilatation of skin blood vessels (350).

In a controlled clinical trial in Malaysia, 26 young men who used kratom daily were given a single oral dose of 1.6 mg/kg mitragynine (as a kratom decoction containing 0.4–0.5 mg/mL mitragynine) showed doubled pain tolerance in the cold pressor test about 1 h after ingestion (319). There was no change in pain threshold 2 h after ingestion. Studies with an experimental MOR-based analgesic (not kratom-derived) provided limited evidence for significantly lower adverse effects than with standard opioid analgesics (351).

5. Toxicology

Animal studies

In mice, the oral acute LD₅₀ was 547.7 mg/kg for kratom, 477.1 mg/kg for mitragynine (352, 353), 173.2 mg/kg or 591.6 mg/kg for a kratom alkaloid extract (20–22% mitragynine) (339, 352) and 4.9 g/kg for kratom methanolic extract (339). Death was preceded by tremor, paralysis, apnoea and seizures, usually within 1 h of administration (339, 352). 7-Hydroxymitragynine was not lethal at the highest dose administered (50 mg/kg), but respiratory depression and seizures were observed at the higher doses (353). The acute LD₅₀ after iv administration is 27.8 mg/kg for mitragynine and 24.7 mg/kg for 7-hydroxymitragynine (353). Death was due to respiratory depression, usually within 10 min of administration. For comparison, the oral LD₅₀ of morphine in mice is 600 mg/kg (354).

In rats, the oral LD₅₀ was 4.9 g/kg for kratom methanolic extract and 173.2 mg/kg for kratom alkaloid extract (339). Mitragynine was acutely lethal at 100 mg/kg but not at 56 mg/kg ip (327) and was not toxic at single oral doses up to 806 mg/kg (355). For comparison, the oral LD₅₀ of morphine in rats is 461 mg/kg (354). Repeated oral dosing with 5 or 50 mg/kg per day on 5 days/week for 6 weeks or 1 or 10 mg/kg per day for 4 weeks was not toxic (355, 356). Repeated oral dosing at 100 mg/kg per day for 4 weeks resulted in no deaths, tremor or seizures but decreased food intake and body weight, increased liver transaminase activity and blood urea nitrogen in female rats and reduced red and white blood cell counts in both female and male rats (356). Histopathological examination of internal organs showed abnormalities in the liver and neuronal damage (but no axonal changes) in the medulla, hippocampus, frontal cortex and cerebellum. There were no inflammatory changes or haemorrhage. A single oral dose of kratom methanolic extract (up to 1000 mg/kg) was not acutely toxic (357). Repeated oral dosing with a kratom methanolic extract (100, 500 or 1000 mg/kg daily for 14 days) resulted in a 10–20% increase in systolic and diastolic blood pressure and increased blood concentrations of urea nitrogen, creatinine, liver transaminases, cholesterol and triglycerides, with no significant changes in food or water intake, body weight, weight of internal organs or blood count (357). The highest dose caused liver damage (sinusoidal congestion, fatty changes, necrosis)

but no changes in kidney, lung or brain.

In dogs, mitragynine at 80 mg/kg orally or 4.6 mg/kg iv had no acute effects, whereas iv doses of 9.2 mg/kg slowed respiration and caused ataxia; 31.8 mg/kg caused respiratory depression and seizures (355). Repeated oral dosing with mitragynine (5 or 20 mg/kg per day 6 days/week for 3 weeks) was not toxic; however, increasing the dose to 40 mg/kg per day on weeks 4–7 decreased white blood cells and caused atypical lymphocytes, bone marrow hyperplasia, hyperplastic lymph nodes and increased diffuse sinusoidal cellularity in the liver. In anaesthetized dogs, mitragynine (cumulative iv dose, 18.5 mg/kg) had no significant effect on mean arterial blood pressure (355). In cats, mitragynine (9.2–46.0 mg/kg ip) produced dose-dependent mydriasis and restlessness. In anesthetized cats, iv mitragynine was lethal at 4.6 or 9.2 mg/kg (355).

Both acute (1, 5 or 10 mg/kg) and chronic (1, 5 or 10 mg/kg daily for 28 days) ip administration of mitragynine impaired the acquisition, consolidation and retrieval of short-term memory in rats (358). These effects were comparable to those of morphine at 5 mg/kg ip.

Intraperitoneal administration of kratom alkaloid extract reduced food and water intake acutely at 45 and 50 mg/kg but not at 15 or 30 mg/kg; weight loss was seen at 40 mg/kg per day for 60 days (359).

Kratom extract had no significant effect on sleep in mice (339) or rats (341).

Mitragynine at 1, 5 or 10 mg/kg ip acutely decreased EEG delta band power in the hippocampus and delta and theta activity in the frontal cortex of freely moving rats in one study (358) but had no effect in another (342). Chronic ip administration of mitragynine (1, 5, 10 mg/kg per day for 60 days) significantly increased delta power in the cortex and decreased alpha power in the cortex and delta power in the hippocampus (342). Kratom alkaloid extract (about 60% mitragynine; 80 mg/kg orally) had no effect on local field potentials in the mouse nucleus accumbens (337).

6. Adverse reactions in humans

No clinically significant adverse events, clinical abnormalities or changes in vital signs were noted in 36 men in Thailand who used kratom regularly and received either a single oral dose of a kratom decoction (mitragynine dose 1.6 mg/kg)³ (319) or eight daily doses of kratom tea (6.25–23 mg mitragynine) (318) in a clinical trial. All the participants who received kratom tea reported transient tongue numbness after drinking the tea (318).

In an observational study conducted in the United Kingdom in the early 1930s, five men given mitragynine acetate orally (50 mg once or twice separated by 2 h) or kratom (0.65 or 1.3 g of powdered leaves) reported transient, mild side-effects at the higher doses, including giddiness, nystagmus, pupillary constriction,

³ Dr Marek Chawarski, personal communication

muscle tenseness, hand or tongue tremor, gastric irritation, nausea, sleepiness and impaired motor coordination (350).

The US National Poison Data System recorded 3859 cases of non-lethal adverse reactions associated with kratom reported to poison control centres between 2010 and 2019 (360–363). The annual number of cases increased from 26 in 2010 to 100 in 2013, 263 in 2015, 568 in 2017 and 1218 in 2019 (360, 362). Most of the 3484 cases reported in 2014–2019 were in men (68.2%) and involved only kratom (63.0%) (362). Almost all the cases were 18–59 years old (95.4%); 1.7% were aged 60–69 years, and 0.9% were aged ≥ 70 years. In the reports with information on route of administration, it was oral in 93.3% of cases, tablet or capsule in 50.0%, powder or granules in 19.1%, liquid in 9.4% and aerosol or topical in 21.3%. Of the 2196 cases in which kratom was the only substance mentioned, 0.8% were considered as having major clinical effects (including death); 39.5% involved moderate effects, 26.6% minor effects and 13.5% minimal or no effects. The major clinical toxic effects were neuropsychiatric (agitation, confusion, sedation, hallucinations, tremor, seizure, coma) in 75.4%, cardiovascular (tachycardia, hypertension) in 44.5%, gastrointestinal (abdominal pain, nausea, vomiting) in 25.2% and respiratory (respiratory depression) in 12.1%. Among the 1174 cases involving only kratom that were reported in 2011–2017, the commonest individual clinical manifestations were agitation or irritability (22.9%), tachycardia (21.4%), nausea (14.6%), drowsiness or lethargy (14.3%), vomiting (13.2%), hypertension (10.1%), confusion (10.9%) and seizure (9.6%) (363). Life-threatening conditions were rare: coma (3.6%), cardiac arrest (0.4%), respiratory arrest (0.5%) and renal failure (0.5%).

A comparison of kratom-associated cases reported between 2010 and 2017 to the US National Poison Data System (760 cases) and the Ramathibodi Poison Centre in Thailand (168 cases) indicated a significantly higher proportion of cases with other substances present (64.8%) in Thailand than in the USA (37.4%) (odds ratio, 3.10; 95% CI, 2.15 ; 4.47); opioids and benzodiazepines were the commonest second substance in both countries (364). Common clinical manifestations in both countries were agitation and irritability, tachycardia and drowsiness or lethargy. Severe medical outcomes (admission to intensive care, death) were significantly more prevalent in the USA (odds ratio, 18.82; 95% CI = 5.85 ; 60.56).

The French Addictovigilance system received 20 reports of kratom-associated cases between 2007 and 2020, of which 14 were after 2016 (365). The major manifestations were dependence and withdrawal, anorexia and psychosis. One death (2018) and one case of severe hepatitis were recorded.

Chronic use of kratom has been associated with at least 92 cases of liver toxicity (366, 367). Common presenting signs and symptoms were abdominal discomfort, jaundice, pruritus and dark-coloured urine, which usually started

about 3 weeks after initiation of kratom use (range, 1–8 weeks) and resolved within 1 month of stopping kratom use. Liver transplantation was reported in one case, who also had a *Salmonella* infection (367). The histological appearance was hepatocellular, cholestatic or mixed.

Small cross-sectional studies of people who use kratom in South-East Asia found no significant association between long-term, frequent kratom use and clinically significant abnormalities in standard clinical blood tests, such as complete blood count, blood chemistry and lipid profiles (368–370) or blood concentrations of gonadal hormones (370). A 42-year-old man in the USA developed hypogonadotropic hypogonadism with elevated prolactin and decreased testosterone blood concentrations, fatigue and decreased libido while taking kratom (371). No other cause was identified in medical evaluation, and his symptoms resolved within 2 months of stopping kratom use.

Several case reports of cardiac arrhythmia or cardiac arrest associated with kratom use in South-East Asia have been published, but all probably involved use of other substances, and mitragynine concentrations were not measured (372). A cross-sectional study of 100 people who use kratom regularly (estimated average mitragynine intake, 7.06 mg/kg per day) in Malaysia found no significant differences in electrocardiographic parameters from those of 100 people who did not use kratom (373). The people who use kratom were significantly more likely to have sinus tachycardia (odds ratio, 8.61; 95% CI, 1.06 ; 70.17). A convenience sample of nine men aged 18–43 years in Malaysia who used long-term daily kratom (2–14 years, two to six glasses per day of “brewed kratom juice”) were examined with an electrocardiogram and a transthoracic echocardiogram, and peripheral blood was collected for mitragynine assay within 2–3 h of their latest kratom ingestion (374). Four respondents had a prolonged QTc interval, associated with a significantly higher serum mitragynine concentration (mean [standard deviation] 15.9 [6.4] mg/L) than the five respondents with normal QTc interval {5.9 [2.7] mg/L}. There were no other electrocardiographic abnormalities. The echocardiograms were normal, except that of one respondent who had left ventricular hypertrophy and that of one with “trivial” tricuspid regurgitation. All the respondents were daily cigarette smokers (≤ 20 /day); none used alcohol or other drugs. None had a personal or family history of cardiovascular disease.

A cross-sectional survey of 150 men in Malaysia (92% employed, 91% with at least secondary education) who used kratom (59% at least 6 years, 55% more than three times a day) indicated current positive psychotic symptoms in 4% (375). None of the men reported a history of psychiatric disorder, and none had used illicit psychoactive substances during the past year (two thirds had never used them).

7. Dependence potential

A. Animal studies

Repeated oral dosing of rats with mitragynine (15 mg/kg ip twice daily for 14 days) (338) or of mice with mitragynine (15 mg/kg ip daily for 5 days) (333) with kratom alkaloid extract (escalating doses of 30–125 mg/kg [equivalent to mitragynine 14.7–60.7 mg/kg] twice daily for 4 days) (333) or with lyophilized kratom tea (escalating doses of 30–125 mg/kg [equivalent to mitragynine 0.21–0.93 mg/kg] twice daily for 4 days) (334) elicited physical dependence, as evidenced by naloxone-precipitated withdrawal signs. The signs were, however, substantially less intense than those elicited by comparable dosing with morphine. Repeated oral dosing of rats with mitragynine (15 mg/kg ip twice daily for 14 days) did not lead to spontaneous withdrawal after dosing was stopped (338).

B. Human studies

A clinical trial was conducted in Malaysia in which the “clinical opioid withdrawal scale”, a standardized, validated rating instrument, was used to evaluate opioid withdrawal signs and symptoms in 26 young men who had used kratom several times daily for at least 3 years (319). The scores after overnight abstinence from kratom or within 24 h of a dose of kratom concoction (containing 1.6 mg/kg mitragynine) were all 0.5 or lower, indicating no opioid-like withdrawal after 10–20 h of abstinence. The assessment period may have been too brief for kratom withdrawal to develop, given that self-reported withdrawal may take up to 48 h (311) and the human elimination half-life of mitragynine was 23 h in one study (318).

In interviews with a convenience sample of people who reported long-term daily kratom use in South-East Asia, up to three fourths reported withdrawal symptoms after cessation of use (225, 376–379). The typical withdrawal symptoms included irritability, anxiety, depression, sleep disturbance, lachrymation, rhinorrhoea, muscle and bone pain, muscle spasm, diarrhoea and decreased appetite. The likelihood and severity of symptoms were associated with the duration, frequency and intensity of kratom use.

Cases of kratom withdrawal symptoms have been reported in the USA, but the overall prevalence is unknown (380). In an online cross-sectional survey of a convenience sample of 8049 people who use kratom in the USA, 43% reported uncomfortable symptoms within 48 h of stopping kratom use (311). The withdrawal symptoms reported were similar to those reported in South-East Asia (380). Withdrawal appears to be more common with long-term, heavy, daily use. Five cases of opioid-like neonatal abstinence syndrome (e.g., jitteriness, irritability, emesis, feeding intolerance) were reported in neonates born to mothers who reported heavy regular kratom use (up to 16–18 g thrice daily) but did not use opioids (381). All the neonates responded to standard treatment for

neonatal opioid abstinence syndrome, i.e., tapering doses of opioids. In some cases, the mother also experienced opioid-like withdrawal while in hospital.

In an anonymous cross-sectional online survey of a convenience sample of 2798 self-selected US adults who use kratom in 2017, 9.5% reported having experienced kratom withdrawal symptoms (310). Their mean score on the “subjective opiate withdrawal scale”, a standardized, validated rating instrument, was 8.8 (8.4), indicating mild withdrawal symptoms.

8. Abuse potential

A. Animal studies

Kratom extract or mitragynine showed rewarding properties in only one of three widely used rat models of abuse potential. Mitragynine (10–90 mg/kg ip) generated a conditioned place preference (349, 358, 382–385), which is considered a sign of rewarding action. This effect is blocked by the MOR antagonist naloxone, suggesting that it is mediated by activation of the MOR (384). A methanolic extract of kratom leaves (50–300 mg/kg ip) did not, however, generate conditioned place preference (386), nor did lyophilized kratom tea (100 mg [equivalent to 0.74 mg mitragynine]/kg, 1 g [7.4 mg mitragynine]/kg orally) in mice (334). In contrast, rats did not self-administer mitragynine (25–150 µg or 0.1–3.0 mg iv) (328, 387), and it did not lower the reward threshold or affect the response latency for intracranial self-stimulation at 1–30 mg/kg ip or intragastrically (388).⁴ Mitragynine increased the reward threshold at the highest dose studied (56 mg/kg ip), suggesting an aversive action (388).

7-Hydroxymitragynine (5 or 10 mg/kg iv) was self-administered by rats (387). The effect was blocked by the selective MOR antagonist naloxonazine and the selective δ -opioid antagonist naltrindole, suggesting dual μ - and δ -opioid receptor mechanisms. 7-Hydroxymitragynine had inconsistent effects on the intracranial self-stimulation reward threshold in two studies. In one study, lower doses (0.1–1.0 mg/kg ip) had no effect, while a higher dose (3.2 mg/kg ip) increased the threshold (with no change in response latency), suggesting an aversive action of high-dose 7-hydroxymitragynine (388). In an unpublished study,⁵ 7-hydroxymitragynine (0.3–3 mg/kg ip) lowered the intracranial self-stimulation threshold. No studies were available of 7-hydroxymitragynine and conditioned place preference.

Rats can be trained to distinguish mitragynine (15 mg/kg ip) or 7-hydroxymitragynine injections from saline injections, suggesting that these two alkaloids produce distinctive internal sensations (327, 389). Rats do not readily distinguish these two alkaloids from morphine, suggesting that the internal sensations are morphine-like. Rats also do not distinguish mitragynine (10 mg/

⁴ Dr Patrick Beardsley, personal communication

kg ip) from methamphetamine (1 mg/kg ip) (349). 7-Hydroxymitragynine is perceived as more morphine-like than mitragynine (327).

A kratom methanolic extract (100 mg/kg orally, 4.4% mitragynine by weight) did not acutely increase the dopamine concentration in the mouse brain nucleus accumbens, in contrast to a reinforcing dose of alcohol (348). Increasing nucleus accumbens dopamine concentration is an acute effect of almost all substances of abuse, including opioids (390).

B. Human studies

In an anonymous online survey in 2018–2019 of a self-selected convenience sample of 59 714 adults weighted to be demographically representative of the entire population of the USA, 490 respondents had used kratom at least once in the previous 12 months (391). About 20% of the people who use kratom were considered at severe or substantial risk of a kratom use disorder according to their responses to a standardized “drug abuse screening test”.

In an anonymous cross-sectional, online survey of a convenience sample of 2798 self-selected adults who use kratom in the USA in 2017, the respondents rated their typical subjective drug experience on a 100-mm visual analogue scale (310). The mean (SD) rating for “drug liking” was 85.7 (23.7), and that for “good effects” was 86.4 (23.0), while the ratings were only 12.0 (20.1) for “high” and 25.1 (27.1) for “euphoric.”

In cross-sectional surveys of convenience samples of people who use kratom regularly in South-East Asia, many respondents reported difficulty in reducing or stopping kratom use (236, 392). The surveys rarely found psychosocial impairment associated with kratom use (309, 393).

A review of 161 unstructured reports of use of kratom posted on a website for people who use psychoactive substances between 2001 and 2012 showed that 30.4% had experienced euphoria and 23.6% relaxation (394). In cross-sectional surveys of motivation for kratom use, the majority of respondents (self-selected convenience samples) in South-East Asia and the USA reported use to self-medicate a physical or psychological condition, cope with a problem or enhance energy (311, 313, 395, 396). Very few respondents reported use for “recreational” purposes; most of the questionnaires did not provide a response option for recreational use. Some respondents in South-East Asia reported using kratom to enhance sociability (392).

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

Kratom and its alkaloids have not been licensed for therapeutic use. Several therapeutic applications have been proposed on the basis of preclinical data (section 4.C.a) and anecdotal reports by people who use kratom (310, 311, 313, 395, 396). The uses include treatment of pain, opioid and alcohol use disorders, opioid and alcohol withdrawal and depression and anxiety.

10. Listing on the WHO Model List of Essential Medicines

Kratom, mitragynine and 7-hydroxymitragynine are not on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicinal product)

None.

12. Industrial use

None.

13. Non-medical use, abuse and dependence

The prevalence of kratom use and misuse are unknown, as kratom was included only recently in large, population-based epidemiological surveys. A cross-sectional survey of a nationally representative probability sample of 56 136 community-dwelling residents aged ≥ 12 years (the National Survey on Drug Use and Health) in the USA in 2019 was estimated kratom (powder, pill, leaf) was used by 0.7% (95% CI 0.6 ; 0.8%) of the population in the previous year (397). Kratom use was significantly more prevalent among people aged 18–49 years, women and non-Hispanic Whites than in other groups. Use of cannabis (adjusted odds ratio, 4.57; 95% CI, 3.29 ; 6.35) and cocaine (1.69; 1.06 ; 2.69) and non-medical use of prescription stimulants (2.10; 1.44 ; 3.05) were all significantly associated with kratom use, while opioid use was not. Prescription opioid use disorder was significantly associated with kratom use (3.20; 1.38 ; 7.41).

An anonymous online survey of a self-selected convenience sample of 59 714 adults weighted to be demographically representative of the entire US population in 2018–2019 estimated a prevalence of kratom use in the previous year of 0.8% (95% CI, 0.7 ; 0.9; an estimated 2.0 million adults) and of lifetime use of 1.3% (95% CI, 1.2 ; 1.4; an estimated 3.35 million adults) (391). People who use kratom were more likely than people who did not use it to be younger than 45 years and male.

An anonymous cross-sectional, online survey of a convenience sample of 2798 self-selected US adult people who use kratom in 2017 found that 9.9% met the criteria for mild, 1.8% for moderate and 0.6% for severe substance use disorder (310).

In a cross-sectional survey of a stratified random sample of 30 411 residents (15–64 years old) weighted to be representative of the national population of Thailand in 2016, 14.3% (95% CI, 13.7 ; 14.9) reported lifetime use of kratom leaves and 14.2% (13.6 ; 14.8) use of kratom cocktail; 2.1% (1.9 ; 2.3) reported use of kratom leaves and 0.7% (0.6 ; 0.8) use of kratom cocktail in the previous year; and 1.4% (1.3 ; 1.5) reported use of kratom leaves and 0.4% (0.3 ; 0.5) of kratom cocktail in the previous month (398).

Few data were available on the prevalence of treatment for kratom use disorder, partly because kratom has only recently been included on most standard questionnaires. In 2018, 16 admissions for treatment of kratom use disorder out of 26 449 total admissions for substance use disorders (excluding alcohol and tobacco) were reported in Malaysia (399).

In an anonymous online survey of more than 110 000 self-selected people who use psychoactive substances in more than 25 countries conducted in November–December 2019, 3.5% of respondents reported having used kratom in the previous 12 months (400). Kratom ranked 21st in prevalence among the psychoactive substances mentioned.

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

More than 300 deaths associated with kratom had been reported in the peer-reviewed medical literature through 2019 (401–404). Most were in western Europe and the USA and had occurred since 2015. Between January 2017 and December 2020, 127 kratom-associated deaths were reported to the UNODC Early Warning Advisory Tox-Portal, 63.8% from the USA, 30.7% from Thailand, 3.1% from Sweden, 1.6% from Australia and 0.8% from Finland (63). More than four fifths of the cases (84%) were men, almost one third (30.7%) were 16–24 years old, almost one half (48%) were 25–44 years old, one fifth (19.3%) were 45–64 years old, and 2% were over 64 years. The causal role of kratom was not indicated in 40% of cases; however, in the remaining cases, a causal relation was considered a “high” likelihood in 20%, a “medium” likelihood in 62.3% and present but not contributory in 17.6%. In the “high likelihood” cases, the mitragynine concentrations were 118–3390 ng/mL in peripheral blood, 320 ng/mL in femoral blood, 39–543 ng/mL in heart blood and 480 ng/mL in blood from a body cavity. A study of 35 deaths in the USA between 2015 and 2020 in which mitragynine was detected in blood post mortem showed no significant difference in mitragynine blood concentration between the 27 cases in which kratom was considered as having contributed to death (mean [SD] 269.4 [392.5] ng/mL; range, 8.7–1800 ng/mL) and the 8 cases for which there were other causes of death (315 [297.2] ng/mL, range 110–980 ng/mL (405). In two small studies of controlled administration of kratom extracts to men who were experienced with kratom use in South-East Asia, administration of 20–23 mg mitragynine as kratom tea or 1.6 mg/kg as kratom decoction, the maximum peripheral blood concentrations were 50–100 ng/mL (318) or 829–5034 ng/mL (319), respectively. The lack of an association between mitragynine blood concentration and lethality suggests that kratom consumption was not a causal factor in most of the kratom-associated deaths but was rather an incidental finding.

A review of 156 kratom-associated deaths identified in the published literature, Internet searches and mortality registries in the United Kingdom in 2019 showed that most were in White (100%), young adult (mean age, 32.3 years) men (80%) with a history of substance abuse (95%) (401). The 152 deaths due to overdose that were associated with kratom reported to the US State Unintentional Drug Overdose Reporting System in 27 states between July 2016 and December 2017 were primarily in White (91.5%) men (76.3%) with a history of substance misuse (80.9%) (404).

In a series of 11 fatalities due to drug overdose in Sweden that were associated with krypton (combination of kratom and the opioid analgesic O-desmethyltramadol), the mitragynine blood concentrations were 20–180 ng/mg, suggesting possible additive MOR action (254).

Attribution of causality in a kratom-associated death can be difficult for several reasons (406). First, identification of the two major active compounds, mitragynine and 7-hydroxymitragynine, can be difficult because of their instability over long periods at room or body temperature and because highly specific assays are necessary to distinguish them from their stereoisomers. Secondly, many cases are not comprehensively evaluated toxicologically, and some NPS remain undetected because accurate assays are not yet available. Thirdly, most cases involve multiple substances and not only a kratom alkaloid. A review of 156 published and otherwise identified cases showed that one or more other drugs were present in 95.6% of the cases for which toxicological evaluation was available (401), the most common being opioids, stimulants and sedatives. Mitragynine or 7-hydroxymitragynine was considered to have contributed to death in 23% of cases, including the six in which no other substances were identified. The mean (range) mitragynine blood concentration was 398 (3.5–890) ng/mL in cases with no other substances present and 890 (0.9–16,000) ng/mL when other substances were present. Among 152 cases reported to the US State Unintentional Drug Overdose Reporting System, other drugs were present in 92% of cases, including fentanyl and fentanyl analogues (65.1%), heroin (32.9%), benzodiazepines (22.4%), prescription opioids (19.7%), cocaine (18.4%), alcohol (12.5%) and methamphetamine (8.6%) (404).

None of 15 kratom-associated deaths in the USA between 1999 and 2017 was considered to be due clearly to kratom after a comprehensive forensic analysis, including toxicology (407). In a series of 20 kratom-associated deaths evaluated in the USA in 2017 and 2018, three were considered to be due to mitragynine (no other drugs were found); in 13 cases, mitragynine was considered to be contributory (other drugs were found); and in four cases mitragynine played no role (403). Mitragynine blood concentrations were 1590–3420 ng/mL in the first group and 24.6–1210 ng/ml in the second. In a series of 35 kratom-associated deaths evaluated in the USA in 2015–2020, eight were considered

definitely not to have been caused by substance toxicity (e.g., death attributed to gunshot wound, cardiac disease) (405). All of the 27 cases considered to be due to substance toxicity included substances other than mitragynine (opioids 81.5%, benzodiazepines 33.3%, ethanol 33.3%, amphetamines 25.9%, nitrous oxide 7.4%, aripiprazole 3.7%). In the case in which aripiprazole was the only other substance identified, phenibut was found at the scene but not tested for. In a convenience sample of 583 post-mortem blood samples sent by US medical examiners to a national forensic reference laboratory between October 2016 and December 2018, the mean (standard deviation) mitragynine concentration was 372 (574) ng/mL, median 140 ng/mL and range 5.9–4400 ng/mL (406). In Thailand, the peak blood concentrations of mitragynine were 18.5–105 ng/mL in 10 people who use kratom who took 6–10 mg mitragynine daily (318).

Kratom was associated with 90 DUID reports between January 2017 and December 2020, all in the USA (63). About four fifths (82%) involved men. A direct causal link with kratom could not be established in most cases. In the USA, mitragynine was identified in only six DUID cases between 2014 and 2017 (406). In 2018, mitragynine was identified in 20 cases (of about 17 500 submissions) at a mean (SD) blood concentration of 106 (117) ng/mL (median, 75 ng/mL; range, 11–490 ng/mL). Urine testing of 1635 consecutive motor vehicle drivers approached at 13 sites in Thailand between December 2005 and May 2006 identified 0.9% as people who use kratom (i.e., mitragynine detected) (408). The substances detected most frequently were alcohol (5.5%), antihistamines (2.0%), amphetamines (1.8%) and cannabis (1.1%).

The number of blood samples received for mitragynine testing by a prominent US national forensic reference laboratory (chiefly post-mortem and DUID cases) increased from fewer than 10 per month in October 2012–January 2016 to 11–40 per month up to July 2017 and to 41–80 per month up to December 2018 (406). The number of samples that tested positive for mitragynine increased from 2 in 2012 to 785 in 2018.

15. Licit production, consumption and international trade

Cultivation of *M. speciosa* is legal in South-East Asia. According to an unverified report (409), Indonesia has a large export trade of kratom leaves to western countries.

16. Illicit manufacture and traffic and related information

More than 99% of global seizures of kratom during the past decade have been in South-East Asia (410). The quantities seized have increased over the past 5 years, from about 57 tonnes in 2015 to 400 tonnes in 2016, 285 tonnes in 2017, 170 tonnes in 2018 and 398 tonnes in 2019.

17. Current international controls and their impact

Kratom, mitragynine and 7-hydroxymitragynine are not currently under international control under United Nations treaties. The Association of South-East Asian Nations banned kratom from inclusion in traditional medicine or health supplements in 2013 on the grounds that it is “harmful to human health” (411). Thailand made kratom a legal herb on 23 August 2021 (412).

18. Current and past national controls

Kratom, mitragynine and 7-hydroxymitragynine have been under national control for about 15 years. They are now banned or regulated as controlled psychoactive substances or herbal supplements in a number of countries. In the USA, kratom cannot be marketed as a dietary supplement and is considered a drug of concern by the DEA. It is banned in six US states and several cities. Canada has banned the marketing of kratom for human consumption (124).

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

None

3.2.2 Phenibut

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstracts Services Registry Number

1078-21-3 (racemate)

35568-36-6 (β R)- β -(Aminomethyl)benzenepropanoic acid

62596-63-8 (β S)- β -(Aminomethyl)benzenepropanoic acid

1256483-50-7 Benzenepropanoic acid, β -(aminomethyl)-, hydrate (1:1)

(ACI)

3060-41-1 Benzenepropanoic acid, β -(aminomethyl)-, hydrochloride (1:1)

52992-48-0 Benzenepropanoic acid, β -(aminomethyl)-, hydrochloride (1:1),

(β R)-

52950-37-5 Benzenepropanoic acid, β -(aminomethyl)-, hydrochloride (1:1),

(β S)-

103095-38-1 Benzenepropanoic acid, β -(aminomethyl)-, hydrobromide

(1:1)

2265218-18-4 Benzenepropanoic acid, β -(aminomethyl)-, lithium salt (1:1)

1201689-48-6 Benzenepropanoic acid, β -(aminomethyl)-, potassium salt

(1:1)

697285-57-7 Benzenepropanoic acid, β -(aminomethyl)-, ethanedioate (2:1)

1379536-43-2 Benzenepropanoic acid, β -(aminomethyl)-, (2Z)-2-butenedioate (2:1)

1379536-45-4 L-Glutamic acid, β -(aminomethyl)benzenepropanoate (1:2)

697285-58-8 Butanedioic acid, 2-hydroxy-, compd. with β -(aminomethyl)benzenepropanoate (1:2)

1379536-44-3 3-Pyridinecarboxylic acid, compd. with β -(aminomethyl)benzenepropanoate (1:1)

1393708-43-4 Benzoic acid, 2-hydroxy-, compd. with β -(aminomethyl)benzenepropanoate (1:1)

697285-55-5 Benzenepropanoic acid, β -(aminomethyl)-, 2-hydroxy-1,2,3-propanetricarboxylate (3:1)

131420-80-9 4-Pyrimidinecarboxylic acid, 1,2,3,6-tetrahydro-2,6-dioxo-, mono[β -(aminomethyl)benzenepropanoate]

C. Other chemical names

Hydrocinnamic acid, β -(aminomethyl) (6CI, 7CI, 8CI)

β -(Aminomethyl)benzenepropanoic acid (ACI)

(\pm)-Fenibut

(\pm)- β -Phenyl-GABA

3-Phenyl-4-aminobutanoic acid

4-Amino-3-phenylbutanoic acid

4-Amino-3-phenylbutyric acid

DL-4-Amino-3-phenylbutanoic acid

DL- β -Phenyl- γ -aminobutyric acid

Anvifen

Fenibut

Fenigam

Fenigama

P-GABA

Phenibut

Phenigam

Phenybut

Phenygam

PhGABA

β -Phenyl-GABA

β -Phenyl- γ -aminobutyric acid

γ -Amino- β -phenylbutyric acid

D. Trade Names

Anvifen

Fenibut

Bifren

Noofen

Phenyl-GABA

From the Register of Medicines of Russia® RLS® (RLS®, 2017):

Phenibut-Akrikhin

Phenibut-Vertex

Phenibut-LekT

Phenibuta tablets

Phenorabin®

Phenibut is marketed (brand names as the racemic HCl salt: Anvifen, Fenibut, Bifren and Noofen; as the citrate: Citrocard) in the Russian Federation and several other eastern European countries (413).

Phenibut is available as a medication in the form of tablets, capsules or powder for oral administration [“Фенибут (Phenybutum)” Fenibut (Phenybutum)]; it has also been reported as a solution for infusion at a concentration of 10 mg/mL (413).

Phenibut is available as a supplement from many online stores and e-commerce sites.

E. Street names

Fenibut

Pbut

Noofen

Phenigam

PhGABA

Pgaba

Phenigamma

Phenygam

Party Powder

Smart Pill

Brain Booster

Russian Wonder Drug

Soviet Smart Drug

F. Physical appearance

Phenibut formulations include tablets, powder and fine crystals (phenibut HCL) (white).

Free base: white solid (414); orange solid, melting-point, 188–190 °C (415).

Phenibut HCl: crystalline solid (416).

G. WHO review history

Phenibut has not been formally reviewed by WHO and is not currently under international control. Phenibut has been under ECDD surveillance since reports from Member States of its abuse and dependence potential. A pre-review was initiated after a proposal was received with supporting information from members of the Expert Committee regarding published reports on dependence, abuse and toxicity.

2. Chemistry

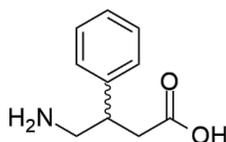
A. Chemical name

IUPAC name: 4-Amino-3-phenylbutanoic acid

Chemical Abstracts Index Name: Benzenepropanoic acid, β -(aminomethyl) (9CI, ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{10}H_{13}NO_2$

Molecular weight: 179.22 g/mol

C. Stereoisomers

The presence of a chiral centre at the β -carbon gives rise to the enantiomeric pair of (3*S*)-4-amino-3-phenylbutanoic acid ((*S*)-phenibut) and (3*R*)-4-amino-3-phenylbutanoic acid ((*R*)-phenibut). Although phenibut is used clinically as the racemic compound, both isomers are biologically active, as shown in pharmacological studies of the GABA B receptor and at the $\alpha 2$ - δ subunit of voltage-dependent calcium channels (417, 418).

D. Methods and ease of illicit Manufacturing

Phenibut was synthesized by Perekalin and associates at the Department of Organic Chemistry of the Herzen Pedagogic Institute in Saint Petersburg, Russian Federation, in 1954 (419). In the initial publications, phenibut was called “phenigamma” (419, 420).

All the reported synthetic procedures require use of chemical reagents that are readily purchased; however, they require a well-equipped chemical laboratory and specialized personnel. The procedure used by Perekalin et al. involved condensation of (2-nitrovinyl)benzene with diethylmalonate to give diethyl 2-(2-nitro-1-phenylethyl)malonate, which was subjected to hydrogenation in the presence of Raney nickel, giving ethyl 2-oxo-4-phenylpyrrolidine-3-carboxylate. This was refluxed with hydrochloric acid to give phenibut. Since the first patent by Perekalin et al., numerous synthetic pathways of phenibut have been published and patented (421–426). A five-step flow-reaction method has been published, with a yield of 65% (414). This type of synthesis requires particular equipment and produces phenibut not in a single batch but as a continuous flow. The equipment is difficult to acquire and requires specialized personnel.

Before 1990, two methods were reported in which phenibut was resolved by fractional crystallization of the cinchonidine salts and α -methylbenzylamine salts of the *N*-carbobenzyloxy-protected racemate (427). This is a simple method for obtaining the single enantiomers of phenibut, as it does not require specialized equipment or personnel. Another synthetic strategy is use of an enzyme (α -chymotrypsin) in a solution buffered at pH 7.4 to obtain the pure enantiomer (*R*)-phenibut (428). Other strategies have been proposed to simplify the procedure by reducing the number of steps, but they all required a well-equipped synthetic chemistry laboratory (429–432).

Several methods for resolution of racemic 3-aryl-4-aminobutyric acids into *R*- and *S*-enantiomers are available. Most are chromatographic separations with or without preventive protection (417, 433–436). Some methods gave reported separation by preferential crystallization of diastereoisomeric salts with an optically active base, cinchonidine or L-(–)- α -methylbenzylamine, as the resolution agent (437, 438). These methods involve the use of specific, specialized equipment in a preparative chiral chromatography laboratory.

E. Chemical properties

Melting-point:

Racemate: 209 °C (419); 206 °C (439)

(*S*)-phenibut: 194–196 °C (417); 190–191 °C (428); 193 °C (435)

(*R*)-phenibut: 190–191 °C (428); 193–194 °C (417); 193 °C (435)

Boiling-point:

No information was available.

Solubility:

Free base: 35 mg/mL in DMSO (195.29 mM) at 25 °C (440)

Hydrochloride salt (416): 25 mg/ml in DMF; 20 mg/ml in DMSO; 14 mg/ml in ethanol; 10 mg/mL in phosphate-buffered saline (pH 7.2).

F. Identification and analysis

Phenibut can be analysed by means of an ion-selective membrane containing poly(vinyl chloride), plasticizer (dioctyl phthalate (60.0–75.0)) and an electrode-active substance (trioctoxybenzolsulfonate γ -amino acid β -phenylbutyric acid (0.05–5.00)) (441). Veveris (442) determined the phenibut concentration in alkaline DMSO solution by differential potentiometric titration with a platinum or glassy-calomel electrode. Phenibut was also analysed in a mixture with orotic acid in a spectrophotometric method combining UV spectrophotometry and a colour reaction of the amino group with 2,4,6-trinitrobenzenesulfonic acid (443).

Other methods reported in the literature are based on chromatographic techniques. Grinberga et al. (444) developed an HPLC-MS/MS method for quantification of phenibut in biological matrices. HPLC-MS/MS was also used to determine phenibut in urine after either acidic hydrolysis or dilution of the sample (445). The limit of quantification was 0.2 ng/mL, and the linear range

was 0.5–50 ng/mL. This highly sensitive analytical system allows determination of narcotic preparations within a certain time after their intake, which may be of particular importance for forensic examinations.

HPLC-HRMS was used to analyse phenibut in urine samples from portable stand-alone urinals in a city centre monthly for over 5 years (446) to determine long-term trends in the use of new psychoactive substances.

Smirnova et al. (447) developed an HPLC method coupled to a UV detector (205 nm).

GC-MS cannot correctly identify or quantify a drug of interest because of undesirable phenomena of thermal degradation, cyclization and/or side-reactions. Lee et al. (448) overcame these issues by either derivatization of phenibut or decreasing the temperature in the injector port to 200 °C and maintaining the GC oven temperature below 190 °C.

Tyurenkov et al. (449) used ion-pair chromatography with a RP-C18 column and UV detection (210 nm) for quantitative analysis of phenibut in rat plasma. The linear range was 1–200 µg/mL. Synthetic phenibut and its enantiomers have also been characterized by ¹H NMR, ¹³C NMR, IR, UV, optical rotatory power and circular dichroism (414, 415, 417, 428, 432).

Chromatographic methods have been used for chiral resolution of the (*R*)- and (*S*)- enantiomers of phenibut. Vaccher et al. (450) reported that cyclodextrin capillary electrokinetic chromatography achieved complete resolution with 25 mM phosphate buffer at pH 2.5 containing 3 (w/v) of highly sulfated cyclodextrins at 25 °C in an applied field of 0.30 kV/cm and capillaries dynamically coated with polyethylene oxide.

Sobocinska et al. (437) used fractional crystallization of the cinchonidine salt of the *N*-carbobenzyloxy derivative of phenibut, followed by removal of the protecting group by hydrogenolysis on a palladium catalyst. Highly stable zirconium-based metal-organic frameworks proved to be efficient chiral stationary phases for reversed-phase HPLC (451).

3. Ease of convertibility into controlled substances

No information was available.

4. General pharmacology

A. Routes of administration and dosage

Phenibut (40–98% purity) (452, 453) is available as a powder, crystals or capsules in doses of 200–500 mg from online websites (454). According to a report from the US Centers for Disease Control and Prevention, phenibut is predominantly (93.2%) ingested but is sometimes inhaled (2.8%), and other routes have also been documented (e.g., dermal, 4%) (455). The recommended therapeutic dose is 250–750 mg per day (456). Consumption for recreational use ranges from 1000

to 2000 mg/day, but it is sometimes recommended that it be used on only 2 or 3 days a week (interspersed with drug-free days), as tolerance to the drug occurs rapidly, and that no more than 1000 g be consumed over a 24-h period (456). Women are sometimes advised to take smaller doses. Nonetheless, reports show that much higher amounts are consumed, up to 8 and even 16 g/day (457, 458). In 40.2% of cases of adult exposure reported to the American Association of Poison Control Centers, phenibut was ingested with one or more other substances (455).

B. Pharmacokinetics

Information on the pharmacokinetics of phenibut is limited. Lapin (420), in a review, concluded that phenibut is not metabolized after iv administration to rabbits or rats and is excreted largely unmetabolized in the urine by glomerular filtration in rats, rabbits, cats and dogs. Phenibut was found in the liver, kidneys, brain, blood and urine after iv administration and dissipated to trace levels by 3 h after injection. In humans, 65% of a 250-mg oral dose was not metabolized and was excreted in the urine, its clearance mimicking that of creatinine. The plasma half-life was 5.3 h. None of these statements was referenced in the review, precluding examination of the primary studies. All other discussions of these effects cite the review by Lapin (420). Grinberga et al. (444) reported that phenibut was found in rat brain tissue 1 h after ip administration of 100 mg/kg per day for 3 days.

People who report recreational use report the onset of effects within 2–4 h of oral administration, with peak “high” effects approximately 6 h after ingestion. The effects last from 15 to 24 h (459).

C. Pharmacodynamics

Phenibut is structurally and functionally similar to the GABA derivatives gabapentin and baclofen. Phenibut is a GABA agonist, which crosses the blood–brain barrier more readily than GABA itself due to the presence of a phenyl group on the β carbon (460). The affinity of phenibut for the GABA B receptor is approximately 15 times less than that of the GABA B agonist, baclofen (461).

Baclofen is used to treat anxiety, alcohol dependence and muscle spasticity (462), while gabapentin is used as an anti-epileptic and also to treat neuropathic pain (463). Like its structural analogue baclofen, phenibut appears to act as a GABA B receptor agonist (464), and thus some of its actions are thought to reflect its interactions at the GABA B metabotropic G protein-coupled receptor, the primary means of inhibitory neurotransmission within the brain. Like GABA and its analogues, phenibut reversibly reduced the firing rate of isolated cat neurons (465).

In a comprehensive set of experiments conducted in rodents, Dambrova et al. (461) examined the comparative pharmacological activity of optical isomers of phenibut. Administration of racemic phenibut and its R enantiomer caused dose-dependent decreases in open field activity, increased analgesia in the

antinociception test and decreased immobility during the forced swim test. Pretreatment with a GABA B antagonist blocked these effects. The Δ enantiomer had little or no effect. The results are congruent with the antidepressant and anxiolytic properties of phenibut. GABA B agonists such as baclofen are used to treat spasticity; however, much higher doses (30 times) of phenibut were necessary to affect muscle function than to affect open field behaviour. Given the minimal effect of phenibut on muscle function, the authors hypothesized that a potential clinical use for phenibut might be in treating disorders in which muscle relaxation is not required.

Radioligand binding studies conducted within the same set of experiments showed that baclofen, racemic phenibut and R phenibut have affinity for GABA B receptors, with K_i constants of 6 ± 1 , 177 ± 2 and 92 ± 3 μM , respectively, while the S enantiomer did not bind to GABA B receptors (461). On GABA B receptors, phenibut activated an outward-rectifying potassium current, suppressing the generation of action potentials (466), thus highlighting its depressant properties.

Although phenibut binds directly to the GABA B receptor (461), it also has strong affinity for the $\alpha 2$ - δ subunit of voltage-dependent calcium channels (418), which is the mechanism associated with the anti-nociceptive properties of gabapentin. The binding affinity of R-phenibut for the $\alpha 2$ - δ subunit of the voltage-dependent calcium channels is four times higher than its affinity for the GABA B receptor. Calculated K_i values of 23 ± 6 μM , 39 ± 5 μM and 156 ± 40 μM were observed for R- and S-phenibut and baclofen, respectively. Further, in rodent models of the anti-nociceptive effects of R-phenibut, antagonism of the $\alpha 2$ - δ subunit of the voltage-dependent calcium channels blocked the anti-nociceptive effects of phenibut, while GABA B antagonism did not (418). Thus, the anti-nociceptive effects were not mediated by the activity of phenibut at the GABA B receptor but by its effects at the $\alpha 2$ - δ subunit of the voltage-dependent calcium channels. Thus, in line with its structural similarity to gabapentin, phenibut also behaves in a functionally similar manner and may be a suitable candidate for treating neuropathic pain.

Lapin (420) discussed the actions of phenibut at the GABA A receptor, which is a major mechanism of action of benzodiazepines; however, no studies have shown that phenibut is active at the GABA A receptor.

5. Toxicology

Although Kupats et al. (467) and others noted that phenibut has a therapeutic index of 90, the data used to calculate the index are not available. Kupats et al. cited the review by Lapin (420), who stated that the LD₅₀ was 900 mg/kg after ip administration to mice, but the original study was not cited. The ED₅₀ was 10 mg/kg (461).

Phenibut is not detected in routine urine toxicology screens (458, 468, 469). It can be detected by LC–MS (452), but this technique is not readily available in emergency rooms, and emergency personnel usually rely on any history or reports provided at the time of admittance to determine the quantity and timing of phenibut consumption (469–472). Further, medical personnel know little about the withdrawal syndrome associated with abstinence or the symptoms of overdose of phenibut, making it difficult to determine whether an individual requires treatment for withdrawal or overdose (472).

Phenibut intoxication can include depressive symptoms (i.e., decreased level of consciousness and muscle tone, stupor, depressed respiration), temperature dysregulation, hyper- or hypotension and tachycardia. In other cases, individuals have presented with psychomotor agitation, hallucinations, seizures and delirium (472, 473). Severe behavioural agitation may require heavy sedation, with airway protection by endotracheal intubation (452, 453, 458, 468). In a study on the clinical effects of phenibut exposure at a poison control centre, a 19.6% intubation rate was observed in a total of 56 calls (473). The doses that lead to toxicity differ widely, with doses of 3 g/day for 4 days and an acute 30-g dose both implicated in phenibut intoxication (453, 470). Generally, phenibut intoxication resolves within 24 h (459).

Two cases of analytically confirmed phenibut toxicity were described by Downes et al. (452). A 20-year-old woman presented to an emergency department showing decreased consciousness and delirium when roused. Evidence of phenibut use was provided on admittance. Supportive care was provided, without an intervention, and the patient recovered within 24 h. She reported online purchase and use of 25 g of phenibut in three doses on the day before admittance. The plasma phenibut concentration was 29.7 mg/mL. In the second case, a 38-year-old man presented to an emergency department with agitated delirium. Information provided upon admittance was that he had ingested phenibut, alcohol and tetrahydrocannabinol. To reduce his extreme behavioural agitation, he was heavily sedated with multiple medications over the next 24 h and required intubation. The next day he confirmed recreational use of phenibut while consuming alcohol. The plasma phenibut concentration was 36.5 mg/mL on admission and 8.92 mg/mL 17 h afterwards. In neither case was other toxicological testing performed.

A case of presumed toxicity was described in a young alcohol-dependent man with depression (470). The patient was found unconscious and taken to an emergency department. Examination revealed depressed consciousness, while vital signs and routine laboratory testing were within normal limits, as were an electrocardiogram, computerized tomography scan and chest radiographs. The patient reported having consumed 3 g/day of phenibut for 4 days. The phenibut was purchased on the Internet (unknown purity), and use was not biologically

confirmed. The patient denied other drug use and was negative for alcohol. He was taking therapeutic doses of venlafaxine and mirtazapine, and the authors suggested possible interaction or potentiation between phenibut and the neuroleptics.

In an abstract presented at a meeting, four cases of presumed phenibut toxicity reported to a poison centre were described, with few details (474). One of the cases was complicated by withdrawal. All the patients recovered within 24 h.

Sankary et al. (469) described a case of a 25-year-old man who presented with a decreased level of consciousness. A friend indicated that the patient had used phenibut pills purchased on the Internet. The patient was treated with iv fluids to enhance excretion and left the hospital against medical advice.

Li and Madhira (468) described a case in which the toxic effects of phenibut and the effects of abstinence were difficult to differentiate. A 24-year-old man with a history of anxiety and attention deficit hyperactivity disorder presented with severe agitation and psychosis. He routinely consumed multiple supplements and anabolic steroids, was taking dextroamphetamine to treat his disorder and had consumed up to 20 250-mg tablets of phenibut daily for the previous 2 months. Urine analysis gave negative results, except for amphetamine. Because of the patient's extreme agitation, the authors speculated that he was suffering from withdrawal, although he had not reduced his intake of phenibut, rather than toxicity, which generally manifests as respiratory depression and lethargy (469, 470).

Li and Sundararajan (475) described the case of a 44-year-old man who regularly took 500–1500 mg of phenibut per day but had increased his dose because of the development of tolerance. He obtained phenibut from the Internet. The patient had a significant history of hospital visits due to overdosing phenibut. He presented to the emergency department in an agitated state with a fluctuating level of consciousness. Despite pharmacotherapy with benzodiazepines, he became increasingly agitated and was intubated and sedated. He experienced a hypertensive crisis and developed pneumonia. By day 3, he was weaned off sedatives but still had some anxiety and headaches.

Isoardi et al. (476) described a case cluster of phenibut poisoning in five adolescent boys. At school, the boys had ingested several capfuls of phenibut powder, accessed on the Internet. All the boys showed severe agitation, and four had fluctuating episodes of sedation, three progressing to coma. All had to be intubated to protect the airways and manage the agitated behavior. Four boys were extubated uneventfully within 24 h, while one continued to have symptoms and was finally extubated after 4 days. Phenibut use was confirmed by LC-QTOF-MS.

6. Adverse reactions in humans

The WHO VigiAccess (477) has been monitoring phenibut use since 2012. Twenty-one adverse drug reactions were reported in 2019 and 14 in 2020; three

had been reported in 2021 as of 26 July. Since its listing in VigiAccess in 2012, most adverse reactions to phenibut have occurred in males (83%) aged 18–44 years (also 83%) in the Americas (55%) and Europe (28%) in countries in which phenibut is not approved for clinical use. The reported adverse reactions (in order of highest to lowest) were: nervous system disorders (17); psychiatric disorders (13); general disorders and administration site conditions (13); injury, poisoning and procedural complications (9); cardiac disorders (5); investigations following abnormal physiological measures (5); vascular disorders (5); musculoskeletal and connective tissue disorders (4); respiratory, thoracic and mediastinal disorders (3); skin and subcutaneous tissue disorders (3); eye disorders (2); gastrointestinal disorders (2); infections and infestations (2); metabolism and nutrition disorders (2); renal and urinary disorders (2); and social circumstances (1).

In the USA, where phenibut is not approved as a pharmaceutical drug but may be possessed legally, the Centers for Disease Control and Prevention conducted an analysis of phenibut exposures reported to poison centres between 2009 and 2019 (455). Exposures were extracted from the national database maintained by the American Association of Poison Control Centers, which were captured from calls made to poison centres with the search terms “phenigam” (2009–2019), “4-amino-3-phenylbutyric acid” from 2012 and “phenibut” from 2015. During the 10-year period, 1320 exposures to phenibut were reported, the numbers increasing over the years as search terms were added. The exposures were not biochemically confirmed. Most occurred in young men. The adverse effects included drowsiness or lethargy (29.0%), agitation (30.4%), tachycardia (21.9%) and confusion (21.3%). Coma was reported in 6.2% cases, including one in an adolescent. Exposure resulted in moderate effects (i.e., no long-term impairment) in 49.6% of cases and major effects (i.e., life-threatening or resulting in significant disability) in 12.6% of cases. Three deaths were reported. Exposure to other drugs or agents was recorded by 29.6% of individuals < 18 years and in 40.2% of all adult cases. When phenibut was used in isolation, 10.2% of cases were associated with major effects, including one death.

One death was reported to the UNODC (478) in a male child (age 2–14) in the Russian Federation. The child had ingested a combination of phenibut, the cannabinoid agonist JWH-081 and potentially other substances.

No randomized controlled trials of phenibut have been reported for any indication. In a review of open-label trials, few adverse events were reported. Kupats et al. (467) summarized the results of 11 clinical trials with phenibut (583 patients) and reported that 5.66% of the patients reported adverse events, the most common being somnolence (1.89%). Kupats et al. (467) also reviewed 14 case reports in which phenibut was purchased on the Internet and used without medical supervision at higher doses than medically indicated. The adverse effects included cardiovascular effects, insomnia, severe anxiety and agitation,

hallucinations, depressed level of consciousness, decreased muscle tone, respiratory effects, temperature dysregulation, seizures and delirium. The case studies summarized by Kupats et al. (467) are described in this report.

7. Dependence potential

A. Animal studies in animals

No information was available.

B. Human studies

The available studies suggest that phenibut use can lead to escalating dosage (tolerance), taking more of the drug than intended and being unable to stop using it, all of which are signs of dependence. Many of the Internet sites that promote and/or sell phenibut warn their clientele of this possibility (454, 479). Tolerance to the drug has been reported in as little as 1–2 weeks, which contributes to its potential addiction liability (459). Van Hout (480) reported that tolerance may be observed in as little as 5 days, but the source was not stated.

A cardinal feature of physical dependence is an abstinence syndrome with abrupt cessation. Abrupt discontinuation of phenibut induces a withdrawal syndrome which may be severe and require hospitalization. This is probably due at least partly to downregulation of GABA B receptors during chronic use. Phenibut withdrawal symptoms include insomnia, psychomotor agitation, delusions, psychosis, disorganized thought patterns, auditory and visual hallucinations, overwhelming anxiety, depression, fatigue, dizziness, seizures, decreased appetite, nausea and vomiting, palpitations and tachycardia (472, 481).

Hardman et al. (472) conducted a literature search to identify the presence and severity of a phenibut abstinence syndrome. Ten cases of phenibut withdrawal and a new case study presented by the authors are described. In 7 of the 11 cases, other substances were also ingested. Several of the cases are derived from conference proceedings or abstracts, with limited information (482–486). The published case studies are described briefly below.

Magsalin and Khan (487) reported a case of a healthy male who experienced withdrawal from phenibut that was similar to withdrawal from benzodiazepine. The patient took 1 g of powdered phenibut in a glass of water for 10 days to self-treat restless legs syndrome. Phenibut was accessed from the Internet and was of unknown purity. The patient experienced relief of symptoms, but, when he abruptly stopped taking phenibut, he experienced nervousness, psychomotor agitation, irritability, tension, fatigue, loss of appetite, heart palpitations, nausea and insomnia within hours. To determine whether his symptoms were related to withdrawal, he took 0.5 g of phenibut. As he experienced relief from symptoms, he continued to wean himself off phenibut for 4 days. Use of phenibut was not verified biochemically.

Samokhvalov et al. (457) described a case of phenibut withdrawal in a patient who had used 8 g/day to self-medicate for anxiety, dysphoria, insomnia and alcohol craving. Concomitant medications included 18 g/day of kratom. The report states that use of both substances was verified biochemically in a laboratory, but the method was not described. The patient was unable to stop taking phenibut on his own because he experienced severe anxiety, anger and irritability, and he sought medical assistance. Kratom use was discontinued without intervention, the patient experiencing only mild withdrawal symptoms. Over 9 weeks, baclofen was titrated upwards while tapering down phenibut to manage alcohol craving, anxiety and irritability. Over the next 15 weeks, the baclofen dose was reduced, and citalopram was added to mitigate symptoms.

Joshi et al. (458) described a case of phenibut intoxication and prolonged withdrawal with agitated delirium. A 32-year-old man in a dissociative state was brought to an emergency department after a suicide attempt. The patient reported not having slept for four nights and use of 8–10 g/day of phenibut, escalating to approximately 16 g/day in the week before hospitalization. He also used self-injected anabolic steroids. Blood alcohol and urine toxicology reports were negative. The patient was treated with a series of benzodiazepines and iv fluids, and his symptoms remitted. On the second day, the patient required intramuscular antipsychotics to treat growing agitation, insomnia and disorganized thought patterns. Additional benzodiazepines were administered, but the symptoms worsened. The patient was then taken off of benzodiazepines, and baclofen was administered. To improve sleep, 8 mg ramelteon were also administered. By day 9, the patient was in complete remission.

Ahuja et al. (471) described a case in which baclofen was used successfully to treat phenibut withdrawal. A 21-year-old man with a history of alcohol binge and anxiety presented to an emergency department after 3 days of increasing anxiety, insomnia and a 1-week binge-drinking episode. The patient denied ever having experienced alcohol withdrawal. He had been taking phenibut purchased on the Internet for several months at the recommended dose (1 scoop, equal to 100–300 mg). During the alcohol binge, the patient had added phenibut to his alcoholic drinks in escalating but unknown doses. Upon admission, he was treated for alcohol withdrawal but continued to report visual hallucinations and overwhelming anxiety. Phenibut withdrawal was suspected. The patient was treated with baclofen, and the symptoms remitted.

Hardman et al. (472) described the case of a 23-year-old man with an extensive history of polysubstance abuse and anxiety and depression managed with the selective serotonin reuptake inhibitor, sertraline. The patient presented to an emergency department with hallucinations and psychomotor agitation. He reported that he had been using 4 g of phenibut every 6 h but had stopped using it 2 days previously. Phenibut use was not verified biochemically. The patient

denied other current drug use, which was verified by urine toxicology. Multiple pharmacological treatments were unsuccessful in reducing his worsening symptoms (i.e., lorazepam, haloperidol, diphenhydramine, melatonin and olanzapine). The patient developed tachycardia, increased muscular tone and inducible clonus; he became severely agitated and was physically restrained. Additional drugs were administered (i.e., dexmedetomidine infusion, lorazepam, baclofen and gabapentin) and the symptoms finally abated over the next 3 days.

8. Abuse potential

A. Animal studies

No information was available.

B. Human studies

No information was available.

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

In the Russian Federation, where phenibut has been approved as a medicine since the 1960s, it is purportedly widely used to treat many neuropsychiatric disorders including insomnia, anxiety, depression, stress and post-traumatic stress disorder. It has also been used to treat general weakness, stuttering and vestibular disorders. It is also reported (unsubstantiated) to be used similarly in Belarus, Estonia, Kazakhstan, Latvia and Ukraine (456, 467). Use in Latvia is mentioned in New Zealand's Medical Device Safety report (488).

Lapin (420) reported a placebo-controlled double-blind study conducted in psychotic patients and healthy controls. Phenibut was administered orally at 250–500 mg three times a day for 1–2 weeks. Lapin stated that phenibut improved intellectual function, enhanced physical strength, had behavioural motivating properties and reduced weakness and tiredness. The reference for these statements is a study described earlier in the review as a preclinical study (489). Lapin (420) also provided a table of clinical indications for phenibut, which lists positive effects on conflict, seizures, cognitive and emotional processes, learning, nystagmus, withdrawal (e.g., alcohol and morphine), neuroprotection (e.g., in trauma, oedema, stress) and hypoxia. Slight or inconsistent effects were found on central muscle relaxation and memory improvement. Only three references are provided for the indications, and unavailable. Other articles refer to the reviews by Lapin (420) and Kupats (467) when providing background information on phenibut. Neither review provides available, verifiable information on clinical indications.

Although most studies mention the nootropic properties of phenibut, and it is described on the Internet as a nootropic agent, only one published study was available of its nootropic effects in a series of experiments conducted in mice in

1990 (489). The results are described by Lapin (420). The authors reported that, in the passive avoidance task, which is used to evaluate learning and memory, mice treated with phenibut spent less time in the environment of an aversive stimulus than untreated mice. In addition, phenibut reversed chloramphenicol-induced amnesia and enhanced performance in swimming and rotating rod tests. It was stated that mice became tolerant to the sedative properties of phenibut, while its nootropic effects were enhanced.

10. Listing on the WHO Model List of Essential Medicines

Phenibut is not on the 20th WHO Essential Medicines List or on the 6th WHO Essential Medicines List for Children.

11. Marketing authorizations (as a medicinal product)

A website selling phenibut states that it is authorized as a medicinal product in Belarus, Latvia, the Russian Federation and Ukraine (456). Kupats et al. (467) also state that phenibut is authorized in those countries, as well as in Estonia and Kazakhstan. No information was found on whether other countries have authorized the use of phenibut and for what indications.

Phenibut is manufactured by a number of companies. China alone has 129 phenibut manufacturers and suppliers (490).

12. Industrial use

Phenibut has no known industrial use.

13. Non-medical use, abuse and dependence

The purity of phenibut purchased on the Internet varies widely. Using LC-MS, Downes et al. (452) reported about 40% purity, and Wong et al. (453) reported 98% purity. The price depends on the vendor, the formulation and the quantity purchased. It generally costs US\$ 0.30–2.00 per gram of powder and US\$ 0.19–0.34 per 250-mg pill (456). People have reported administering up to 16 g/day of phenibut (458), which is at least 16 times even the highest recommended dose (454, 456, 479).

Commercially available phenibut is used widely as an anti-anxiety supplement. Advertisements include phrases such as “unlock your social side” and “it is calming, mood lifting, eases stress and supports a positive, social mood”. It is also used recreationally to get high. In 56 calls between 2000 and 2009 to a poison control centre in the USA., 48% people cited “to abuse” as the reason for use, while 23% cited “to treat anxiety” (473). Some Internet sites state that it can increase growth hormone, citing literature from the 1980s on the potential of GABA-ergics to stimulate growth hormone production (479, 491, 492).

Use of phenibut has increased rapidly in recent years. It is readily available and is described as being a “safe and natural” alternative to psychiatric medication. For example, phenibut is one of the more widely discussed drugs on Reddit, the largest Internet forum on which people discuss and comment on drugs. Phenibut has its own online forum, “subreddit” (493). It is mentioned about 10 times less frequently than the most frequent terms (e.g., fentanyl) but 10–100 times more frequently than most other substances in drug subreddits. In a compilation of Redditt comments between January 2020 and July 2021, it can be seen that phenibut is mentioned consistently, although the recent rise in mentions by unique commenters is outpacing the growth of Reddit in general. “Unique commenters” indicates how many mentions of phenibut in a 4-week period were first mentions of the drug by commenters who had never mentioned it previously on Reddit.⁵ The discussions revolve around how much to take and when, how to mitigate bad effects on off days, when to stop using it altogether and withdrawal effects (493). Currently, much of the discussion relates to concerns that phenibut will be banned because WHO has placed it on the list of substances to be pre-reviewed to determine whether it should be investigated further. Many individuals describe “stocking up” in the event that it is banned.

Many discussions on sites for people who use drugs such as Bluelight (494) and Erowid (495) describe use of phenibut to minimize withdrawal from benzodiazepines, opiates, alcohol and other substances. Many discussions refer to the fact that it is relatively easy to become dependent on phenibut and that tolerance builds rapidly. People on these forums sometimes warn others not to try it. There are also discussions of its use as a sexual enhancer (in males) (479, 496), which is not clearly supported by the literature.

In a review conducted in 2015, 48 unrelated Internet suppliers selling phenibut were identified in the United Kingdom alone (459). A Google Chrome Internet search in July 2021 with the search terms “phenibut” and “buy” identified 21 suppliers: Nootropics Depot, Zack attack, Liftmode, HR (Hard Rhino) Supplements, SportPoeders, Primaforce, Raw Powders, Nootropic Source, MOSPharma, Grabr, SG Asesores Industriales, Cosmicnootropic, Absorb Health, Newmind, ELV Bioscience, Intellimeds, SuperSmart, RUPharma’Science. bio, TheSmartShopOnline, Cosmic Nootropic and NutriVitaShop. Phenibut is no longer available on Amazon or Walmart (497, 498).

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

Newspaper articles have been written, sparked by incidents such as the case of five adolescent boys in Australia (476), about nonmedical use of phenibut but have not discussed the scope of the problem (499, 500).

⁵ Personal Communication, Paul Morris

Several addiction treatment centres provide information on phenibut and offer treatment (501–504), but, again, the scope of the problem has not been discussed.

The RADARS system does not currently acquire data on phenibut.⁶

15. Licit production, consumption and international trade

No information was found on the licit production or consumption of phenibut, although it is a registered product in the Russian Federation.

16. Illicit manufacture and traffic and related information

No incidents involving phenibut have been communicated to the International Narcotics Control Board (505).

17. Current international controls and their impact

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

18. Current and past national controls

Phenibut was relatively unknown outside of the Russian Federation until 2011, when a drug seizure in Sweden prompted an alert to the European authorities (480, original source unknown). Because of concern about abuse and misuse after the seizure, the European Monitoring Centre for Drugs and Addiction noted that it is used as a dietary supplement and sold illegally (506). After notification to EMCDDA, phenibut was classified as an NPS in 2012 by the UNODC (480).

Phenibut is approved for medical use with a prescription in the Russian Federation. It may also be approved in Belarus, Estonia, Kazakhstan, Latvia and Ukraine (456, 467).

Phenibut is listed as a controlled psychoactive substance in only a few countries: France (507), Hungary (508), Italy (509) and Lithuania (510). In 2018, Australia declared phenibut a schedule 9 substance (prohibited substance), because (i) the perceived benefits outweigh the substantial risks; (ii) its use, although prohibited in Australia, is becoming increasingly prevalent as consumers access it through the Internet; (iii) published reports of its toxicity are showing significant risks associated with overdose and withdrawal; and (iv) tolerance and dependence develop rapidly (511). In the United Kingdom, phenibut may legally be purchased for personal use, but it is illegal to supply it or sell it (unscheduled). Phenibut remains unscheduled in Canada and most of Europe.

New Zealand has put a request to their Medications Classification Committee, but it remains uncontrolled (488).

⁶ Personal communication, Elise Bailey, Client Operations Manager; RADARS® System

Phenibut is not controlled in the USA, but it is unlawful for any product sold in the country to contain it because it does not meet the definition of a dietary ingredient under the Federal Food, Drug, and Cosmetic Act. The US Food and Drug Administration is requesting public comment, which will be used to prepare an evaluation of phenibut for WHO (512).

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

A number of potentially relevant studies on phenibut have been published in non-English language journals, and were not included in this preliminary review.

Much of the information in the scientific and clinical literature on phenibut was retrieved from a review by Lapin (420). A number of primary studies cited in this review could not be obtained. As a result, these studies are described as reported by Lapin, and findings were unable to be verified from the primary studies. For clinical trial data that could be of potential importance for assessment of phenibut, Lapin cites only three references. Of these, one study cited in the review but not discussed; the abstract describes a small open-label trial (513). Another study is listed as being published in an English-language indexed journal (514), but it could not be retrieved. The third reference that might refer to a clinical trial is cited in the discussion of the results of preclinical studies (515). Other articles on phenibut, including reviews, such as those of Kupats et al. (467) and Hardman et al. (472), cite Lapin (420), rather than referring to primary studies.

References

1. Single Convention on Narcotic Drugs, 1961. Vienna: United Nations Office on Drugs and Crime; 1961 (https://www.unodc.org/pdf/convention_1961_en.pdf).
2. Convention on Psychotropic Substances, 1971. Vienna: United Nations Office on Drugs and Crime; 1971 (https://www.unodc.org/pdf/convention_1971_en.pdf).
3. Regulations for expert advisory panels and committees: Report by the secretariat. Geneva: World Health Organization; 1998 (<http://apps.who.int/iris/bitstream/handle/10665/79146/ee21.pdf?sequence=1&isAllowed=y>).
4. Guidance on the WHO review of psychoactive substances for international control. Geneva: World Health Organization; 2010 (http://www.who.int/medicines/areas/quality_safety/GLS_WHORev_PsychoactSubst_IntC_2010.pdf).
5. 4-Fluoro MDMB-BUTICA. Product information. Ann Arbor (MI): Cayman Chemical Co.; 2021 (<https://www.caymanchem.com/pdfs/31075.pdf>; accessed 28 June 2021).
6. Rompos É, Baráth NE, Zsóka MB, Lohner K, Haller J. A „bika drog” rendészeti neurobiológiája. *Belügyi Szemle*. 2021;69:531–52.
7. EMCDDA initial report on the new psychoactive substance 4F-MDMB-BICA. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2020.
8. EMCDDA initial report on the new psychoactive substance methyl 2-((1-(4-fluorobutyl)-1H-indol-3-yl)carbonyl)amino)-3,3-dimethylbutanoate (4F-MDMB-BICA). Luxembourg: Publications Office of the European Union; 2020.
9. 4-Fluoro-MDMB-BUTICA. Product description. Ann Arbor (MI): Cayman Chemical Co.; 2021 (<https://www.caymanchem.com/product/31075/4-fluoro-mdmb-butica>, accessed 9 August 2021).
10. Cammaert A, Sparkes A, Sparkes E, Pike E, Luo JL, Fang A et al. Synthesis and in vitro cannabinoid receptor 1 activity of recently detected synthetic cannabinoids 4F-MDMB-BICA, 5F-MPP-PICA, MMB-4en-PICA, CUMYL-CBMICA, ADB-BINACA, APP-BINACA, 4F-MDMB-BINACA, MDMB-4en-PINACA, A-CHMINACA, 5F-AB-P7AICA, 5F-MDMB-P7AICA, and 5F-AP7AICA. *ACS Chem Neurosci*. 2020;11:4434–46.
11. 4-Fluoro MDMB-BUTICA. Safety data sheet. Ann Arbor (MI): Cayman Chemical Co.; 2021 (<https://www.caymanchem.com/msdss/31075m.pdf>, accessed 28 June 2021).
12. Risk assessment report on a new psychoactive substance: methyl 2-[[1-(4-fluorobutyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (4F-MDMB-BICA) in accordance with Article 5c of Regulation (EC) No 1920/2006 (as amended) Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2021.
13. Analytical data for 4F-MDMB-BICA (Report HIFS-020). Budapest: Hungarian Institute for Forensic Sciences; 2020.
14. Analytical report. 4F-MDMB-BICA (C20H27FN2O3). Ljubljana: National Forensic Laboratory, European Project Response; 2020.
15. Norman C, Mckirdy B, Walker G, Dugard P, Nicdaéid N, Mckenzie C. Large-scale evaluation of ion mobility spectrometry for the rapid detection of synthetic cannabinoid receptor agonists in infused papers in prisons. *Drug Test Anal*. 2021;13:644–63.
16. Kleis JN, Hess C, Germerott T, Roehrich J. Sensitive screening of synthetic cannabinoids using liquid chromatography quadrupole time-of-flight mass spectrometry after solid phase extraction. *Drug Test Anal*. 2021 (<https://doi.org/10.1002/dta.3052>).
17. Körmöczy T, Sija É, Institóris L, Kereszty ÉM, Ilisz I, Berkecz R. Analytical methodologies for the characterization and analysis of the parent compound and phase I metabolites of 4F-MDMB-BICA in human microsome, urine, and blood samples. *J Anal Toxicol*. 2021 (<https://doi.org/10.1093/jat/bkab004>).
18. Yue L, Xiang P, Shen B, Xu D, Song F, Yan H. Metabolism of 4F-MDMB-BICA in zebrafish by liquid chromatography–high resolution mass spectrometry. *Drug Test Anal*. 2021;13:1223–9.
19. 4F-MDMB-BICA super potent. User report. Reddit; 2020 (https://www.reddit.com/r/researchchemicals/comments/isgj5g/4f_mdmb_bica_super_potent/, accessed 26 July 2021).
20. 4F-MDMB-BICA. User report. Reddit; 2021 (https://www.reddit.com/r/noids/comments/j8dInt/looking_for_personal_experiences_with_4fmdmbbica, accessed 15 July 2021).

21. European Monitoring Centre for Drugs and Drug Addiction, Europol. EMCDDA technical report on the new psychoactive substance methyl 2-[[1-(4-fluorobutyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (4F-MDMB-BICA). Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2020.
22. Persson M, Kronstrand R, Gréen H. Rapport Angående Aktivering av CB1 Receptor För 4-fluoro MDMB-BUTICA. [Report Regarding Activation of CB1 Receptor For 4-fluoro MDMB-BUTICA] Stockholm: National Board of Forensic Medicine; 2020.
23. European Monitoring Centre for Drugs and Drug Addiction. Risk assessment report on a new psychoactive substance: methyl 2-[[1-(4-fluorobutyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (4F-MDMB-BICA) in accordance with Article 5c of Regulation (EC) No. 1920/2006 (as amended). Luxembourg: Publications Office of the European Union; 2020.
24. Ongoing harm linked to dangerous “batch” of synthetic cannabinoids in Taranaki. Manatu Hauora: Ministry of Health; 2021 (<https://www.health.govt.nz/news-media/news-items/ongoing-harm-linked-dangerous-batch-synthetic-cannabinoids-taranaki>, accessed 10 August 2021).
25. Positivity of new synthetic cannabinoid 4F-MDMB-BICA increasing in US as prevalence of 5F-MDMB-PICA wanes. Willow Grove (PA): Center for Forensic Science Research and Education; 2021 (https://www.npsdiscovery.org/wp-content/uploads/2021/02/Public-Alert_4F-MDMB-BICA_NPS-Discovery_020921.pdf, accessed 26 July 2021).
26. Quarterly trend reports for synthetic cannabinoids. Willow Grove (PA): Center for Forensic Science Research and Education; 2021 (<https://www.npsdiscovery.org/reports/trend-reports/>, accessed 26 July 2021).
27. Food and Drug Administration. International drug scheduling; convention on psychotropic substances; single convention on narcotic drugs; 4F-MDMB-BICA (4F-MDMB-BUTICA); bupropion; metonitazene; eutylone (bk-EBDB); BMDP (3,4-methylenedioxy-N-benzylcathinone); kratom (mitragynine, 7-hydroxymitragynine); phenibut; request for comments. Fed Reg. 2021;86:39038–40.
28. Analytical report. Brorphine. 1-[1-[1-(4-Bromophenyl)ethyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one. Ausbau analytischer Datenbanken, Erhebung und bundesweite Bereitstellung von analytischen Daten, pharmakologischen Daten, Verfahrensvorschriften und Referenzmaterialien für neu auf dem Drogenmarkt auftretende Stoffe. [1- [1- [1- (4-Bromophenyl) ethyl] -4-piperidinyl] -1,3-dihydro-2H-benzimidazol-2-ones. Expansion of analytical databases, collection and nationwide provision of analytical data, pharmacological data, procedural regulations and reference materials for substances emerging on the drug market.] ADEBAR; 2020 (<https://www.projekt-adebar.eu/index.php?id=11>).
29. Brorphine (hydrochloride). Product Information. Item No. 27816. 28 April 2021. Ann Arbor (MI): Cayman Chemical Co.; 2021 (<https://www.caymanchem.com/pdfs/27816.pdf>).
30. Brorphine. European Database on New Drugs. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2021 (<https://ednd2.emcdda.europa.eu/ednd/substanceProfiles/1108>).
31. Indicators point to rise in brorphine’s domestic availability. DEA Bull. DEA-DCI-BUL-076-21. Arlington (VA): Drug Enforcement Administration; 2021.
32. Kennedy NM, Schmid CL, Ross NC, Lovell KM, Yue Z, Chen YT et al. Optimization of a series of mu opioid receptor (MOR) agonists with high G protein signaling bias. *J Med Chem*. 2018;61(19):8895–907.
33. Derivatives of benzimidazolyl piperidine (US3318900A). Beerse: Janssen Pharmaceutica NV; 1967 (<https://worldwide.espacenet.com/patent/search/family/023439235/publication/US3318900A?q=prn%3DUS3318900A>).
34. Analytical report. Brorphine (C20H22BrN3O). Sample ID: 2178-20. European project RESPONSE. Ljubljana: Slovenian National Forensic Laboratory; 2020 (https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/Brorphine-ID-2178-20_report.pdf).
35. Krotulski AJ, Papsun DM, Noble C, Kacinko SL, Logan BK. Brorphine – Investigation and quantitation of a new potent synthetic opioid in forensic toxicology casework using liquid chromatography-mass spectrometry. *J Forensic Sci*. 2021;66(2):664–76 (<https://doi.org/10.1111/1556-4029.14623>).
36. Verougstraete N, Vandeputte MM, Cannaraert A, Stove C, Verougstraete N, Verstraete AG et al First report on brorphine: the next opioid on the deadly new psychoactive substance horizon? *J Anal Toxicol*. 2021;44 (9):937–46 (<https://doi.org/10.1093/jat/bkaa094>).
37. Brorphine hydrochloride. GC–MS data sheet. Ann Arbor (MI): Cayman Chemical Co.; 2019 (<https://www.caymanchem.com/gcms/27816-0567046-GCMS.pdf>).

38. Krotulski AJ, Fogarty MF, Logan BK. Buprenorphine monograph. Latest revision: 17 July 2020. NMS Labs. Willow Grove (PA): Center for Forensic Science Research & Education; 2020 (https://www.npsdiscovery.org/wp-content/uploads/2020/07/Buprenorphine_071720_CFSRE-Toxicology_Report.pdf).
39. Yellow list. Annex to forms A, B and C, 59th edition, July 2020. List of narcotic drugs under international control. Single Convention on Narcotic Drugs, 1961. Protocol of 25 March 1972 amending the Single Convention on Narcotic Drugs. Vienna: International Narcotics Control Board; 2020 (https://www.incb.org/documents/Narcotic-Drugs/Yellow_List/59_edition/59_YL_2020_EN.pdf).
40. Kawaguchi M, Hayashi O, Sakai N, Hamada M, Yamamoto Y, Oda J. An asymmetric synthesis of 2-substituted piperidines through ozonolysis of cyclopentenones and reductive aminocyclization. *Agric Biol Chem.* 1986;50(12):3107–12 (<https://doi.org/10.1271/abb1961.50.3107>).
41. Olszewska B, Jabłońska A, Zawisza A. Diastereoselective synthesis of 2-vinylpyrrolidines and 2-vinylpiperidines by the palladium-catalysed cyclization of amino-allylic carbonates containing a chiral protecting group. *Arkivoc.* 2018;(5):254–71 (doi.org/10.24820/ark.5550190.p010.591).
42. Janssen C. Nieuwe reeks van organische verbindingen. Patent BE633495. Beersse: Research Laboratorium Dr C. Janssen NV; 1963.
43. Janssen PAJ. Benzimidazolyl piperidines. Patent US3196157A. Beersse: Research Laboratorium Dr C. Janssen NV; 1965 (<https://worldwide.espacenet.com/patent/search/family/026897320/publication/US3196157A?q=pn%3DUS3196157A>).
44. Beginner and veteran buprenorphine guide and overview. Reddit; 2020 (https://www.reddit.com/r/researchchemicals/comments/j3nn92/beginner_and_veteran_buprenorphine_guide_and_overview/, accessed 23 July 2021).
45. My experience with buprenorphine. Reddit; 2020 (https://www.reddit.com/r/researchchemicals/comments/j03l4m/my_experience_with_buprenorphine/, accessed 24 July 2021).
46. Buprenorphine. Reddit 2021 (https://www.reddit.com/r/Opioid_RCs/comments/kphokj/buprenorphine/gkm4stc/?utm_source=share&utm_medium=web2x&context=3, accessed 23 July 2021).
47. Suggest buprenorphine oral or vaped? Reddit; 2021 (https://www.reddit.com/r/researchchemicals/comments/l1yg55/suggest_buprenorphine_oral_or_vaped/, accessed 24 July 2021).
48. Volumic dosing for buprenorphine. Reddit 2020 (https://www.reddit.com/r/researchchemicals/comments/ixasyk/volumic_dosing_for_buprenorphine/, accessed 24 July 2021).
49. My experience with buprenorphine. Reddit; 2021 (https://www.reddit.com/r/researchchemicals/comments/j03l4m/my_experience_with_buprenorphine/, accessed 25 July 2021).
50. Buprenorphine. Reddit; 2020 (<https://www.reddit.com/r/researchchemicals/comments/fd5337/buprenorphine/>, accessed 24 July 2021).
51. Warning: buprenorphine is a severe overdose risk. Bluelight; 2021 (<https://www.bluelight.org/xf/threads/warning-buprenorphine-is-a-severe-overdose-risk.886363/> - post-15061994, accessed 24 July 2021).
52. Buprenorphine is the tofu of opioids. Bluelight; 2021 (<https://www.bluelight.org/xf/threads/buprenorphine-is-the-tofu-of-opioids.885922/> - post-15078584, accessed 24 July 2021).
53. Grafinger KE, Wilde M, Otte L, Auwärter V. Pharmacological and metabolic characterization of the novel synthetic opioid buprenorphine and its detection in routine casework. *Forensic Sci Int.* 2021;327:110989 (<https://doi.org/10.1016/j.forsciint.2021.110989>).
54. Whats with all the buprenorphine hate? Reddit 2020 (https://www.reddit.com/r/researchchemicals/comments/hzoxlr/whats_with_all_the_buprenorphine_hate/, accessed 23 July 2021).
55. Kennedy NM, Schmid CL, Ross NC, Lovell KM, Yue Z, Chen YT et al. Optimization of a series of my opioid receptor (MOR) agonists with high G protein signaling bias. *Med Chem.* 2018;6(19):8895–907 (<https://doi.org/10.1021/acs.jmedchem.8b01136>).
56. Vandeputte MM, Krotulski AJ, Papsun DM, Logan BK, Stove CP. The rise and fall of isotonitazene and buprenorphine: two recent stars in the synthetic opioid firmament. *J Anal Toxicol.* 2021 (<https://doi.org/10.1093/jat/bkab082>).
57. Vandeputte MM, Cannaert A, Stove CP. In vitro functional characterization of a panel of non-fentanyl opioid new psychoactive substances. *Arch Toxicol.* 2020;94(11):3819–30. (<https://doi.org/10.1007/s00204-020-02855-7>).
58. Temporary schedule I placement of 1-(1-(1-(4-bromophenyl)ethyl)piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (buprenorphine). Background, data, and analysis: three factor analysis pursuant to 21 U.S.C. 811(h)(3). Arlington (VA): Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; 2020 (<https://www.regulations.gov/document/DEA-2020-0038-0003>).

59. Vohra V, King AM, Jacobs E, Aaron C. Death associated with bromphine, an emerging novel synthetic opioid. *Clin Toxicol*. 2021 (<https://doi.org/10.1080/15563650.2021.1879111>).
60. Razinger G, Grenc D, Brvar M, Pezdir T, Kranvogel R, Brvar M (2021) Severe rhabdomyolysis and acute kidney failure due to synthetic opioid bromphine exposure in combination with chronic sertraline therapy. *European Journal of Clinical Pharmacology*. <https://doi.org/10.1007/s00228-021-03136-7>
61. Vohra V, Aaron C. The color purple: death associated with bromphine, an emerging novel synthetic opioid. *Clinical Toxicol*. 2021;59 (6):556–7.
62. Verstraete A, Hyde E. Une méthode de dépistage des NPS utilisant les plateformes collaboratives HighresNPS et Mzcloud [Screening methods for NPS on the HighresNPS et Mzcloud platforms]. *Toxicol Anal Clin*. 2020;32(4 Suppl):S47–8 (doi.org/10.1016/j.toxac.2020.09.017).
63. Early warning advisory (Tox-Portal). Vienna: United Nations Office on Drugs and Crime; 2021 (<https://www.unodc.org/tox/-/admin/incident/view/1935>, accessed 25 July 2021).
64. Krotulski AJ, Papsun DM, Walton SE, Logan BK. Metonitazene in the United States – forensic toxicology assessment of a potent new synthetic opioid using liquid chromatography mass spectrometry. *Drug Test Anal*. 2021. (<https://doi.org/10.1002/dta.3115>).
65. Krotulski AJ, Mohr ALA, Logan BK. NPS opioids in the United States. Trend report: Q3 2020. NPS Discovery. Willow Grove (PA): Center for Forensic Science Research & Education; 2020 (https://www.npsdiscovery.org/wp-content/uploads/2020/10/2020-Q3_NPS-Opioids_Trend-Report.pdf).
66. Krotulski AJ, Walton SE, Mohr ALA, Logan BK. NPS opioids in the United States. Trend report: Q4 2020. NPS Discovery. Willow Grove (PA): Center for Forensic Science Research & Education; 2020 (https://www.npsdiscovery.org/wp-content/uploads/2021/01/2020-Q4_NPS-Opioids_Trend-Report.pdf).
67. Krotulski AJ, Walton SE, Mohr ALA, Logan BK. NPS opioids in the United States. Trend report: Q1 2021. NPS Discovery. Willow Grove (PA): Center for Forensic Science Research & Education; 2021 (https://www.npsdiscovery.org/wp-content/uploads/2021/04/2021-Q1_NPS-Opioids_Trend-Report.pdf).
68. Krotulski AJ, Walton SE, Mohr ALA, Logan BK. NPS opioids in the United States. Trend report: Q2 2021. NPS Discovery. Willow Grove (PA): Center for Forensic Science Research & Education; 2021 (https://www.npsdiscovery.org/wp-content/uploads/2021/07/2021-Q2_NPS-Opioids_Trend-Report.pdf).
69. Bromphine. Reddit; 2021 (<https://www.reddit.com/r/fentanyl/comments/of8mjo/bromphine/>, accessed 25 July 2021).
70. Gatch MB. Final study report. Evaluation of abuse potential of synthetic opioids using in vivo pharmacological studies. Test of substitution for the discriminative stimulus effects of morphine. Fort Worth (TX): University of North Texas, Health Science Center; 2020.
71. Gatch MB. Final study report. Evaluation of abuse potential of synthetic opioids using in vivo pharmacological studies. Test of analgesic effects alone and in combination with naltrexone. Fort Worth (TX): University of North Texas, Health Science Center; 2020.
72. Lamy FR, Daniulaityte R, Barratt MJ, Lokala U, Sheth A, Carlson RG. “Etazene, safer than heroin and fentanyl”: non-fentanyl novel synthetic opioid listings on one darknet market. *Drug Alcohol Depend*. 2021;225:108790 (doi.org/10.1016/j.drugalcdep.2021.108790).
73. Barenholtz E, Krotulski AJ, Morris P, Fitzgerald ND, Le A, Papsun DM et al. Online surveillance of novel psychoactive substances (NPS): Monitoring Reddit discussions as a predictor of increased NPS-related exposures. *Int J Drug Policy*. 2021;98 103393 (doi.org/10.1016/j.drugpo.2021.103393).
74. Catalani V, Arillotta D, Corkery JM, Guirguis A, Vento A, Schifano F. Identifying new/emerging psychoactive substances at the time of COVID-19; a web-based approach. *Front Psychiatry*. 2021;11:1638 (doi.org/10.3389/fpsy.2020.632405).
75. Fake oxycodone tablets containing bromphine – Slovenia, 2021. EU Early Warning System advisory, 22 January 2021 (RCS ID: EU-EWS-RCS-AD-2021-0001). Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2021.
76. Early Warning Advisory (EWA) on new psychoactive substances (NPS) database. Vienna: United Nations Office on Drugs and Crime; 2021 (<https://www.unodc.org/LSS/NPSFinding/List>, accessed 25 July 2021).
77. Drug Enforcement Administration. Schedules of controlled substances: temporary placement of bromphine in Schedule I. *Fed Reg*. 2021;86(38):11862–7 (<https://www.govinfo.gov/content/pkg/FR-2021-03-01/pdf/2021-04242.pdf>).
78. National Forensic Laboratory Information System-Drug 2019 Annual report. Arlington (VA): Drug Enforcement Administration, Diversion Control Division; 2019 (https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS-DRUG_2019_Annual_Report.pdf).

79. National Forensic Laboratory Information System-Drug 2020 Midyear report. Springfield (VA): Drug Enforcement Administration, Diversion Control Division; 2020 (<https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/13915NFLISdrugMidYear2020.pdf>).
80. NFLIS Drug Snapshot (March 2021). Reported to NFLIS-Drug for the first time between 01 January 2021 and 31 March 2021. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2021 (https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS_Snapshot_032021.pdf).
81. DEA emerging threat report: Annual 2019. Arlington (VA): Drug Enforcement Administration, Special Testing and Research Laboratory; 2019 <https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/DEA-Emerging-Threat-Report-2019-Annual.pdf>
82. DEA emerging threat report: Annual 2020. Arlington (VA): Drug Enforcement Administration Special Testing and Research Laboratory; 2020 (<https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/DEA-Emerging-Threat-Report-2020-Annual.pdf>).
83. Metonitazene. Ann Arbor (MI): Cayman Chemical Co.; 2020.
84. Krotulski AJ, Papsun DM, Walton SE, Logan BK. Metonitazene in the United States – Forensic toxicology assessment of a potent new synthetic opioid using liquid chromatography mass spectrometry. *Drug Test Anal.* 2021 (doi: 10.1002/dta.3115).
85. Metonitazene. PubChem. Bethesda (MD): National Center for Biotechnology Information (<https://pubchem.ncbi.nlm.nih.gov/compound/53316366>, accessed 29 August 2021).
86. Metonitazene (citrate). Product information. Ann Arbor (MI): Cayman Chemical Co.; 2021 (<https://www.caymanchem.com/pdfs/31303.pdf>, accessed 1 July 2021).
87. r/Opioid_RCs – [NSFW] Insufflating metonitazene. Reddit; 2020 (https://www.reddit.com/r/Opioid_RCs/comments/nz236q/insufflating_metonitazene/, accessed 29 August 2021).
88. Buy metonitazene U-47-700 (id:11401603). Buy China Metonitazene – EC21. Global B2B Marketplace; 2021 (<https://www.ec21.com/product-details/Buy-Metonitazene-U-47-700--11401603.html>, accessed 29 August 2021).
89. Ujváry I, Christie R, Evans-Brown M, Gallegos A, Jorge R, de Moraes J et al. DARK classics in chemical neuroscience: Etonitazene and related benzimidazoles. *ACS Chem Neurosci.* 2021;12(7):1072–92.
90. Hunger A, Kebrle J, Rossi A, Hoffmann K. Synthese basisch substituierter, analgetisch wirksamer Benzimidazol-Derivate.[Synthesis of basic substituted, analgesic benzimidazole derivatives] *Experientia.* 1957;13 (10):400–1.
91. Hunger A, Kebrle J, Rossi A, Hoffmann K. Benzimidazol-Derivate und verwandte Heterocyclen III. Synthese von 1-Aminoalkyl-2-nenzyl-nitro-benzimidazolen. [Benzimidazole Derivatives and Related Heterocycles III. Synthesis of 1-aminoalkyl-2-nenzyl-nitro-benzimidazoles]. *Helv Chim Acta;* 1960;43:1032–46.
92. Hunger A, Kebrle J, Rossi A, Hoffmann K. Benzimidazol-Derivate und verwandte Heterocyclen. II. Synthese von 1-Aminoalkyl-2-benzyl-benzimidazolen. [Benzimidazole Derivatives and Related Heterocycles. II. Synthesis of 1-aminoalkyl-2-benzyl-benzimidazoles] *Helvetica Chimica Acta.* 1960;43:800–9.
93. Hoffmann K, Hunger A, Kebrle J, Rossi A. Verfahren für Herstellung analgetisch wirksamer benzimidazole.[Process for the preparation of benzimidazoles with analgesic activity] 1959 (<https://www.emcdda.europa.eu/system/files/publications/12879/emcdda-covid-update-1>
94. Hoffmann K, Hunger A, Rossi A. 1960. Benzimidazoles.
95. Kim Y, Kumar MR, Park N, Heo Y, Lee S. Copper-catalyzed, one-pot, three-component synthesis of benzimidazoles by condensation and C–N bond formation. *J Organic Chem.* 2011;76:9577–83.
96. Renton P, Green B, Maddaford S, Rakhit S, Andrews JS. NOPiates: Novel dual action neuronal nitric oxide synthase inhibitors with μ -opioid agonist activity. *ACS Med Chem Lett.* 2012;3:227–31.
97. Thomas JB, Fall MJ, Cooper JB, Burgess JP, Carroll FI. Rapid in-plate generation of benzimidazole libraries and amide formation using EEDQ. *Tetrahedron Lett.* 1997;38:5099–102.
98. Bucha M, Eppakayala L, Chary MT. A facile synthesis and molecular docking for anti-inflammatory activity of 2-(4-chlorobenzyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1H-benzo[d]imidazol-5-amine and 2-(4-chlorobenzyl)-1-((1-ethylpyrrolidin-2-yl)methyl)-1H-benzo[d]imidazol-5-amine. *Indian J Heterocyclic Chem.* 2018;28:321.

99. Vandeputte MM, Van Uytfanghe K, Layle NK, St Germaine DM, Lula DM, Stove CP. Synthesis, chemical characterization, and μ -opioid receptor activity assessment of the emerging group of "nitazene" 2-benzylbenzimidazole synthetic opioids. *ACS Chem Neurosci*. 2021;12(7):1241–51.
100. Metonitazene. Product information. Ann Arbor (MI): Cayman Chemical Co.; 2021 (<https://www.caymanchem.com/product/26398/metonitazene>, accessed 1 July 2021).
101. r/Fentanyl – Etazene and metonitazene vaping dose? Reddit; 2015 (https://www.reddit.com/r/fentanyl/comments/la8ghl/etazene_and_metonitazene_vaping_dose/).
102. r/Opioid_RCs – [NSFW] metonitazene HCL. Reddit; 2019 (https://www.reddit.com/r/Opioid_RCs/comments/ip4wd9/metonitazene_hcl/, accessed 29 August 2021).
103. r/Opioid_RCs – [NSFW] Is metonitazene a good opioid? Reddit; 2021 (https://www.reddit.com/r/Opioid_RCs/comments/om34kh/is_metonitazene_a_good_opioid/, accessed 29 August 2021).
104. Opioids – etodesnitazene (etazene) and metonitazene (opioid RCs). *Bluelight.org*; 2020 (<https://www.bluelight.org/xf/threads/etodesnitazene-etazene-and-metonitazene-opioid-rCs.891168/>, accessed 29 August 2021).
105. r/Opioid_RCs – [NSFW] metonitazene IV use. Help? Reddit; 2021 (https://www.reddit.com/r/Opioid_RCs/comments/oljhsd/metonitazene_iv_use_help/, accessed 29 August 2021).
106. r/Opioid_RCs – [NSFW] metonitazene cold-turkey withdrawal: one week later. Reddit; 2020 (https://www.reddit.com/r/Opioid_RCs/comments/jxf1m2/metonitazene_coldturkey_withdrawal_one_week_later/, accessed 29 August 2021).
107. Babalonis S, Comer SD, Jones JD, Nuzzo P, Lofwall MR, Manubay J et al. Relative potency of intravenous oxymorphone compared to other μ opioid agonists in humans — pilot study outcomes. *Psychopharmacology*. 2021;238(9):2503–14.
108. Gyang EA, Kosterlitz HW, Lees GM. The inhibition of autonomic neuro-effector transmission by morphine-like drugs and its use as a screening test for narcotic analgesic drugs. *Naunyn-Schmiedebergs Arch Exp Pathol Pharmacol*. 1964;248:231–46.
109. Hughes J, Kosterlitz HW, Leslie FM. Effect of morphine on adrenergic transmission in the mouse vas deferens. Assessment of agonist and antagonist potencies of narcotic analgesics. *Br J Pharmacol*. 1975;53:371–81.
110. Gharagozlou P, Hashemi E, DeLorey TM, Clark JD, Lameh J. Pharmacological profiles of opioid ligands at kappa opioid receptors. *BMC Pharmacol*. 2006;6(1):3.
111. Hunger A, Kebrle J, Rossi A, Hoffmann K. Benzimidazol-Derivate und verwandte Heterocyclen II. Synthese von 1-Aminoalkyl-2-benzyl-benzimidazolen. [Benzimidazole derivatives and related heterocycles II. Synthesis of 1-aminoalkyl-2-benzyl-benzimidazoles] *Helv Chim Acta*. 1960;43(3):800–9.
112. Ujváry, I., Christie, R., Evans-Brown, M., Gallegos, A., Jorge, R., de Morais, J. and Sedefov, R. (2021). DARK Classics in Chemical Neuroscience: Etonitazene and Related Benzimidazoles. *ACS Chemical Neuroscience*, 12(7), pp.1072–1092
113. Paronis CA. Metonitazene: Test of antinociceptive effects. 15DDHQ20P00000709, Evaluation of synthetic opioid substances using analgesia and drug discrimination assays. 2021.
114. Bromig G. Über neue starkwirkende Analgetika und ihre klinische Erprobung. [About new strong analgesics and their clinical trials] *Klin Wochenschr*. 1958;36(20):960–63.
115. Gross F, Turrian H. Über Benzimidazol-Derivate mit starker analgetischer Wirkung. [About benzimidazole derivatives with a strong analgesic effect] *Experientia*. 1957;13(10):401–3.
116. Burns G, DeRienz RT, Baker DD, Casavant M, Spiller HA. (2016). Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse? *Clinical Toxicol*. 2016;54(5):420–3.
117. Torralva R, Janowsky A. Noradrenergic mechanisms in fentanyl-mediated rapid death explain failure of naloxone in the opioid crisis. *J Pharmacol Exp Therapeut*. 2019;371(2):453–75.
118. Barnett A, Goldstein J, Fiedler E, Taber R. Etonitazene-induced rigidity and its antagonism by centrally acting muscle relaxants. *Eur J Pharmacol*. 1975;30(1):23–8.
119. Krotulski AJ, Papsun DM, Walton SE, Logan BK. Metonitazene begins proliferation as newest synthetic opioid among latest cycle of non-fentanyl related drugs. January 2021. NPS Discovery. Willow Grove (PA): Center for Forensic Science Research & Education; 2021 (https://www.npsdiscovery.org/wp-content/uploads/2021/01/Public-Alert_Metonitazene_NPS-Discovery_012521.pdf, accessed 6 August 2021).

120. Aceto MD, Bowman ER, Harris LS, May EL. Dependence studies of new compounds in the rhesus monkey and mouse (1991). In: Harris LS, editor. Problems of drug dependence (NIDA Research Monograph Series 119), 1992:513–558. Rockville (MD): Department of Health and Human Services.
121. Deneau GA, McCarthy DA, Seevers MH. Addendum 1. Physical dependence liability studies in the monkey. Presented at the 20th Meeting, Washington DC, January 10–11, 1959. Committee on Drug Addiction and Narcotics, National Academy of Sciences, National Research Council; 1959:1–13.
122. Special Advisory Committee on the Epidemic of Opioid Overdoses. Opioid- and stimulant-related harms in Canada. Ottawa: Public Health Agency of Canada; 2021 (<https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants>, accessed 29 August 2021).
123. Anderson E. Drug bust leads to discovery of synthetic opioid. KitchenerToday, 10 May 2021 (<https://www.kitchenertoday.com/police-beat/drug-bust-leads-to-discovery-of-synthetic-opioid-3764713>, accessed 30 August 2021).
124. Global SMART update 2020: the growing complexity of the opioid crisis. Vienna: United Nations Office on Drugs and Crime; 2021 (https://www.unodc.org/documents/scientific/Global_SMART_Update_2020-Vol.24-Eng-Final.pdf, accessed 6 August 2021). update on the implications of COVID-19 for people who use drugs (PWUD) and drug service
125. EMCDDA providers., Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2020.
126. Krotulski AJ, Shuda SA, Fogarty MF, Decker SE, Logan BK. Metonitazene (https://www.npsdiscovery.org/wp-content/uploads/2020/07/Metonitazene_073020_NMSLabs_Report.pdf).
127. National Forensics Laboratory Information System. Arlington (VA): Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; 2021 (https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS_Snapshot_032021.pdf, accessed 8 August 2021).
128. International drug scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; 4F-MDMB-BICA (4F-MDMB-BUTICA); bromphine; metonitazene; eutylone (bk-EBDB); BMDP (3,4-methylenedioxy-N-benzylcathinone); kratom (mitragynine, 7-hydroxymitragynine); phenibut; request for comments. Fed Regist. 2021 (<https://www.federalregister.gov/documents/2021/07/23/2021-15685/international-drug-scheduling-convention-on-psychotropic-substances-single-convention-on-narcotic>, accessed 29 August 2021).
129. Drugs of abuse A. DEA Resouce Guide 2020 edition. Arlington (VA): Drug Enforcement Administration; 2020 (https://www.dea.gov/sites/default/files/2020-04/Drugs%20of%20Abuse%202020-Web%20Version-508%20compliant-4-24-20_0.pdf).
130. Administrative Code. 18VAC110-20-322. Placement of chemicals in Schedule I. Richmond (VA): Virginia Assembly; 2021 (<https://law.lis.virginia.gov/admincode/title18/agency110/chapter20/section322/>, accessed 29 August 2021).
131. Bill summaries: S321 Irs.sog.unc.edu. Chapel Hill (NC): Legislative Reporting Service; 2021 (<https://lrs.sog.unc.edu/bill-summaries-lookup/S/321/2021/S321>, accessed 29 August 2021).
132. High levels of eutylone substitution found in O week testing in South Island. KnowYourStuffNZ; 2021 (<https://knowyourstuff.nz/2021/02/23/high-levels-of-eutylone-substitution-found-in-o-week-testing-in-south-island/>, accessed 27 July 2021).
133. Krotulski AJ, Papsun DM, Chronister CW, Homan J, Crosby MM, Hoyer Jet al. Eutylone intoxications – An emerging synthetic stimulant in forensic investigations. *J Anal Toxicol.* 2020;45(1):8–20 (doi: 10.1093/jat/bkaa113).
134. Eutylone (hydrochloride). Product information. Item No. 9001103. Ann Arbor (MI): Cayman Chemical Co.; 2021 (<https://www.caymanchem.com/product/9001103>, accessed 28 June 2021).
135. Glatfelter GC, Walther D, Evans-Brown M, Baumann MH Eutylone and its structural isomers interact with monoamine transporters and induce locomotor stimulation. *ACS Chem Neurosci.* 2021;12(7):1170–7 (doi: 10.1021/acscchemneuro.0c00797).
136. Recommended methods for the identification and analysis of synthetic cathinones in seized materials (revised and updated). Vienna: United Nations Office on Drugs and Crime; 2020
137. Boehringer Sohn AG and Co KG Boehringer Ingelheim GmbH (1967). Substituted phenyl- α -amino ketones. Patent number: GB1085135A.
138. Analytical report: Eutylone (C13H17NO3). 1-(2H-1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one. Ljubljana: National Forensic Laboratory – European Project Response; 2017.

139. Eutylone (hydrochloride). Safety data sheet. Ann Arbor (MI): Cayman Chemical Co.; 2021 (<https://www.caymanchem.com/msdss/9001103m.pdf>, accessed 28 June 2021).
140. Krotulski AJ, Papsun DM, Chronister CW, Homan J, Crosby MM, Hoyer J, Goldberger BA, Logan BK (2020). Eutylone intoxications - An emerging synthetic stimulant in forensic investigations. *Journal of Analytical Toxicology*. 45 (1):8-20. doi: 10.1093/jat/bkaa113
141. Boehringer Sohn AG & Co., KG Boehringer Ingelheim GmbH. Substituted phenyl- α -amino ketones. Patent number: GB1085135A. Ingelheim; 1967.
142. "Ekstasis-//7". Eutylone (N-ethylbutylone) trip report & summary of 3 different trials. Bluelight; 2020 (<https://www.bluelight.org/xf/threads/eutylone-n-ethylbutylone-trip-report-summary-of-3-different-trials.890861/>, accessed 28 July 2021).
143. "Nick". Erowid experience vaults report ID: 115241. Very nice but habit forming. Erowid; 2021 (<https://erowid.org/experiences/exp.php?ID=115241>, accessed 28 July 2021).
144. "xammy". PD social tripping thread: tripping past 2020. Bluelight; 2021 (<https://www.bluelight.org/xf/threads/pd-social-tripping-thread-tripping-past-2020.896059/page-2#post-15052538>, accessed 28 July 2021).
145. Zaitso K. Metabolism of synthetic cathinones. In: Zawilska JB, editor. *Synthetic cathinones: novel addictive and stimulatory psychoactive substances*. Cham: Springer International; 2018:71–96.
146. Kerrigan S, Glicksberg L. Long-term stability of synthetic cathinones in forensic toxicology samples. Office of Justice Programs' National Criminal Justice Reference Service; 2017.
147. Janowsky A. Eutylone. bk-EBDB, β -keto-ethylbenzodioxolylbutanamine. 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)-1-butanone, HCl. Binding and functional activity at biogenic amine transporters. DEA-VA Interagency Agreement. In: *In vitro receptor and transporter assays for abuse liability testing for the DEA by the VA*. Drug Enforcement Administration; 2019.
148. Gatch MB. Final study report. Time-course (6-h) mouse locomotor activity test. Evaluation of abuse potential of synthetic cathinones and other substances that have stimulant effects using in vivo pharmacological studies. Call order: 15DDHQ19F00001152. Fort Worth (TX): University of North Texas, Health Science Center; 2020
149. Chen HY, Chien WC, Huang MN, Fang CC, Weng TI. Analytically confirmed eutylone (bk-EBDB) exposure in emergency department patients. *Clin Toxicol*. 2021;1–6 (doi: 10.1080/15563650.2020.1868491).
150. ToxPortal – United Nations Office on Drugs and Crime Early Warning Advisory (<https://www.unodc.org/tox/#/login>, accessed 2 August 2021).
151. 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one (eutylone) ["Bath salt," bk-EBDB]. Springfield (VA): Drug Enforcement Administration, Diversion Control Division, Drug & Chemical Evaluation Section; 2020.
152. "nerewing". Erowid experience vaults report ID: 114422. Sweet Little Stim. Erowid; 2021 (<https://erowid.org/experiences/exp.php?ID=114422>, accessed 28 July 2021).
153. Autopsy: Man died of drug overdose after fight with deputies. AP News, 4 July 2020 (<https://apnews.com/article/4dbb1c5c37131f85995f42f6b3be6cb9>, accessed 28 July 2021).
154. Gatch MB. Final study report. Test of substitution for the discriminative stimulus effects of methamphetamine. Evaluation of abuse potential of synthetic cathinones and other substances that have stimulant effects using in vivo pharmacological studies. Call Order: 15DDHQ19F00001152. Fort Worth (TX): University of North Texas, Health Science Center; 2020
155. 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one (eutylone). Arlington (VA): Drug Enforcement Administration, Drug & Chemical Evaluation Section; 2020.
156. "Gaffy". Usine valium to counter impatience and restlessness caused by haldol. Bluelight; 2020 (<https://www.bluelight.org/xf/threads/usine-valium-to-counter-impatience-and-restlessness-caused-by-haldol.888763/>, accessed 28 July 2021).
157. Wedinos – Welsh Emerging Drugs & Identification of Novel Substances Project (<https://www.wedinos.org/db/samples/search>, accessed 24 August 2021).
158. European Monitoring Centre for Drugs and Drug Addiction. EMCDDA–Europol 2014 annual report on the implementation of Council Decision 2005/387/JHA. Implementation reports. Luxembourg: Publications Office of the European Union; 2015.
159. Bade R, White JM, Nguyen L, Tscharke BJ, Mueller JF, O'Brien JW et al. Determining changes in new psychoactive substance use in Australia by wastewater analysis. *Sci Total Environ*. 2020;731:139209 (doi.org/10.1016/j.scitotenv.2020.139209).

160. ONDCP scheduling recommendation for review and prioritization by the World Health Organization's (WHO) Expert Committee on Drug Dependence. Washington DC: Office of National Drug Control Policy; 2021.
161. Trend reports, 2018–2020. Willow Grove (PA): Center for Forensic Science Research and Education; 2021 (<https://www.npsdiscovery.org/reports/trend-reports/>).
162. Ordinance amending the Ordinance (1999:58) banning certain products that are harmful to health. Stockholm: Public Health Agency of Sweden; 2019.
163. 3,4-Methylenedioxy-N-benzylcathinone (hydrochloride). Product information. Item No. 900133. 01 April 2016. Ann Arbor (MI): Cayman Chemical Co.; 2016 (<https://www.caymanchem.com/pdfs/9001330.pdf>).
164. 3,4-Methylenedioxy-N-benzylcathinone. Monograph. Arlington (VA): Drug Enforcement Administration's Special Testing and Research Laboratory; 2019 (<https://www.swgdrug.org/Monographs/3,4-methylenedioxy-N-benzylcathinone.pdf>).
165. Köppe H, Ludwig G, Zeile K. 1-(3,4'-Methylenedioxy-phenyl)-2-pyrrolidino-alkanones-(1). Patent US 3478050. Ingelheim: Boehringer Ingelheim GmbH; 1967 (<https://worldwide.espacenet.com/patent/search/family/006981404/publication/US3478050A?q=pn%3DUS3478050A>).
166. Analytical report. BMDP (C17H17NO3). Sample ID: 1875-17. European project Response. Ljubljana: Slovenian National Forensic Laboratory; 2017 (https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/BMDP-ID-1875-17_report.pdf).
167. Nagashima M, Suzuki J, Moriyasu T, Yoshida M, Shimizu M, Hamano T et al. Analysis of uncontrolled drugs purchased in the fiscal year 2010. Annual report. Tokyo: Metropolitan Institute of Public Health. 2011;62:99–105.
168. Elie MP, Elie LE, Baron MG. Keeping pace with NPS releases: fast GC–MS screening of legal high products. *Drug Test Anal.* 2013;5(5):281–90 (doi.org/10.1002/dta.1434).
169. Fornal E, Stachniuk A, Wojtyła A. LC-Q/TOF mass spectrometry data driven identification and spectroscopic characterisation of a new 3,4-methylenedioxy-N-benzyl cathinone (BMDP). *J Pharmaceut Biomed Anal.* 2013;72:139–44 (doi.org/10.1016/j.jpba.2012.09.019).
170. Adamowicz P, Tokarczyk B. Simple and rapid screening procedure for 143 new psychoactive substances by liquid chromatography–tandem mass spectrometry. *Drug Test Anal.* 2016;8(7):652–67 (doi.org/10.1002/dta.1815).
171. Adamowicz P, Tokarczyk B. Screening analysis for designer stimulants by LC-MS/MS. In: Langman L, Snozek C, editors. *Methods in molecular biology*, vol. 1872. New York City (NY): Humana Press; 2019:165–80 (doi.org/10.1007/978-1-4939-8823-5_16).
172. Ameline A, Garnier D, Gheddar L, Richeval C, Gaulier JM, Raul JS et al. Identification and analytical characterization of seven NPS, by combination of 1H NMR spectroscopy, GC–MS and UPLC–MS/MS[®], to resolve a complex toxicological fatal case. *Forensic Sci Int.* 2019;298:140–8 (doi.org/10.1016/j.forsciint.2019.03.003).
173. Fornal E. Identification of substituted cathinones: 3,4-methylenedioxy derivatives by high performance liquid chromatography–quadrupole time of flight mass spectrometry. *J Pharmaceut Biomed Anal.* 2013;81–82:13–9 (doi.org/10.1016/j.jpba.2013.03.016).
174. Fornal E. Study of collision-induced dissociation of electrospray-generated protonated cathinones. *Drug Testing Anal.* 2014;6(7–8):705–15 (doi.org/10.1002/dta.1573).
175. Lau T, Concheiro M, Cooper G. Determination of 30 synthetic cathinones in postmortem blood using LC-MS-MS. *J Anal Toxicol.* 2020;44 (7):679–87 (doi.org/10.1093/jat/bkaa071).
176. Yap S, Drummer OH. Prevalence of new psychoactive substances in Victorian fatally-injured drivers. *Aust J Forensic Sci.* 2016;48(2):230–43 (doi.org/10.1080/00450618.2015.1050066).
177. Zuba D, Adamowicz P. Analytical methods used for identification and determination of synthetic cathinones and their metabolites. In: Zawilska JB, editor. *Synthetic cathinones: Novel addictive and stimulatory psychoactive substances*. Cham: Springer International Publishing; 2018:41–69.
178. Fowble KL, Shepard JRE, Musah RA. Identification and classification of cathinone unknowns by statistical analysis processing of direct analysis in real time-high resolution mass spectrometry-derived “neutral loss” spectra. *Talanta.* 2018;179:546–53 (doi.org/10.1016/j.talanta.2017.11.020).
179. Musah RA, Cody RB, Domin MA, Lesiak AD, Dane AJ, Shepard JRE. DART–MS in-source collision induced dissociation and high mass accuracy for new psychoactive substance determinations. *Forensic Sci Int.* 2014;244:42–9 (doi.org/10.1016/j.forsciint.2014.07.028).

180. Ameline A, Garnier D, Raul JS, Kintz P. Use of nuclear magnetic resonance (NMR) spectroscopy to identify unknown powders. *Toxicol Anal Clin*. 2019;31(4):197–250 (doi.org/10.1016/j.toxac.2019.05.002).
181. Sisco E, Burns A, Moorthy AS. Development and evaluation of a synthetic cathinone targeted gas chromatography mass spectrometry (GC–MS) method. *J Forensic Sci*. 2021 (doi.org/10.1111/1556-4029.14789).
182. 3,4-Methylenedioxy-N-benzylcathinone. GC–MS data sheet. Ann Arbor (MI): Cayman Chemical Co.; 2012 (<https://www.caymanchem.com/gcms/9001330-0441190-GCMS.pdf>).
183. Krotulski AJ, Fogarty MF, Logan BK. Benzylone (BMDP). Monograph. Latest revision: 22 July 2019. Willow Grove (PA): NMS Labs; 2019 (https://www.npsdiscovery.org/wp-content/uploads/2019/06/Benzylone_072219_NMSLabs_Report.pdf).
184. Erowid's anonymous drug analysis program, formerly called EcstasyData. Batman. MDMA. Sold as: MDMA. ID: 7123. *DrugsData.org*; 2021 (<https://drugsdata.org/view.php?id=7123>).
185. Erowid's anonymous drug analysis program, formerly called EcstasyData. Batman. Sold as: MDMA. ID: 7471. *DrugsData.org*; 2021 (<https://drugsdata.org/view.php?id=7471>).
186. Erowid's anonymous drug analysis program, formerly called EcstasyData. Ketamine rocks. Sold as: ketamine. ID: 7695. *DrugsData.org*; 2021 (<https://drugsdata.org/view.php?id=7695>).
187. Benzylone vs mephedrone. *Reddit*; 2020 (https://www.reddit.com/r/researchchemicals/comments/evu1mb/benzylone_vs_mephedrone/).
188. BMDP. Anyone have any useful information on this chemical. *Reddit*; 2020 (https://www.reddit.com/r/researchchemicals/comments/dxkk60/bmdp_anyone_have_any_useful_information_on_this/).
189. BMDP. *Reddit*; 2020 (<https://www.reddit.com/r/researchchemicals/comments/f09jyd/bmdp/>).
190. BMDP (3,4-Methylenedioxy-N-benzylcathinone). Reagent testing. *Reddit*; 2021 (https://www.reddit.com/r/ReagentTesting/comments/mfegb9/bmdp_34methylenedioxybenzylcathinone/).
191. Bmdp. *Bluelight*; 2018 (<https://www.bluelight.org/xf/threads/bmdp.857782/> - post-14424919, accessed 11 July 2021).
192. BMDP what is it like? *Bluelight*; 2019 (<https://www.bluelight.org/xf/threads/bmdp-what-is-it-like.857786/> - post-14588736, accessed 11 July 2021).
193. Dal Cason TA, Young R, Glennon RA. Cathinone: an investigation of several N-alkyl and methylenedioxy-substituted analogs. *Pharmacol Biochem Behav*. 1997;58(4):1109–16 ([https://doi.org/10.1016/S0091-3057\(97\)00323-7](https://doi.org/10.1016/S0091-3057(97)00323-7)).
194. Luethi D, Kolaczynska KE, Walter M, Suzuki M, Rice KC, Blough BE et al. Metabolites of the ring-substituted stimulants MDMA, methylone and MDPV differentially affect human monoaminergic systems. *J Psychopharmacol*. 2019;33(7):831–41 (doi.org/10.1177/0269881119844185).
195. Rickli A, Kopf S, Hoener MC, Liechti ME. Pharmacological profile of novel psychoactive benzofurans. *Br J Pharmacol*. 2015;172(13):3412–25 (doi.org/10.1111/bph.13128).
196. Smith DA, Blough BE, Banks ML. Cocaine-like discriminative stimulus effects of amphetamine, cathinone, methamphetamine, and their 3,4-methylenedioxy analogs in male rhesus monkeys. *Psychopharmacology*. 2017;234(1):17–27 (doi.org/10.1007/s00213-016-4444-1).
197. Elmore JS, Dillon-Carter O, Partilla JS, Ellefsen KN, Concheiro M, Suzuki M et al. Pharmacokinetic profiles and pharmacodynamic effects for methylone and its metabolites in rats. *Neuropsychopharmacology*. 2017;42(3):649–60 (doi.org/10.1038/npp.2016.213).
198. Janowsky A. 3,4-Methylenedioxy-N-benzylcathinone. BMDP. 1-(1,3-Benzodioxol-5-yl)-2-[(phenylmethyl)amino]-1-propanone, HCl. Binding and functional activity at biogenic amine transporters. DEA-VA Interagency Agreement title: In vitro receptor and transporter assays for abuse liability testing for the DEA by the VA. Portland (OR): Departments of Psychiatry and Behavioral Neuroscience, Oregon Health & Science University, VA Medical Center; 2019.
199. Iversen L, Gibbons S, Treble R, Setola V, Huang XP, Roth BL. Neurochemical profiles of some novel psychoactive substances. *Eur J Pharmacol*. 2013;700(1–3):147–51 (doi.org/10.1016/j.ejphar.2012.12.006).
200. Early warning advisory (Tox-Portal). Vienna: United Nations Office on Drugs and Crime; 2021 (<https://www.unodc.org/tox/-/admin/incident/view/1908>, accessed 14 July 2021).
201. EMCDDA response to request for information on the new psychoactive substance benzylone for a WHO critical review. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2021.

202. Krotulski AJ, Papsun DM, Logan BK. Eutylone (bk-EBDB) and benzylone (BMDP): increasing prevalence of new synthetic stimulants in the United States (March 2020). NPS Discovery. Willow Grove (PA): Center for Forensic Science Research & Education; 2020 (https://www.npsdiscovery.org/wp-content/uploads/2020/03/Public-Alert_Eutylone_Benzylone_NPS-Discovery_033120.pdf).
203. Krotulski AJ, Walton SE, Mohr ALA, Logan BK (2020) NPS stimulants & hallucinogens in the United States. Trend report: Q4 2020. NPS Discovery. Willow Grove (PA): Center for Forensic Science Research & Education; 2020 (https://www.npsdiscovery.org/wp-content/uploads/2021/01/2020-Q4_NPS-Stimulants-and-Hallucinogens_Trend-Report.pdf).
204. Gatch MB. BMDP (3,4-methylenedioxy-N-benzylcathinone). Final study report. Evaluation of abuse potential of synthetic cathinones and other substances that have stimulant effects using in vivo pharmacological studies. Time-course (6-h) mouse locomotor activity test. Fort Worth (TX): University of North Texas, Health Science Center; 2020.
205. Gatch MB.a) 3,4-Methylenedioxy-N-benzylcathinone (BMDP). Final study report. Evaluation of abuse potential of synthetic cathinones and other substances that have stimulant effects using in vivo pharmacological studies. Test of substitution for the discriminative stimulus effects of MDMA. Fort Worth (TX): University of North Texas, Health Science Center; 2020.
206. Gatch MB. 3,4-Methylenedioxy-N-benzylcathinone HCl (BMDP). Final study report. Evaluation of abuse potential of synthetic cathinones and other substances that have stimulant effects using in vivo pharmacological studies. Test of substitution for the discriminative stimulus effects of methamphetamine. Fort Worth (TX): University of North Texas, Health Science Center; 2020.
207. De Moraes J, Brandt SD, Jorge R, Christie R, Gallegos A, Sedefov R et al. EMCDDA technical report on the new psychoactive substance methyl 3,3-dimethyl-2-[[1-(pent-4-en-1-yl)-1H-indazole-3-carbonyl]amino]butanoate (MDMB-4en-PINACA). Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2020 (https://www.emcdda.europa.eu/system/files/publications/13478/TR-MDMB-4en-PINACA_Advanced-release.pdf).
208. EMCDDA–Europol 2010 annual report on the implementation of Council Decision 2005/387/JHA. In accordance with Article 10 of Council Decision 2005/387/JHA on the information exchange, risk-assessment and control of new psychoactive substances. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2011 (https://www.emcdda.europa.eu/system/files/publications/644/European Monitoring Centre for Drugs and Drug Addiction-Europol_Annual_Report_2010A_281336.pdf).
209. UNODC early warning advisory (EWA) on new psychoactive substances (NPS) database. Vienna: United Nations Office on Drugs and Crime; 2021 (<https://www.unodc.org/LSS/NpsFinding/List?pageNumber=0>, accessed 10 July 2021).
210. Synthetic drugs in East and Southeast Asia. Latest developments and challenges. Global SMART programme. Vienna: United Nations Office on Drugs and Crime; 2020 (https://www.unodc.org/documents/scientific/ATS/2020_ESEA_Regional_Synthetic_Drug_Report_web.pdf).
211. Synthetic drugs in East and Southeast Asia. Latest developments and challenges. Global SMART programme. Vienna: United Nations Office on Drugs and Crime; 2021 (https://www.unodc.org/documents/scientific/ATS/2021_ESEA_Regional_Synthetic_Drugs_Report.pdf).
212. Synthetic drugs. 2018 report. Brasília: Serviço Público Federal, Polícia Federal, Instituto Nacional de Criminalística; 2018 (https://www.gov.br/pf/pt-br/acao-a-informacao/acoes-e-programas/relatorio-de-drogas-sinteticas-2018/drogas_sinteticas_2018_eng.pdf).
213. NFLIS-Drug 2018 annual report. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2019 (<https://www.nflis.deadiversion.usdoj.gov/publicationsRedesign.xhtml>).
214. NFLIS-Drug 2019 Midyear report. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2020.
215. NFLIS-Drug 2019 Annual report. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2020 (https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS-Drug_2019_Annual_Report.pdf).
216. NFLIS-Drug 2020 Midyear report. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2020 (<https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/13915NFLISdrugMidYear2020.pdf>).
217. 2020 national drug threat assessment. March 2021. Springfield (VA): Drug Enforcement Administration; 2020 (https://www.dea.gov/sites/default/files/2021-02/DIR-008-21_2020_National_Drug_Threat_Assessment_WEB.pdf).

218. NFLIS Drug Snapshot (March 2020). Reported to NFLIS-Drug for the first time between 01 January 2020 and 31 March 2020. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2020 (<https://www.nflis.deadiversion.usdoj.gov/publicationsRedesign.xhtml>).
219. NFLIS Drug Snapshot (June 2020). Reported to NFLIS-Drug for the first time between 01 April 2020 and 30 June 2020. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2020 (https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS-Drug_Snapshot_june_2020.pdf).
220. NFLIS Drug Snapshot (December 2020). Reported to NFLIS-Drug for the first time between 01 October 2020 and 31 December 2020. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2020 (https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS-Drug_Snapshot_December_2020.pdf).
221. NFLIS Drug Snapshot (March 2021). Reported to NFLIS-Drug for the first time between 01 January 2021 and 31 March 2021. Springfield (VA): National Forensic Laboratory Information System, Drug Enforcement Administration, Diversion Control Division; 2021 (https://www.nflis.deadiversion.usdoj.gov/nflisdata/docs/NFLIS_Snapshot_032021.pdf).
222. DEA emerging threat report: Annual 2018. Arlington (VA): Drug Enforcement Administration Special Testing and Research Laboratory; 2018 (<https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/DEA-Emerging-Threat-Report-2018-Annual.pdf>).
223. DEA emerging threat report: Annual 2019. Arlington (VA): Drug Enforcement Administration Special Testing and Research Laboratory; 2019 (<https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/DEA-Emerging-Threat-Report-2019-Annual.pdf>).
224. DEA emerging threat report: Annual 2020. Arlington (VA): Drug Enforcement Administration Special Testing and Research Laboratory; 2020 (<https://cesar.umd.edu/sites/cesar.umd.edu/files/pubs/DEA-Emerging-Threat-Report-2020-Annual.pdf>).
225. Suwanlert S. A study of kratom eaters in Thailand. *Bull Narcotics*. 1975;27(3):21–7.
226. Sukrong S, Zhu S, Ruangrungrui N, Phadungcharoen T, Palanuvej C, Komatsu K. Molecular analysis of the genus *Mitragyna* existing in Thailand based on rDNA ITS sequences and its application to identify a narcotic species: *Mitragyna speciosa*. *Biol Pharm Bull*. 2007;30, 1284–8.
227. Raffa RB. *Kratom and other mitragynines: the chemistry and pharmacology of opioids from a non-opium source*. Boca Raton (FL): CRC Press; 2014.
228. Braley C, Hondrogiannis EM. Differentiation of commercially available kratom by purported country of origin using inductively coupled plasma–mass spectrometry. *J Forensic Sci*. 2020;65:428–37.
229. Todd DA, Kellogg JJ, Wallace ED, Khin M, Flores-Bocanegra L, Tanna RS et al. Chemical composition and biological effects of kratom (*Mitragyna speciosa*): In vitro studies with implications for efficacy and drug interactions. *Sci Rep*. 2020;10:19158.
230. Phillip AA, Meyer MR, Wissenbach DK, Weber AA, Zoerntlein SW, Zweipfenning PGM et al. Monitoring of kratom or Krypton intake in urine using GC–MS in clinical and forensic toxicology. *Anal Bioanal Chem*. 2011;400:127–35.
231. *Kratom drug profile available*. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2015 (<https://www.emcdda.europa.eu/publications/drug-profiles/kratom#control>, accessed 12 August 2021).
232. Razafimandimbison SG, Bremer B. Tribal delimitation of Naucleaeae (Cinchonoideae, Rubiaceae): Inference from molecular and morphological data. *System Geogr Plants*. 2001;71:515–38.
233. Korthals PG. *Observationes de Naucleis indicis*. Bonnae: C. Georgii; 1839.
234. Haviland GD. A revision of the tribe Naucleaeae. *Bot J Linn Soc*. 1897;33:1–94.
235. Tungtananuwat W, Lawanprasert S. Fatal 4x100; home-made kratom juice cocktail. *J Health Res*. 2018;24:43–7.
236. Ahmad K, Aziz Z. *Mitragyna speciosa* use in the northern states of Malaysia: a cross-sectional study. *J Ethnopharmacol*. 2012;141:446–50.
237. *Kratom (Mitragyna speciosa korth) (Street names: Thang, Kakuam, Thom, Ketum, Biak)*. Springfield (VA): Drug Enforcement Administration, Diversion Control Division, Drug & Chemical Evaluation Section; 2019.

238. Hilmas CJ, Fabricant DS. Chapter 35 – Biomarkers of toxicity for dietary ingredients contained in dietary supplements. In: Gupta RC, editor. Biomarkers in toxicology. Boston: Academic Press; 2014.
239. Horie S, Koyama F, Takayama H, Ishikawa H, Aimi N, Ponglux D et al. Indole alkaloids of a Thai medicinal herb, *Mitragyna speciosa*, that has opioid agonistic effect in guinea-pig ileum. *Planta Med.* 2005;71:231–6.
240. Ramanathan S, León F, Chear NJY, Yusof SR, Murugaiyah V, McMahon LR et al. Chapter 5. Kratom (*Mitragyna speciosa* Korth.): a description on the ethnobotany, alkaloid chemistry, and neuropharmacology. In: Atta-ur-Rahman, editor. Studies in natural products chemistry. Amsterdam: Elsevier; 2021.
241. Flores-Bocanegra L, Raja HA, Graf TN, Augustinović M, Wallace ED, Hematian S et al. The chemistry of kratom [*Mitragyna speciosa*]: updated characterization data and methods to elucidate indole and oxindole alkaloids. *J NatProducts.* 2020;83:2165–77.
242. Field E. XCVIII. Mitragynine and mitraversine, two new alkaloids from species of mitragyne. *J Chem SocTrans.* 1921;119:887–91.
243. Beckett A, Shellard E, Tackie A. The *Mitragyna* species of Asia, Part IV, The alkaloids of the leaves of *M. speciosa* Korth. Isolation of mitragynine and speciofoline. *Planta Medica.* 2009;13:241–6.
244. Brown PN, Lund JA, Murch SJ. A botanical, phytochemical and ethnomedicinal review of the genus *Mitragyna* korth: Implications for products sold as kratom. *J Ethnopharmacol.* 2017;202:302–25.
245. Tanko H, Carrier DJ, Duan L, Clausen E. Pre- and post-harvest processing of medicinal plants. *Plant Genetic Resources Characterization Utilization.* 2005;3:304–13.
246. Tong X, Shi B, Liu Q, Huo Y, Xia C. Retro-biosynthetic construction of corynanthe alkaloid skeletons from rhynchophylline alkaloids. *Organic Biomol Chem.* 2019;17:8062–6.
247. Kruegel AC, Uprety R, Grinnell SG, Langreck C, Pekarskaya EA, Le Rouzic V et al. 7-Hydroxymitragynine is an active metabolite of mitragynine and a key mediator of its analgesic effects. *ACS Central Sci.* 2019;5:992–1001.
248. Lopes AA, Chioca B, Musquiari B, Crevelin EJ, França SDC, Fernandes Da Silva MFDG et al. Unnatural spirocyclic oxindole alkaloids biosynthesis in *Uncaria guianensis*. *Sci Rep.* 2019;9:11349.
249. Heitzman ME, Neto CC, Winiarz E, Vaisberg AJ, Hammond GB. Ethnobotany, phytochemistry and pharmacology of *Uncaria* (Rubiaceae). *Phytochemistry.* 2005;66:5–29.
250. Phongprueksapattana S, Putalun W, Keawpradub N, Wungsintaweekul J. *Mitragyna speciosa*: hairy root culture for triterpenoid production and high yield of mitragynine by regenerated plants. *Z Naturforsch C J Biosci.* 2008 ;63 :691–8.
251. Yamamoto LT, Horie S, Takayama H, Aimi N, Sakai S, Yano S et al. Opioid receptor agonistic characteristics of mitragynine pseudoindoxyl in comparison with mitragynine derived from Thai medicinal plant *Mitragyna speciosa*. *Gen Pharmacol.* 1999;33:73–81.
252. Hinou J, Harvala C. Polyphenolic compounds from the leaves of *Mitragyna speciosa*. *Fitoterapia.* 1988;59:156.
253. Arndt T, Claussen U, Güssregen B, Schröfel S, Stürzer B, Werle A et al. Kratom alkaloids and O-desmethyltramadol in urine of a “Krypton” herbal mixture consumer. *Forensic Sci Int.* 2011;208:47–52.
254. Kronstrand R, Roman M, Thelander G, Eriksson A. Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend krypton. *J Anal Toxicol.* 2011;35:242–7.
255. Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, Boyer EW. Suspected adulteration of commercial kratom products with 7-hydroxymitragynine. *J Med Toxicol.* 2016;12:341–9.
256. Chan KB, Pakiam C, Rahim RA. Psychoactive plant abuse: the identification of mitragynine in ketum and in ketum preparations. *Bull Narc.* 2005;57:249–56.
257. Orio L, Alexandru L, Cravotto G, Mantegna S, Barge A. UAE, MAE, SFE-CO₂ and classical methods for the extraction of *Mitragyna speciosa* leaves. *Ultrason Sonochem.* 2012;19:591–5.
258. Takayama H, Maeda M, Ohbayashi S, Kitajima M, Sakai SI, Aimi N. The first total synthesis of (–)-mitragynine, an analgesic indole alkaloid in *mitragyna speciosa*. *Tetrahedron Lett.* 1995;36:9337–40.
259. Ma J, Yin W, Zhou H, Liao X, Cook JM. General approach to the total synthesis of 9-methoxy-substituted indole alkaloids: synthesis of mitragynine, as well as 9-methoxygeissoschizol and 9-methoxy-N-b-methylgeissoschizol. *J Organic Chem.* 2009;74:264–73.

260. Sun X, Ma D. Organocatalytic approach for the syntheses of corynantheidol, dihydrocorynantheol, protoemetinol, protoemetine, and mitragynine. *Chem Asian J.* 2011;6:2158–65.
261. Kerschgens IP, Claveau E, Wanner MJ, Ingemann S, Van Maarseveen JH, Hiemstra H. Total syntheses of mitragynine, paynantheine and speciogynine via an enantioselective thiourea-catalysed Pictet–Spengler reaction. *Chem Commun.* 2012;48:12243–5.
262. Kruegel AC, Gassaway MM, Kapoor A, Váradi A, Majumdar S, Filizola M et al. Synthetic and receptor signaling explorations of the *Mitragyna* alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators. *J Am Chem Soc.* 2016;138:6754–64.
263. Takayama H, Ishikawa H, Kurihara M, Kitajima M, Aimi N, Ponglux D et al. 2002. Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. *J Med Chem.* 2002;45:1949–56.
264. Kong WM, Chik Z, Mohamed Z, Alshawsh MA. Physicochemical characterization of *Mitragyna speciosa* alkaloid extract and mitragynine using in vitro high throughput Assays. *Comb Chem High Throughput Screen.* 2017;20:796–803.
265. Ramanathan S, Parthasarathy S, Murugaiyah V, Magosso E, Tan SC, Mansor SM. Understanding the physicochemical properties of mitragynine, a principal alkaloid of *Mitragyna speciosa*, for preclinical evaluation. *Molecules.* 2015;20:4915–27.
266. Basiliere S, Kerrigan S. Temperature and pH-dependent stability of *Mitragyna* alkaloids. *J Anal Toxicol.* 2020;44:314–24.
267. Ponglux D, Tantivatana P, Pummangura S. Alkaloids from the leaves of *Uncaria homomalla*. *Planta Med.* 1977;31:26–30.
268. Lersten NR, Horner HT. Unique calcium oxalate “duplex” and “concretion” idioblasts in leaves of tribe Naucleaceae (Rubiaceae). *Am J Bot.* 2011;98:1–11.
269. Jaipaew J, Padungchareon T, Sukrong S. PCR-reverse dot blot of the nucleotide signature sequences of matK for the identification of *Mitragyna speciosa*, a narcotic species. *Plant Genet.* 2018;14:46–54.
270. Tungphatthong C, Urumarudappa SKJ, Awachai S, Sooksawate T, Sukrong S. Differentiation of *Mitragyna speciosa*, a narcotic plant, from allied *Mitragyna* species using DNA barcoding-high-resolution melting (Bar-HRM) analysis. *Sci Rep.* 2021;11:6738.
271. Kowalczyk AP, Łozak A., Zjawiony JK. Comprehensive methodology for identification of kratom in police laboratories. *Forensic Sci Int.* 2013;233:238–43.
272. Philipp AA, Meyer MR, Wissenbach DK, Weber AA, Zoerntlein SW, Zweipfenning PG et al. Monitoring of kratom or Krypton intake in urine using GC–MS in clinical and forensic toxicology. *Anal Bioanal Chem.* 2011;400:127–35.
273. Cornara L, Borghesi B, Canali C, Andrenacci M, Basso M, Federici S et al. Smart drugs: green shuttle or real drug? *Int J Legal Med.* 2013;127:1109–23.
274. Wang M, Carrell EJ, Ali Z, Avula B, Avonto C, Parcher JF et al. Comparison of three chromatographic techniques for the detection of mitragynine and other indole and oxindole alkaloids in *Mitragyna speciosa* (kratom) plants. *J Sep Sci.* 2014;37:1411–8.
275. Sanagi MM, Ayob MFM, Wan Ibrahim WA, Hussain I. Determination of mitragynine for the identification of mitragynine species in kedah (Malaysia) by gas chromatography-mass spectrometry. *Pharma Chem.* 2013;5:131–8.
276. Basiliere S, Bryand K, Kerrigan S. Identification of five *Mitragyna* alkaloids in urine using liquid chromatography–quadrupole/time of flight mass spectrometry. *J Chromatogr B Anal Technol Biomed Life Sci.* 2018;1080:11–9.
277. Chittrakarn S, Penjamras P, Keawpradub N. Quantitative analysis of mitragynine, codeine, caffeine, chlorpheniramine and phenylephrine in a kratom (*Mitragyna speciosa* Korth.) cocktail using high-performance liquid chromatography. *Forensic Sci Int.* 2012;217:81–6.
278. Parthasarathy S, Ramanathan S, Murugaiyah V, Hamdan MR, Mohd Said MI, Lai CS et al. A simple HPLC–DAD method for the detection and quantification of psychotropic mitragynine in *Mitragyna speciosa* (ketum) and its products for the application in forensic investigation. *Forensic Sci Int.* 2013;226:183–7.
279. Mudge EM, Brown PN. Determination of mitragynine in *Mitragyna speciosa* raw materials and finished products by liquid chromatography with UV detection: single-laboratory validation. *J AOAC Int.* 2017;100:18–24.

280. Parthasarathy S, Ramanathan S, Ismail S, Adenan MI, Mansor SM, Murugaiyah V. Determination of mitragynine in plasma with solid-phase extraction and rapid HPLC-UV analysis, and its application to a pharmacokinetic study in rat. *Anal Bioanal Chem.* 2010;397:2023–30.
281. Neng NR, Ahmad SM, Gaspar H, Nogueira JMF. Determination of mitragynine in urine matrices by bar adsorptive microextraction and HPLC analysis. *Talanta.* 2015;144:105–9.
282. Le D, Goggin MM, Janis GC. Analysis of mitragynine and metabolites in human urine for detecting the use of the psychoactive plant kratom. *J Anal Toxicol.* 2012;36:616–25.
283. Kikura-Hanajiri R, Kawamura M, Maruyama T, Kitajima M, Takayama H, Goda Y. Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant “kratom” (*Mitragyna speciosa*) by LC-ESI-MS. *Forensic Toxicol.* 2009;27:67–74.
284. Lu S, Tran BN, Nelsen JL, Aldous KM. Quantitative analysis of mitragynine in human urine by high performance liquid chromatography–tandem mass spectrometry. *J Chromatogr B Anal Technol Biomed Life Sci.* 2009;877:2499–505.
285. Philipp AA, Wissenbach DK, Weber AA, Zapp J, Maurer HH. Phase I and II metabolites of speciogynine, a diastereomer of the main kratom alkaloid mitragynine, identified in rat and human urine by liquid chromatography coupled to low- and high-resolution linear ion trap mass spectrometry. *J Mass Spectrom.* 2010;45:1344–57.
286. Philipp AA, Wissenbach DK, Weber AA, Zapp J, Zoerntlein SW, Kanogsunthornrat J et al. Use of liquid chromatography coupled to low- and high-resolution linear ion trap mass spectrometry for studying the metabolism of paynantheine, an alkaloid of the herbal drug kratom in rat and human urine. *Anal Bioanal Chem.* 2010;396:2379–91.
287. Philipp AA, Wissenbach DK, Weber AA, Zapp J, Maurer HH. Metabolism studies of the kratom alkaloid speciociliatine, a diastereomer of the main alkaloid mitragynine, in rat and human urine using liquid chromatography-linear ion trap mass spectrometry. *Anal Bioanal Chem.* 2011;399:2747–53.
288. Philipp AA, Wissenbach DK, Weber AA, Zapp J, Maurer HH. Metabolism studies of the kratom alkaloids mitraciliatine and isopaynantheine, diastereomers of the main alkaloids mitragynine and paynantheine, in rat and human urine using liquid chromatography-linear ion trap-mass spectrometry. *J Chromatogr B Anal Technol Biomed Life Sci.* 2011;879:1049–55.
289. Holler JM, Vorce SP, McDonough-Bender PC, Maglulilo J Jr, Solomon CJ, Levine B. A drug toxicity death involving propylhexedrine and mitragynine. *J Anal Toxicol.* 2011;35:54–9.
290. Lee MJ, Ramanathan S, Mansor SM, Yeong KY, Tan SC. Method validation in quantitative analysis of phase I and phase II metabolites of mitragynine in human urine using liquid chromatography-tandem mass spectrometry. *Anal Biochem.* 2018;543:146–61.
291. Sharma A, Kamble SH, León F, Chear NJ, King TI, Berthold EC et al. Simultaneous quantification of ten key kratom alkaloids in *Mitragyna speciosa* leaf extracts and commercial products by ultra-performance liquid chromatography-tandem mass spectrometry. *Drug Test Anal.* 2019;11:1162–71.
292. Avery BA, Boddu SP, Sharma A, Furr EB, Leon F, Cutler SJ et al. Comparative pharmacokinetics of mitragynine after oral administration of *Mitragyna speciosa* (kratom) leaf extracts in rats. *Planta Medica.* 2019;85(4):340–6.
293. Basiliere S, Kerrigan S. Identification of metabolites and potential biomarkers of kratom in urine. *J Chromatogr B.* 2020;1140:121971.
294. Meier U, Mercer-Chalmers-Bender K, Scheurer E, Dussy F. Development, validation, and application of an LC-MS/MS method for mitragynine and 7-hydroxymitragynine analysis in hair. *Drug Test Anal.* 2020;12:280–4.
295. Posch TN, Müller A, Schulz W, Pütz M, Huhn C. Implementation of a design of experiments to study the influence of the background electrolyte on separation and detection in non-aqueous capillary electrophoresis-mass spectrometry. *Electrophoresis.* 2012;33:583–98.
296. Lesiak AD, Cody RB, Dane AJ, Musah RA. Rapid detection by direct analysis in real time-mass spectrometry (DART-MS) of psychoactive plant drugs of abuse: the case of *Mitragyna speciosa* aka “Kratom”. *Forensic Sci Int.* 2014;242:210–8.
297. Fowble KL, Musah RA. A validated method for the quantification of mitragynine in sixteen commercially available kratom (*Mitragyna speciosa*) products. *Forensic Sci Int.* 2019;299:195–202.
298. Fuenfingger N, Ritchie M, Ruth A, Gryniewicz-Ruzicka C. Evaluation of ion mobility spectrometry for the detection of mitragynine in kratom products. *J Pharm Biomed Anal.* 2017;134:282–6.

299. Lanzarotta A, Thatcher MD, Lorenz LM, Batson JS. Detection of mitragynine in *Mitragyna speciosa* (kratom) using surface-enhanced Raman spectroscopy with handheld devices. *J Forensic Sci.* 2020;65:1443–9.
300. Voelker SE, Kern SE, Falconer TM, Thatcher MD, Skelton DM, Gaston KW et al. Evaluation of four field portable devices for the rapid detection of mitragynine in suspected kratom products. *J Pharm Biomed Anal.* 2021;201:114104.
301. Schütz H, Paine A, Erdmann F, Weiler G, Verhoff MA. Immunoassays for drug screening in urine: chances, challenges, and pitfalls. *Forensic Sci Med Pathol.* 2006;2:75–83.
302. Limsuwanchote S, Putalun W, Keawpradub N, Tanaka H, Morimoto S, Wungsintaweekul J. Anti-mitragynine monoclonal antibody-based ELISA for determination of alkaloids in the kratom cocktail. *Forensic Toxicol.* 2017;35:167–72.
303. Lee MJ, Ramanathan S, Mansor SM Tan SC. Development of an ELISA for detection of mitragynine and its metabolites in human urine. *Anal Biochem.* 2020;599:113733.
304. Singh D, Narayanan S, Vicknasingam B. Traditional and non-traditional uses of mitragynine (kratom): a survey of the literature. *Brain Res Bull.* 2016;126:41–9.
305. Toce MS, Chai PR, Burns MM, Boyer EW. Pharmacologic treatment of opioid use disorder: a review of pharmacotherapy, adjuncts, and toxicity. *J Med Toxicol.* 2018;14:306–22.
306. Zhou Y, Ramsey S, Provasi D, El Daibani A, Appourchaux K, Chakraborty S et al. Predicted mode of binding to and allosteric modulation of the μ -opioid receptor by kratom's alkaloids with reported antinociception in vivo. *Biochemistry.* 2021;60:1420–9.
307. Kamble SH, Leon F, King TI, Berthold EC, Lopera-Londoño C, Rama KSR et al. Metabolism of a kratom alkaloid metabolite in human plasma increases its opioid potency and efficacy. *ACS Pharmacol Translational Sci.* 2020;3:1063–8.
308. Leon F, Habib E, Adkins JE, Furr EB, McCurdy CR, Cutler SJ. Phytochemical characterization of the leaves of *Mitragyna speciosa* grown in USA. *Nat Product Commun.* 2009;4(7):907–10.
309. Singh D, Narayanan S, Vicknasingam B, Corazza O, Santacroce R, Roman-Urrestarazu A. Changing trends in the use of kratom (*Mitragyna speciosa*) in Southeast Asia. *Hum Psychopharmacol.* 2017;32:e2582.
310. Garcia-Romeu A, Cox DJ, Smith KE, Dunn KE, Griffiths RR. Kratom (*Mitragyna speciosa*): user demographics, use patterns, and implications for the opioid epidemic. *Drug Alcohol Depend.* 2020;208:107849.
311. Grundmann O. Patterns of kratom use and health impact in the US – Results from an online survey. *Drug Alcohol Depend.* 2017;176:63–70.
312. Pearce MR, Smith ME, Poklis JL. The analysis of commercially available products recommended for use in electronic cigarettes. *Rapid Commun Mass Spectrom.* 2020;34(17):e771.
313. Saref A, Suraya S, Singh D, Grundmann O, et al. (2019) Self-reported prevalence and severity of opioid and kratom (*Mitragyna speciosa* korth.) side effects. *Journal of Ethnopharmacology* 238:111876.
314. Ramachandram DS, Damodaran T, Zainal H, Murugalyah V, Narayanan S, Swogger MT et al. Pharmacokinetics and pharmacodynamics of mitragynine, the principle alkaloid of *Mitragyna speciosa*: present knowledge and future directions in perspective of pain. *J Basic Clin Physiol Pharmacol.* 2020;2019-0138.
315. Ya K, Tangamornsuksan W, Scholfield CN, Methaneethorn J, Lohitnavy M. Pharmacokinetics of mitragynine, a major analgesic alkaloid in kratom (*Mitragyna speciosa*): a systematic review. *Asian J Psychiatry.* 2019;43:73–82.
316. Maxwell EA, King TL, Kambie SH, Raju KSR, Berthold EC, Léon F et al. Pharmacokinetics and safety of mitragynine in beagle dogs. *Planta Medica.* 2020;86(17):1278–85.
317. Kong WM, Mohamed Z, Alshawsh MA, Chik Z. Evaluation of pharmacokinetics and blood–brain barrier permeability of mitragynine using in vivo microdialysis technique. *J Pharmaceut Biomed Anal.* 2017;143:43–7.
318. Trakulsrichai S, Sathirakul K, Auparakkitanon J, Krongvorakul J, Sueajai J, Noumjad N et al. Pharmacokinetics of mitragynine in man. *Drug Design Dev Ther.* 2015;9:2421–9.
319. Vicknasingam B, Chooi WT, Rahim AA, Ramachandram D, Singh D, Ramanathan S et al. Kratom and pain tolerance: a randomized, placebo-controlled, double-blind study. *Yale J Biol Med.* 2020;93:229–38.

320. Lim EL, Seah TC, Koe XF, Wahab HA, Adenan MI, Jamil MF et al. In vitro evaluation of cytochrome P450 induction and the inhibition potential of mitragynine, a stimulant alkaloid. *Toxicol In Vitro*. 2013;27:812–24.
321. Drug development and drug interactions. Table of substrates, inhibitors and inducers. Silver Spring (MD): US Food and Drug Administration; 2020 (<https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table2-1>, accessed 26 August 2021).
322. Gutridge AM, Robins MT, Cassell RJ, Uprety R, Mores KL, Ko MJ et al. G-protein-biased kratom-alkaloids and synthetic carfentanil-amid opioids as potential treatments for alcohol use disorder. *Br J Pharmacol*. 2020;177:1497–513.
323. Varadi A, Marrone GF, Palmer TC, Narayan A, Szabó MR, Le Rouzic V et al. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit β -arrestin-2t. *J Med Chem*. 2016;59:8381–97.
324. De Neve J, Barlow TMA, Tourwe D, Bihel F, Simonin F, Ballet S. Comprehensive overview of biased pharmacology at the opioid receptors: based ligands and bias factors. *RSC Med Chem*. 2021;12:828–70.
325. Faouzi A, Varga BR, Majumdar S. Biased opioid ligands. *Molecules*. 2020;25:4257.
326. Obeng S, Kamble SH, Reeves ME, Restrepo LF. Investigation of the adrenergic and opioid binding affinities, metabolic stability, plasma protein binding properties, and function effects of selected indole-based kratom alkaloids. *J Med Chem*. 2020;65:433–9.
327. Obeng S, Wilkerson JL, Leon F, Reeves ME, Restrepo LF, Gamez-Jimenez LR et al. Pharmacological comparison of mitragynine and 7-hydroxymitragynine: In vitro affinity and efficacy for μ -opioid and opioid-like behavioral effects on rats. *J Pharmacol Experimental Ther*. 2021;376:410–27.
328. Yue K, Kopajtic TA, Katz JL. Abuse liability of mitragynine assessed with a self-administration procedure in rats. *Psychopharmacology*. 2018;235:2823–39.
329. Ellis CR, Racz R, Kruhlak NL, Kim MT, Zakharov AV, Southall N et al. Evaluating kratom alkaloids using PHASE. *PLoS One*. 2020;15(3):e0229646.
330. Stolt AC, Schroder H, Neurath H, Greckach G, Höllt V, Meyer MR et al. Behavioral and neurochemical characterization of kratom (*Mitragyna speciosa*) extract. *Psychopharmacology*. 2014;231:13–25.
331. Prevete E, Kuypers KPC, Theunissen EL, Corazza O, Bersani G, Ramaekers JG et al. (2021) A systematic review of (pre)clinical studies on the therapeutic potential and safety profile of kratom in humans. *Hum Psychopharmacol*. 2021:e2805.
332. Chin KY, Mark-Lee WF. A review on the antinociceptive effects of *Mitragyna speciosa* and its derivatives on animal model. *Curr Drug Targets*. 2018;19:1359–65.
333. Wilson LL, Chakraborty S, Eans SO, Cirino TJ, Stacy HM, Simons CA et al. Kratom alkaloids, natural and semi-synthetic, show less physical dependence and ameliorate opioid withdrawal. *Cell Mol Neurobiol*. 2021;41(5):1131–43.
334. Wilson LL, Harris HM, Eans SO, Brice-Tutt AC, Cirino T, Stacy HM et al. Lyophilized kratom tea as a therapeutic option for opioid dependence. *Drug Alcohol Depend*. 2020;218:108310.
335. Bhowmik S, Galeta J, Havel V, Nelson M, Faouzi A, Bechand B et al. Site selective C-H functionalization of *Mitragyna* alkaloids reveals a molecular switch for tuning opioid receptor signaling efficacy. *Nature Commun*. 2021;12:3858.
336. Carpenter JM, Criddle CA, Craig HK, Ali Z, Zhang Z, Khan IA et al. Comparative effects of *Mitragyna speciosa* extract, mitragynine, and opioid agonists on thermal nociception in rats. *Fitoterapia*. 2016;109:87–90.
337. Cheaha D, Reakkamnuan C, Nukitram J, Chitttrakarn S, Phukpattaranont P, Keawpradub N et al. Effects of alkaloid-rich extract from *Mitragyna speciosa* (Korth.) Havil. on naloxone-precipitated morphine withdrawal symptoms and local field potential in the nucleus accumbens of mice. *J Ethnopharmacol*. 2017;208:129–37.
338. Harun N, Johari IS, Manor SM, Shoaib M. Assessing physiological dependence and withdrawal potential of mitragynine using schedule-controlled behavior in rats. *Psychopharmacology*. 2020;237:855–67.
339. Reanmongkol W, Keawpradub N, Sawangjaroen K. Effects of the extracts from *Mitragyna speciosa* Korth. leaves on analgesic and behavioral activities in experimental animals. *Songklanakarin J Sci Technol*. 2007;29(Suppl 1):39–48.

340. Matsumoto K, Mizowaki M, Takayama H, Sakai SI, et al. 1997. Suppressive effect of mitragynine on the 5-methoxy-N,N-dimethyltryptamine-induced head-twitch response in mice. *Pharmacology Biochemistry and Behavior*, 57(1/2), 319–323.
341. Cheaha D, Keawpradub N, Sawangjaroen K, Phukpattaranont P, Kumarnsit E. Effects of an alkaloid-rich extract from *Mitragyna speciosa* leaves and fluoxetine on sleep profiles, EEG spectral frequency and ethanol withdrawal symptoms in rats. *Phytomedicine*. 2015;22:1000–8.
342. Suhaimi FW, Hassan Z, Mansor SM, Muller CP. The effects of chronic mitragynine (kratom) exposure on the EEG in rats. *Neurosci Lett*. 2021;245:135632.
343. Fossa JD, Nayaka SU, Tallaridab CS, Farkasa DJ, et al. 2020. Mitragynine, bioactive alkaloid of kratom, reduces chemotherapy-induced neuropathic pain in rats through α -adrenoceptor mechanism. *Drug and Alcohol Dependence*, 209, 107946
344. Buckhalter S, Soubeyrand E, Ferrone SAE, Rasmussne DJ, et al. (2021) The antidepressant-like and analgesic effects of kratom alkaloids are accompanied by changes in low frequency oscillations but not Δ FosB accumulation. *Frontiers in Pharmacology* 12:696461.
345. Idayu NF, Hidayat MT, Moklas MAM, Sharida F, Raudzah ARN, Shamima AR et al. Antidepressant-like effect of mitragyline isolated from *Mitrogyna speciosa* Korth in mice model of depression. *Phytomedicine*. 2011;18:402–7.
346. Vijeepallam K, Pandey V, Kunasegaran T, Murugan DD, Naidu M. *Mitragyna speciosa* leaf extract exhibits antipsychotic-like effect with the potential to alleviate positive and negative symptoms of psychosis in mice. *Front Pharmacol*. 2016;7:464.
347. Kumnsit E, Keawpradub N, Nuankaew W. Effect of *Mitragyna speciosa* aqueous extract on ethanol withdrawal symptoms in mice. *Fitoterapia*. 2007;78:182–5.
348. Vijeepallam K, Pandey V, Murugan DD, Naidu M. Methanolic extract of *Mitragyna speciosa* Korth leaf inhibits ethanol seeking behavior in mice: involvement of antiodopaminergic mechanism. *Metab Brain Dis*. 2019;34:1713–22.
349. Meepong R, Sooksawate T. Mitragynine reduced morphine-induced conditioned place preference and withdrawal in rats. *Thai J Pharmaceut Sci*. 2019;43(1):21–9.
350. Grewal KS. The effect of mitragynine on man. *Br J Med Psychol*. 1932;12(1):41–58.
351. Tan HS, Habib AS. Oliceridine: a novel drug for the management of moderate to severe acute pain – a review of current evidence. *J Pain Manage*. 2021;14:969–79.
352. Sabetghamadan A, Navaratnam V, Mansor SM. Dose–response relationship, acute toxicity, and therapeutic index between the alkaloid extract of *Mitragyna speciosa* and its main active compound mitragynine in mice. *Drug Dev Res*. 2012;74:23–30.
353. Smith LC, Lin L, Hwang CS, Zhou B, Kubitz DM, Wang H et al. Lateral flow assessment and unanticipated toxicity of kratom. *Chem Res Toxicol*. 2019;32:113–21.
354. Safety data sheet for morphine sulfate. Version 1.1 01 April, 2017. New York City (NY): Pfizer; 2017.
355. Macko E, Weisbach JA, Douglas B. Some observations on the pharmacology of mitragynine. *Arch Int Pharmacodynam*. 1972;198:145–61.
356. Sabetghamadan A, Ramanathan S, Sasidharan S, Manor SM. Subchronic exposure to mitragynine, the principal alkaloid of *Mitragyna speciosa*, in rats. *J Ethnopharmacol*. 2013;146:815–23.
357. Harizal SN, Manour SM, Hasnan J, Tharakan KJK, Abdullah J. Acute toxicity study of the standardized methanolic extract of *Mitragyna speciosa* Korth in rodent. *J Ethnopharmacol*. 2010;131:404–9.
358. Yusoff NHM, Suhaimi FW, Vadivelu RK, Hassan Z, Rümmler A, Rotter A et al. Abuse potential and adverse cognitive effects of mitragynine (kratom). *Addict Biol*. 2014;21:98–110.
359. Kumarnsit E, Keawpradub N, Muankaew W. Acute and long-term effects of alkaloid extract of *Mitragyna speciosa* on food and water intake and body weight in rats. *Fitoterapia*. 2006;77:339–45.
360. Anwar M, Law R, Schier J. Kratom (*Mitragyna speciosa*) exposures reported to poison center –United States, 2010–2015. *Morbidity Mortal Wkly Rep*. 2016;65(29):748–9.
361. Cumpston KL, Wills RK, Carter M. Clinical outcomes after kratom exposures: a poison center case series. *Am J Emergency Med*. 2018;36:166–8.
362. Graves JM, Dilley JA, Terpak L, Brooks-Russell A, Whitehill JM, Klein TA et al. Kratom exposures among older adults reported to U.S. poison centers, 2014–2019. *J Am Geriatr Soc*. 2021;69:2176–84.

363. Post S, Spiller HA, Chounthirath T, Smith GA. Kratom exposures reported to United States poison control centers: 2011–2017. *Clin Toxicol.* 2019;57(10):847–54.
364. Davidson C, Cao D, King T, Weiss ST. A comparative analysis of kratom exposure cases in Thailand and the United States from 2010–2017. *Am J Drug Alcohol Abuse.* 2021;47(1):74–83.
365. Le Boisselier R, Bourguine J, Chretien B, Lelong-Boulouard V, Pain S. Kratom (*Mitragyna speciosa*), mitragynine and 7-hydroxymitragynine are now officially psychotropic substances: The reasons for the new regulations in France. *Fundam Clin Pharmacol.* 2021;35(Suppl 1):153–4.
366. Ballotin VR, Bigarella LG, de Mello Brandão AB, Balbinot RA, Balbinot SS, Soldara J. Herb-induced liver injury: systematic review and meta-analysis. *World J Clin Cases* 2021;9(20):5490–513.
367. Schimmel J, Dart RC. Kratom (*Mitragyna speciosa*) liver injury: a comprehensive review. *Drugs.* 2020;80:263–83.
368. Leong bin Abdullah MFI, Tan KL, Mohd IS, Yusoff NS, Chear NJY, Singh D. Lipid profile of regular kratom (*Mitragyna speciosa* Korth.) users in the community setting. *PLoS One.* 2020;15(6):e0234630.
369. La-up A, Saengow U, Aramrattana A. High serum high-density lipoprotein and low serum triglycerides in kratom users: a study of kratom users in Thailand. *Heliyon.* 2021;7(4):e06931.
370. Singh D, Murugaiyah V, Hamid SBS, Kasinather V, Chan MS, Ho ET et al. Assessment of gonadotropins and testosterone hormone levels in regular *Mitragyna speciosa* (Korth.) users. *J Ethnopharmacol.* 2018;221:30–6.
371. LeBryer L, Sharma R, Chaudhari KS, Talsania M, Scofield RH. Kratom, an emerging drug of abuse, raises prolactin and causes secondary hypogonadism: case report. *J Invest Med High Impact Case Rep.* 2018;6:103.
372. Leong bin Abdullah MFI, Singh D. The adverse cardiovascular effects and cardiotoxicity of kratom (*Mitragyna speciosa* Korth.): A comprehensive review. *Front Pharmacol.* 2021;12:726003.
373. Leong bin Abdullah MFI, Tan KL, Narayanan S, Yuvashnee N, Chear NJY, Singh D et al. Is kratom (*Mitragyna speciosa* Korth.) use associated with ECG abnormalities? Electrocardiogram comparisons between regular kratom users and controls. *Clin Toxicol (Phila).* 2021;59(5):400–8.
374. Leong bin Abdullah MFI, Singh D. Assessment of cardiovascular functioning among regular kratom (*Mitragyna speciosa* Korth.) users: A case series. *Front Pharmacol.* 2021;12:723567.
375. Leong bin Abdullah MFI, Singh D, Swogger MT, Rahim AA, Vicknasingam B. The prevalence of psychotic symptoms in kratom (*Mitragyna speciosa* Korth.) users in Malaysia. *Asian J Psychiatry.* 2019;43:197–201.
376. Saingam D, Assanangkomchai S, Geater AF, Lerkiatbundit S. Factor analytic investigation of kratom (*Mitragyna speciosa* Korth.) withdrawal syndrome in Thailand. *J Psychoactive Drugs.* 2016;48(2):76–85.
377. Singh D, Muller C, Vicknasingam BK. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. *Drug Alcohol Depend.* 2014;139:132–7.
378. Singh D, Narayanan S, Müller CP, Swogger MT, Rahim AA, Leong bin Abdullah FI et al. Severity of kratom (*Mitragyna speciosa* Korth.) psychological withdrawal symptoms. *Jo Psychoactive Drugs.* 2018;50(5):445–50.
379. Singh D, Narayanan S, Vicknasingam BK, Prozialeck WC, Ramanathan S, Zainal H et al. Severity of pain and sleep problems during kratom (*Mitragyna speciosa* Korth.) cessation among regular kratom users. *J Psychoactive Drugs.* 2018;50(3):266–74.
380. Stanciu C, Gnanasegaram SA, Ahmed S, Penders T. Kratom withdrawal: a systematic review with case series. *J Psychoactive Drugs.* 2019;51(1):12–8.
381. Wright ME, Ginsberg C, Parkison AM, Dubose M, Sherbondy M, Shores E. Outcomes of mothers and newborns to prenatal exposure to kratom: a systematic review. *J Perinatol.* 2021;41:1236–43.
382. Japarin RA, Yusoff NH, Hassan Z, Müller CP, Harun N. Cross-reinstatement of mitragynine and morphine place preference in rats. *Behav Brain Res.* 2021;399:113021.
383. Sufka KJ, Loria MJ, Lewellyn K, Zjawiony JK, Ali Z, Abe N et al. The effect of *Salvia divinorum* and *Mitragyna speciosa* extracts, fraction and major constituents on place aversion and place preference in rats. *J Ethnopharmacol.* 2014;151(10):361–4.
384. Yusoff NHM, Mansor SM, Muller CP, Hassan Z. Opioid receptors mediate the acquisition, but not the expression of mitragynine-induced conditioned place preference in rats. *Behav Brain Res.* 2017;332:1–6.

385. Yusoff NHM, Mansor SM, Muller CP, Hassan Z. Baclofen blocks the acquisition and expression of mitragynine-induced conditioned place preference in rats. *Behav Brain Res.* 2018;345:65–71.
386. Sufka KJ, Loria MJ, Lewellyn K, Zjawiony JK, et al. (2014) The effect of *Salvia divinorum* and *Mitragyna speciosa* extracts, fraction and major constituents on place aversion and place preference in rats. *Journal of Ethnopharmacology* 151(10):361–364.
387. Hemby SE, McIntosh S, Leon F, Cutler SJ, McCurdy CR. Abuse liability and therapeutic potential of the *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine. *Addiction Biol.* 2018;24:874–85.
388. Behnood-Rod A, Chellian R, Wilson R, Hiranita T, Sharma A, Leon F et al. Evaluation of the rewarding effects of mitragynine and 7-hydroxymitragynine in an intracranial self-stimulation procedure in male and female rats. *Drug Alcohol Depend.* 2020;215:108235.
389. Harun N, Hassan Z, Navaratnam V, Mansor SM, Shoaib M. Discriminative stimulus properties of mitragynine (kratom) in rats. *Psychopharmacology.* 2015;232:2227–38.
390. Gardner EL. Introduction: addiction and brain reward and anti-reward pathways. *Adv Psychosomat Med.* 2011;30:22–60.
391. Schimmel J, Amioka E, Rockhill K, Haynes CM, Black JC, Dart RC et al. Prevalence and description of kratom (*Mitragyna speciosa*) use in the United States: a cross-sectional study. *Addiction.* 2020;116:176–81.
392. Saingam D, Assanangkornchai S, Geater AF, Balhithip Q. Pattern and consequences of kratom (*Mitragyna speciosa* Korth.) use among male villagers in southern Thailand: a qualitative study. *Int J Drug Policy.* 2013;24:351–8.
393. Singh D, Muller CP, Vicknasingam BK, Mansor SM. Social functioning of kratom (*Mitragyna speciosa*) users in Malaysia. *J Psychoactive Drugs.* 2015;47(2):125–31.
394. Swogger MT, Hart E, Erowid F, Erowid E, Trabold N, Yee K et al. Experiences of kratom users: a qualitative analysis. *J Psychoactive Drugs.* 2015;47(5):360–7.
395. Bath R, Bucholz T, Buros AF, Singh D, Smith KE, Veltri CA et al. Self-reported health diagnoses and demographic correlates with kratom use: results from an online survey. *J Addiction Med.* 2020;14(3):244–52.
396. Singh D, Narayanan S, Muller CP, Swogger MT, Chear NJY, Dzulkapli EB et al. Motives for using kratom (*Mitragyna speciosa* Korth.) among regular users in Malaysia. *J Ethnopharmacol.* 2019;233:34–40.
397. Palamar JJ. Past-year kratom use in the US: estimates from a nationally representative sample. *Am J Prev Med.* 2021;61(2):240–5.
398. Wonguppa R, Kanato M. The prevalence and associated factors of new psychoactive substance use: a 2016 Thailand national household survey. *Addict Behav Rep.* 2018;7:111–5.
399. Synthetic drugs in East and Southeast Asia: latest developments and challenges. Vienna: United Nations Office on Drugs and Crime; 2020.
400. Global Drug Survey 2020 Executive summary. London: Global Drug Survey; 2020 (<https://www.globaldrugsurvey.com/gds-2020/>).
401. Corkery JM, Streete P, Claridge H, Goodair C, Papanti D, Orsolini L et al. Characteristics of deaths associated with kratom use. *J Psychopharmacol.* 2019;33(9):1102–23.
402. Eggleston W, Stoppacher R, Suen K, Marraffa JM, Nelson S. kratom use and toxicities in the United States. *Pharmacotherapy.* 2019;39(7):775–7.
403. Mata DC, Anders KM. Case series: mitragynine blood and tissue concentrations in fatalities from 2017 to 2018 in Orange County, CA, USA. *Forensic Chem.* 2019;17:100205.
404. Olsen EO, O'Donnell J, Matteson CL, Schier JG, Wilson N. Unintentional drug overdose deaths with kratom – 27 states, July 2016–December 2017. *Morbidity Mortality Wkly Rep.* 2019;68(14):326–7.
405. Schmitt J, Bingham K, Knight KD. Kratom-associated fatalities in Northern Nevada – what mitragynine level is fatal? *Am J Forensic Med Pathol.* 2021 (doi:10.1097/PAF.0000000000000695).
406. Papsun DM, Chan-Hosokawa A, Friederich L, Brower J, Graf K, Logan B. The trouble with kratom: analytical and interpretive issues involving mitragynine. *J Anal Toxicol.* 2019; 43(8):615–29.
407. Gershman K, Timm K, Frank M, Lampi L, Melamed J, Gerona R et al. Deaths in Colorado attributed to kratom. *NEMJ.* 2019;380(1):97–8.

408. Ingasathit A, Ratanasiri S, Lim S, Rattanasiri S, Chatchaipun P. Prevalence of psychoactive drug use among drivers in Thailand: a roadside survey. *Accident Anal Prev.* 2009;41:474–8.
409. *Mitragyna speciosa*. Wikipedia; 2021 (https://en.wikipedia.org/wiki/Mitragyna_speciosa, accessed 26 August 2021).
410. World Drug Report 2021. Vienna: United Nations Office on Drugs and Crime; 2021.
411. ASEAN guiding principles for inclusion into or exclusion from the negative list of substances for traditional medicines and health supplements. Annex I. Version 3.0. Association of South-East Asian Nations; 2013 ([http://www.fda.gov.ph/attachments/article/218035/ANNEX I ASEAN GP for the Negative List Ver 3.0 \(14Nov14\).pdf](http://www.fda.gov.ph/attachments/article/218035/ANNEX_I_ASEAN_GP_for_the_Negative_List_Ver_3.0_(14Nov14).pdf), accessed 3 August 2021).
412. Laohong KO. Kratom now listed as legal herb. *Bangkok Post*, 23 August 2021 (<https://www.bangkokpost.com/thailand/general/2169411/kratom-now-listed-as-legal-herb>, accessed 26 August 2021).
413. Kent CN, Park C, Lindsley CW. Classics in Chemical Neuroscience: Baclofen. *ACS Chem Neurosci.* 2020;11:1740–55.
414. Ghislieri D, Gilmore K, Seeberger PH. Chemical assembly systems: layered control for divergent, continuous, multistep syntheses of active pharmaceutical ingredients. *Angew Chem Int Ed.* 2015;54:678–82.
415. D'Oca CRM, Naciuk FF, Silva JC, Guedes EP, Moro CC, D'Oca MGM et al. New multicomponent reaction for the direct synthesis of β -aryl- γ -nitroesters promoted by hydrotalcite-derived mixed oxides as heterogeneous catalyst. *J Braz Chem Soc.* 2017;28:285–98.
416. Phenibut hydrochloride. Product information. Ann Arbor (MI): Cayman Chemical Co.; 2016 ([https://www.caymanchem.com/product/9002652/phenibut-\(hydrochloride\)](https://www.caymanchem.com/product/9002652/phenibut-(hydrochloride)), accessed 19 July 2021).
417. Allan R, Bates M, Drew C, Duke R, Hambley T, Johnston G et al. A new synthesis, resolution and in vitro activities of (R)- and (S)-²-phenyl-GABA. *ChemInform.* 1990;21.
418. Zvejniece L, Vavers E, Svalbe B, Veinberg G, Rizhanova K, Liepins A et al. R-phenibut binds to the α 2- δ subunit of voltage-dependent calcium channels and exerts gabapentin-like anti-nociceptive effects. *Pharmacol Biochem Behav.* 2015;137:23–9.
419. Perekalin VV. Synthesis of derivatives of γ -amino acids. *Dokl Akad Nauk SSSR.* 1954;95:993–5.
420. Lapin I. Phenibut (β -phenyl-GABA): a tranquilizer and nootropic drug. *CNS Drug Rev.* 2006;7(4):471–81 (doi: 10.1111/j.1527-3458.2001.tb00211.x).
421. Cologne J, Pouchal JM. Préparation de pyrrolidones-2 et de aminoacides [Preparation of 2-pyrrolidones and γ -amino acids]. *Bull Soc Chim Fr.* 1962;598–603.
422. Cignarella G, Fontanella L, Aresi V, Testa E. [Derivatives of phenylbutyrate. 3. Synthesis of compounds with potential anti-inflammatory activity correlated to 3,3'-diphenyl-N,N'-dipyrrolidine-2,2'-dione]. *Farmaco Sci.* 1968;23:321–43.
423. Gareev GA, Bovt VV, Kovalev VA, Kovalev VV. 2002. Synthesis of 3-phenyl-4-aminobutanoic acid derivatives. Russian Patent 02190595 C2. International Patent Classification: 7C07C 227/18 A; 7C07C 229/34 B.
424. Su Y, L. Z., Zhang Q. Method of preparing 4-amino-3-phenylbutyric acid. CN101033195A. China patent application; 2011.
425. Liepins V, A. L., Revjuka J. Method for producing intermediates of phenibut. Latvia patent application; 2015.
426. Zelenov MP, P. S. Z., Smirnov SI, Koryakov NYa, Arevkov YuA, Andreev VN et al. Method of preparation 3-phenyl-4-aminobutyric acid or 3-phenyl-4-aminobutyric acid chlorohydrate. Russian Federation patent application; 2001.
427. Sobocjdska M, Kupryszewski G, Zobaczewa MM. Resolution of racemic beta-phenyl-gamma-aminobutyric acid into its enantiomers and determination of their absolute configuration. *ChemInform.* 1974;5.
428. Felluga F, Gombac V, Pitacco G, Valentini E. A short and convenient chemoenzymatic synthesis of both enantiomers of 3-phenylGABA and 3-(4-chlorophenyl)GABA (Baclofen). *Tetrahedron Asymmetry.* 2005;16:1341–5.

429. Sivchik VV, H. O. G., Survilo VL, Trukhachova TV. Synthesis of β -phenyl- γ -aminobutyric acid (phenibut). Name of the journal: Фармакологический фундамент современной медицины, проблемы и пути их решения (Pharmacological foundation of modern medicine, problems and solutions). 2012, pp. 448–450
430. Biswas K, Gholap R, Srinivas P, Kanyal S, Sarma KD. β -Substituted γ -butyrolactams from mucochloric acid: synthesis of (\pm)-baclofen and other γ -aminobutyric acids and useful building blocks. RSC Adv. 2014;4:2538–45.
431. Liu H, Yuan J, Tian Q, Ji N, He W. An efficient synthesis of enantiomerically pure γ -aminobutyric acid (GABA) derivatives. J Materials Sci Chem Eng. 2017;5:25–32.
432. Biewenga L, Saravanan T, Kunzendorf A, Van Der Meer JY, Pijning T, Tepper PG et al. Enantioselective synthesis of pharmacologically active γ -aminobutyric acids using a tailor-made artificial michaelase in one-pot cascade reactions. ACS Catalysis. 2019;9:1503–13.
433. Zelle RE. Resolution of 4-phenyl-2-pyrrolidinone: a versatile synthetic intermediate. Synthesis. 1991;1023–6.
434. Vaccher C, Berthelot P, Flouquet N, Debaert M. Preparative liquid chromatographic separation of isomers of 4-amino-3-(4-chlorophenyl)butyric acid. J Chromatogr A. 1991;542:502–7.
435. Langlois N, Dahuron N, Wang HS. Enantioselective syntheses of (R)-3-phenyl GABA, (R)-baclofen and 4-arylpyrrolidin-2-ones. Tetrahedron. 1996;52:15117–26.
436. Veinberg G, Maksim. V., Lebedeva A, Chernobrovijs A, Kalvinsh I. Enzymatic resolution of racemic 3-aryl-4-aminobutyric acids. Application n.: P-06-28 (2006) PCT/EP2007/051538. Patent n.: WO2007096314A3. Issuing body: European Patent Office
437. Sobocinska M, M. M. Z., Perekalin VV, Kupryszewski G. Configuration of 4-aryl-2-pyrrolidinones and their 3-carboxy derivatives. Pol J Chem. 1979;53:435–46.
438. Wildervanck AF, M. R. C., Scott JL, Nassimbeni LR, Clauss R, Easter BRD. Process for the optical resolution of 3-(p-chlorophenyl)-glutaramide. 2000. Patent n.: EP0874804B1. Issuing body: European Patent Office
439. Sattur NBK, S. N., Nargund KS. Possible plant hormones. II. J Karnatak Univ. 1956;1:56–60.
440. Phenibut. Houston (TX): Selleckchem; 2019 (<https://www.selleckchem.com/datasheet/phenibut-S489200-DataSheet.html>, accessed 25 July 2021).
441. Starobinets GL, E. M. R. K., Sednev YuM, Lushchik YaF. Composition of ion-selective electrode membrane for determining concentration of phenibut in solutions. USSR patent application; 1985.
442. Veveris AY, Luse IA. Potentiometric differential titration of β -phenyl- γ -aminobutyric acid hydrochloride and its synthetic intermediates. Khim Farmat Zh. 1990;24:77–80.
443. Veveris AY, V. K., Birska IA, Markuns M. Spectrophotometric determination of orotic and γ -amino- β -phenylbutyric acids in their mixtures. Khim Farmat Zh. 1991;25:72–5.
444. Grinberga S, Zvejniece L, Liepinsh E, Dambrova M, Pugovics O. Quantitative analysis of phenibut in rat brain tissue extracts by liquid chromatography-tandem mass spectrometry. Biomed Chromatogr. 2008;22(12):1321–4 (doi: 10.1002/bmc.1059).
445. Azaryan AA, Temerdashev AZ, Svetlichnaya EV, Kal'nitskii AG, Balabaev IA. Determination of some cathinones, tropane alkaloids, and "pharmaceutical narcotics" in urine. J Anal Chem. 2016;71:955–64.
446. Archer JRH, Mendes F, Hudson S, Layne K, Dargan PI, Wood DM. Evaluation of long-term detection trends of new psychoactive substances in pooled urine from city street portable urinals (London, UK). Br J Clin Pharmacol. 2020;86:517–27.
447. Smirnova LA, Ryabukha AF, Kuznetsov KA, Velikopol'skaya MV, Perfilova VN, Vasil'eva OS et al. Method development for quantitative determination of the gaba derivative solifen. Pharmaceut Chem J. 2020;53:1090–2.
448. Lee HZS, Ong MC, Lim JLW, Yap TWA. Challenges in GC-MS analysis: case studies on phenibut and ethylphenidate. Forensic Sci Int. 2017;277:166–78.
449. Tyurenkov I, Perfilova VN, Smirnova LA, Ryabukha AF, Suchkov EA, Lebedeva SA. Development of a chromatographic method for quantitative analysis of phenibut in biological samples. Pharmaceut Chem J. 2011;44(12) (doi: 10.1007/s11094-011-0547-5).
450. Vaccher MP, Bonte JP, Vaccher C. Capillary electrophoretic resolution of enantiomers of aromatic amino-acids with highly sulfated α -, β - and γ -cyclodextrins. Chromatographia. 2006;64:51–5.

451. Jiang H, Yang K, Zhao X, Zhang W, Liu Y, Jiang J et al. Highly stable Zr(IV)-based metal-organic frameworks for chiral separation in reversed-phase liquid chromatography. *J Am Chem Soc.* 2021;143:390–8.
452. Downes MA, Berling IL, Mostafa A, Grice J, Roberts MS, Isbister GK. Acute behavioural disturbance associated with phenibut purchased via an internet supplier. *Clin Toxicol (Phila).* 2015;53(7):636–8 (doi: 10.3109/15563650.2015.1059945).
453. Wong A, Little M, Caldicott D, Easton C, Andres D, Greene SL. Analytically confirmed recreational use of phenibut (β -phenyl- γ -aminobutyric acid) bought over the internet. *Clin Toxicol (Phila).* 2015;53(7):783–4 (doi: 10.3109/15563650.2015.1059944).
454. Buy the best brain boosters & dietary supplements. Liftmode; 2021 (<https://liftmode.com/>, accessed 23 August 2021).
455. Graves JM, Centers for Disease Control and Prevention. Notes from the field: Phenibut exposures reported to poison centers – United States, 2009–2019. *Morbid Mortal Wkly Rep.* 2020;69 (doi: 10.15585/mmwr.mm6935a5).
456. Phenibut manufacturers, suppliers, distributors. pipelinepharma; 2021 (<https://www.pipelinepharma.com>, accessed 27 July 2021).
457. Samokhvalov AV, Paton-Gay CL, Balchand K, Rehm J. Phenibut dependence. *BMJ Case Rep.* 2013;bcr2012008381 (doi: 10.1136/bcr-2012-008381).
458. Joshi YB, Friend SF, Jimenez B, Steiger LR. Dissociative intoxication and prolonged withdrawal associated with phenibut: a case report. *J Clin Psychopharmacol.* 2017;37(4):478–80 (doi: 10.1097/JCP.0000000000000731).
459. Owen DR, Wood DM, Archer JRH, Dargan PI. Phenibut (4-amino-3-phenyl-butyric acid): availability, prevalence of use, desired effects and acute toxicity. *Drug Alcohol Rev.* 2016;35(5):591–6 (doi: 10.1111/dar.12356).
460. Maslova M, Khaunina RA. Penetration of gamma-aminobutyric acid and its phenyl derivative into the brain and their pharmacological effects in mice and rats during ontogenesis. *Evol Neurofiziol Neurokhim.* 1967;5:186–91.
461. Dambrova M, Zvejniece L, Liepinsh E, Cirule H, Zharkova O, Veinberg G et al. Comparative pharmacological activity of optical isomers of phenibut. *Eur J Pharmacol.* 2008;583(1):128–34 (doi: 10.1016/j.ejphar.2008.01.015).
462. Morley KC, Baillie A, Leung S, Addolorato G, Leggio L, Haber PS. Baclofen for the treatment of alcohol dependence and possible role of comorbid anxiety. *Alcohol Alcoholism.* 2014;49(6):654–60 (doi: 10.1093/alcalc/agu062).
463. Kukkar A, Bali A, Singh N, Singh Jaggi A. Implications and mechanism of action of gabapentin in neuropathic pain. *Arch Pharmacol Res.* 2013;36(3):237–51 (doi: 10.1007/s12272-013-0057-y).
464. Buu NT, Van Gelder NM. Biological actions in vivo and in vitro of two gamma-aminobutyric acid (GABA) analogues: beta-chloro GABA and beta-phenyl GABA. *Br Jo Pharmacol.* 1974;52(3):401–6 (doi: 10.1111/j.1476-5381.1974.tb08609.x).
465. Davies J, Watkins JC. The action of beta-phenyl-GABA derivatives on neurones of the cat cerebral cortex. *Brain Res.* 1974;70(3):501–5 (doi: 10.1016/0006-8993(74)90258-3).
466. Irie T, Yamazaki D, Kikura-Hanajiri R. F-phenibut (β -(4-Fluorophenyl)-GABA), a potent GABAB receptor agonist, activates an outward-rectifying K⁺ current and suppresses the generation of action potentials in mouse cerebellar Purkinje cells. *Eur J Pharmacol.* 2020;884:173437 (doi: 10.1016/j.ejphar.2020.173437).
467. Kupats E, Vrublevska J, Zvejniece B, Vavers E, Stelfa G, Zvejniece L et al. Safety and tolerability of the anxiolytic and nootropic drug phenibut: a systematic review of clinical trials and case reports. *Pharmacopsychiatry.* 2020;53(5):201–8 (doi: 10.1055/a-1151-5017).
468. Li W, Madhira B. Phenibut (β -phenyl- γ -aminobutyric acid) psychosis. *Am J Therapeut.* 2017;24(5):e639–40 (doi: 10.1097/MJT.0000000000000618).
469. Sankary S, Canino P, Jackson J. Phenibut overdose. *Am J Emergency Med.* 2017;35(3):516.e1–2 (doi: 10.1016/j.ajem.2016.08.067).
470. O'Connell CW, Schneir AB, Hwang JQ, Cantrell FL. Phenibut, the appearance of another potentially dangerous product in the United States. *Am J Med.* 2014;127(8):e3–4 (doi: 10.1016/j.amjmed.2014.03.029).

471. Ahuja T, Mgbako O, Katzman C, Grssman A. Phenibut (β -phenyl- γ -aminobutyric acid) dependence and management of withdrawal: emerging nootropics of abuse. *Case Rep Psychiatry*. 2018;2018:9864285 (doi: 10.1155/2018/9864285).
472. Hardman MI, Sprung J, Weingarten TN. Acute phenibut withdrawal: a comprehensive literature review and illustrative case report. *Bosnian J Basic Med Sci*. 2019;19(2):125–9 (doi: 10.17305/bjbms.2018.4008).
473. McCabe DJ, Bangh SA, Arens AM, Cole JB. Phenibut exposures and clinical effects reported to a regional poison center. *Am J Emergency Med*. 2019;37(11):2066–71 (doi: 10.1016/j.ajem.2019.02.044).
474. Marraffa JM, Nacca N, Stork CM, Hodgman M. Phenibut: one poison center's experience. *Clin Toxicol*. 2014;52:736–7.
475. Li C, Sundararajan K. An uncommon case of phenibut toxicity in an intensive care unit. *Int J Med Pharmaceut Case Rep*. 2015;5:1–621689 (doi: 10.9734/IJMP/2015/21689).
476. Isoardi KZ, Kulawickrama S, Isbister GK. Severe phenibut poisoning: an adolescent case cluster. *J Paediatrics Child Health*. 2020;56(2):330–1 (doi: 10.1111/jpc.14605).
477. VigiAccess. Geneva: World Health Organization (<http://www.vigiaccess.org/>, accessed 26 July 2021).
478. UNODC early warning advisory (EWA) on new psychoactive substances (NPS). Vienna: United Nations Office on Drugs and Crime; 2021 (<https://www.unodc.org/LSS/Home/NPS>, accessed 29 July 2021).
479. Hensselmans M. Phenibut: The Soviet smart drug. *MennoHensselmans.com*;2014 (<https://mennohensselmans.com/phenibut-dosage-effects/>, accessed 24 August 2021).
480. Van Hout MC. A narrative review of the naturally occurring inhibitory neurotransmitter gamma-aminobutyric acid (GABA) called phenibut in dietary supplements. *Performance Enhancement Health*. 2018;6(1):33–5 (doi: 10.1016/j.peh.2018.02.001).
481. Zheng KH, Khan A, Espiridion ED. Phenibut addiction in a patient with substance use disorder. *Cureus*. 2019;11(7):e5230 (doi: 10.7759/cureus.5230).
482. Goertemoeller S, Behrman A, Goetz R, Spiller HA. Retrospective review of phenibut exposures reported to Ohio poison control centers. *Clin Toxicol*. 2015;53:272.
483. Huntington S, Vohra R, Lewis JC, Iknolan J. GABA GABA Hey (I wanna be sedated): phenybut exposures reported to a statewide poison control system. *Clin Toxicol*. 2015;53(7):721–2.
484. Elamin M, Dunn M, Thomas SHL, Thanacoody HKR. Massive accidental caffeine overdose treated with continuous veno-venous haemodiafiltration (CVVHDF). In: 36th International Congress of the European Association of Poisons Centres and Clinical Toxicologists. *Clin Toxicol*. 2016;54(4):494. doi: 10.3109/15563650.2016.1165952.
485. Deyo, Z, S Stuppy, E Breden, and J Moran. "Nootropic-Lnduced Psychosis: A Case Report." In *College of Psychiatric and Neurologic Pharmacists*, (date unknown) .
486. Teter C, Varne S, Kruse C. Phenibut: High school vital sign lows, patient woes, and poison center kudos (abstract). 2017 North American Congress of Clinical Toxicology. *Clin Toxicol*. 2017;55(7).
487. Magsalin RMM, Khan AY. Withdrawal symptoms after Internet purchase of phenibut (β -phenyl- γ -aminobutyric acid)HCl. *J Clin Psychopharmacol*. 2010;30(5):648–9 (doi: 10.1097/JCP.0b013e3181f057c8).
488. 5.5.1 Phenibut submission. Wellington: New Zealand Medicines and Medical Devices Safety Authority; 2018 (<https://www.medsafe.govt.nz/profs/class/Agendas/Agen60/5.5.1-Phenibut-submission.pdf>, accessed 26 July 2021).
489. Mehilane L, Rago L, Allikmets L. *Pharmacology and clinic of phenibut*. Tartu: Ild TGU; 1990 (in Russian with English summary).
490. Phenibut manufacturers and suppliers. China phenibut manufacturers and factories. Made-in-China; 2021 (<https://www.made-in-china.com/manufacturers/phenibut.html>, accessed 27 July 2021).
491. Cavagnini F, Benti G, Invitti C, Ramella G, Pinto M, Lazza M et al. Effect of gamma-aminobutyric acid on growth hormone and prolactin secretion in man: influence of pimoizide and domperidone. *J Clin Endocrinol Metab*. 1980;51(4):789–92 (doi: 10.1210/jcem-51-4-789).
492. Psychonaut; 2021 (<https://www.psychonaut.fr/portal.php>, accessed 27 July 2021).
493. r/phenibut. Redditt; 2021 (<https://www.reddit.com/r/phenibut/>, accessed 16 July 2021).
494. Search results for query: phenibut. *Bluelight.org*; 2021 (<https://www.bluelight.org/xf/search/1265872/?q=phenibut&o=date>, accessed 23 August 2021).
495. Erowid search results for phenibut. *Erowid*; 2021 (<https://erowid.org/search.php?exclude=&q=phenibut&x=11&y=3>, accessed 23 August 2021).

496. Does phenibut support a healthy libido? Top 3 facts explored, LiftMode blog. Liftmode; 2017 (<https://liftmode.com/blog/phenibut-libido-connection/>, accessed 23 August 2021).
497. Daniel. Wondering where to buy phenibut? A summary of 13 vendors that carry the powder and capsules. Orgonlight Health; 2020 (<https://www.orgonlighthealth.com/phenibut-powder-capsules-vendors/>, accessed 27 July 2021).
498. Morris W. 5 legit places you can safely buy phenibut from. Morris Health; 2020 (<https://medium.com/morris-health/places-you-can-safely-buy-phenibut-from-71d30af15cff>, accessed 27 July 2021).
499. McNeilage A. Drug used by cosmonauts may have caused Queensland students' overdose. The Guardian, 23 February 2018 (<http://www.theguardian.com/australia-news/2018/feb/23/banned-anti-anxiety-drug-phenibut-may-have-caused-gold-coast-students-overdose>, accessed 24 August 2021).
500. Mellor L. The cosmonaut drug that may have caused a school overdose. ABC News, 22 February 2018 (<https://www.abc.net.au/news/2018-02-23/what-is-phenibut-the-drug-suspected-in-school-overdose/9475814>, accessed 24 August 2021).
501. What Is phenibut? Landmark Recovery; 2019 (<https://landmarkrecovery.com/what-is-phenibut/>, accessed 14 July 2021).
502. Phenibut: a guide to history, side effects & risk of addiction. Brentwood (TN): American Addiction Centers; 2021 (<https://americanaddictioncenters.org/phenibut>, accessed 23 August 2021).
503. The small pill (phenibut). Asheville (NC): Asheville Recovery Center; 2020 (<https://www.ashevillerecoverycenter.com/party-smart-pill-phenibut/>, accessed 19 July 2021).
504. Phenibut addiction: side effects, detox, withdrawal, and treatment. Wimberley (TX): Nova Recovery Center; 2021 (<https://novarecoverycenter.com/drugs/phenibut/>, accessed 23 August 2021).
505. IONICS. International Narcotics Control Board (2021) (https://www.incb.org/incb/en/project_ion/ionics.html, accessed 29 July 2021).
506. European Monitoring Centre for Drugs and Drug Addictio. The EU early warning system on new psychoactive substances (NPS). 2012 Annual report on the implementation of Council Decision 2005/387/JHA. Luxembourg: Publications Office of the European Union; 2013 (https://www.emcdda.europa.eu/publications/topic-overviews/eu-early-warning-system_en, accessed 29 July 2021).
507. Phenibut. Légifrance. 2021 (https://www.legifrance.gouv.fr/search/all?tab_selection=all&searchField=ALL&query=phenibut&page=1&init=true, accessed 26 July 2021).
508. Walters-Kluwer H. 55/2014 (XII. 30) EMMI Decree substances or groups of compounds classified as new psychoactive substances 55/2014. (XII. 30) EMMI rendelet az új pszichoaktív anyagok minősített anyagokról vagy vegyületsoportokról – Hatályos Jogszabályok Gyűjteménye; 2021 (<https://net.jogtar.hu/jogszabaly?docid=A1400055.EMM&searchUrl=%2Fgyorskereso%3Fkeyword%3Dphenibut>, accessed 26 July 2021).
509. Official Gazette. Rome: Ministry of Health; Decree 11 August, 2020 (<https://www.gazzettaufficiale.it/eli/id/2020/08/21/20A04540/SG?fbclid=IwAR2NYeYWpr9u2AwfyTESbUZxtsKg7ZxLQ05X3GB7VSwH2AE4sh9AcIPKBns>, accessed 26 July 2021).
510. V-1431 regarding the Minister of Health of the Republic of Lithuania in 2000 January 6 order no. 5 Amending the Lists of Narcotic Drugs and Psychotropic Substances 2019 (<https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/9aff1ef11ce911e0adfcfdb735b57421?jfwid=-bgd9aafbv>, accessed 26 July 2021).
511. 3.3. Phenibut. Canberra: Office of Health, Therapeutic Drugs Administration, Australian Government, Department of Health; 2017 (<https://www.tga.gov.au/book-page/33-phenibut>, accessed 26 July 2021).
512. International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; 4F-MDMB-BICA (4F MDMB-BUTICA); Brorphine; Metonitazene; Eutylone (bk-EBDB); BMDP (3,4-Methylenedioxy-N benzylcathinone); Kratom (mitragynine, 7-hydroxymitragynine); Phenibut; request for comments. Washington DC: Regulations.gov; 2021 (<https://www.regulations.gov/document/FDA-2021-N-0739-0001>, accessed 26 July 2021).
513. Gol'dblat IV, Lapin IP. [Phenibut potentiation of the therapeutic action of antiparkinson agents]. Zh Nevropatol Psikhiatrii Imeni S.S. Korsakova. 1986;86(8):1146–8.
514. Lapin I, Krupitsky E, Melnik V. Phenibut (-phenyl-GABA) and baclofen (chlor-phenibut) in treatment of affective disorders in alcoholic patients. Alcohol Alcoholism. 1995;30:549.
515. Orlikov A. Comparison of efficacy of imipramine, diazepam, baclofen, propranolol and placebo in patients with panic disorders. Obozr Psikh Med Psikhol Bekhtereva. 1994;4:43–8.

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

Background

As per the “Guidance on the WHO review of psychoactive substances for international control” (EB126/2010/REC1, Annex 6), Member States are invited on an annual basis to contribute to the Expert Committee on Drug Dependence review process by providing up-to-date and accurate information concerning the substances under review in advance of each meeting. For this purpose, a questionnaire is sent to Member States to gather country information on the legitimate use, harmful use, the status of national control and the potential impact of international control for each substance under evaluation. For this meeting, national focal points provided data to the Expert Committee on Drug Dependence Secretariat through the questionnaire between July and August 2021 in accordance with the WHO data-sharing policy.

The data provided by Member States have not been verified by WHO and are published as received by WHO. Moreover, the names of the countries have been removed.

Discrepancies between the data obtained through critical and pre-review reports that contain information from peer-reviewed literature and other data sources and those obtained directly from Member States may occur for the following reasons: (i) published and unpublished sources cited in critical and pre-reviews do not always reflect the most up-to-date Member State data; (ii) countries that are represented in the questionnaire may not be the same as those whose data are published in the peer-reviewed literature; and (iii) countries that publish their data in peer-reviewed literature and other reports may do so in different ways and using different reporting timelines.

Ninety-eight of 194 Member States responded to the invitation to participate to the questionnaire (12 African Region, 12 Eastern Mediterranean Region, 37 European Region, 14 Region of the Americas, 7 South-East Asia Region and 16 Western Pacific Region). Eighty-nine countries agreed to provide data in accordance with WHO data-sharing policy.

4F-MDMB-BICA

Of the 89 countries that agreed to provide data, 30 had information on 4F-MDMB-BICA (Table A1).

Table A1. Numbers of countries providing information on 4F-MDMB-BICA

Region	No. of countries that had no information	No. of countries that had information
African	8	0
Americas	9	3
Eastern Mediterranean	7	1
European	11	20
South-East Asia	2	2
Western Pacific	9	4
Total	46	30

Approved medical, scientific or industrial use

Approved medical, scientific or industrial use

None of the countries reported approved therapeutic indications for 4F-MDMB-BICA. None reported that 4F-MDMB-BICA 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

Fifteen countries (12 European, 1 Eastern Mediterranean, 1 Americas and 1 Western Pacific) reported evidence of the use of 4F-MDMB-BICA for non-medical purposes (outside the medical, industrial or scientific context). This evidence was derived primarily from data on seizures and customs (n=9).

Routes of administration and formulations

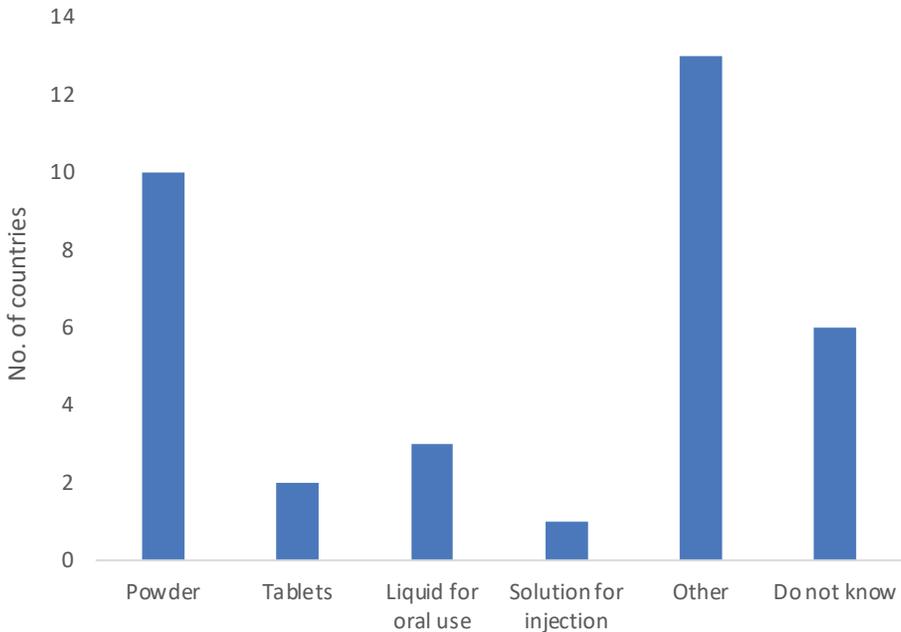
The most common reported route of administration was smoking, followed by oral and inhalation (Table A2).

Table A2. Reported routes of 4F-MDMB-BICA administration

Route of administration	No. of countries
Smoking	14
Oral	5
Inhalation	2
Sniffing	0
Injection	0
Other ^a	2
Do not know	10

^a Vaping (n=1) and “oral, but accidental” (n=1)

The most common known formulations of 4F-MDMB-BICA reported were as a powder and as part of a herbal mixture (Fig. A1).

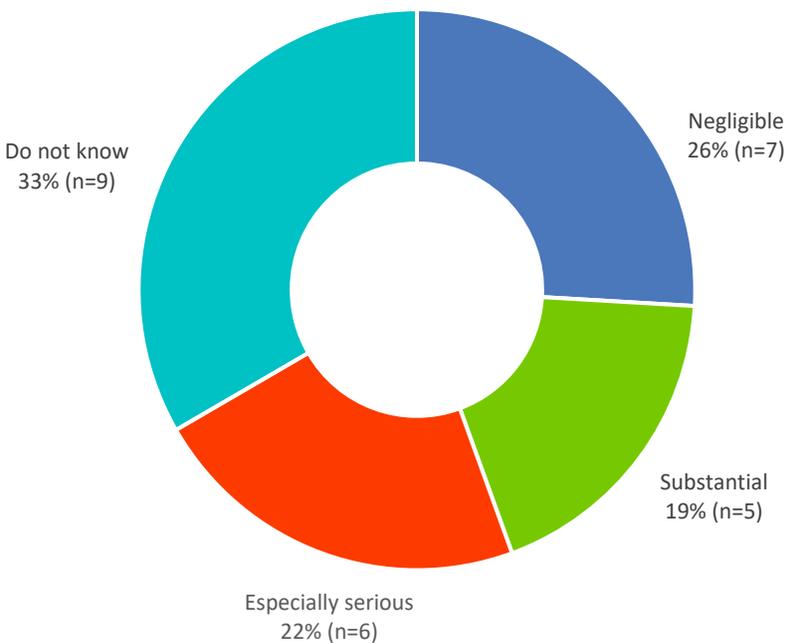
Fig. A1. Formulations of 4F-MDMB-BICA

Other formulations most commonly referred to were herbal mixture or plant material (n=11) and blotters or paper (n=2).

Perceived negative health impact

Eleven 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 4F-MDMB-BICA was “especially serious” or “substantial” (Fig. A2). Four countries (European) reported the occurrence of seizures, and four (2 European, 1 Eastern Mediterranean, 1 South-East Asia) described effects such as psychological dependence, hallucinations, mood disorders, paranoia, aggression, chest pain, respiratory problems, tremor and seizures. An additional country (Americas) noted that 4F-MDMB-BICA had been identified in over 26 toxicology cases.

Fig. A2. Negative health impacts of non-medical consumption of 4F-MDMB-BICA



Emergency department visits

Four countries (3 European, 1 South-East Asia) were aware of emergency department visits related to 4F-MDMB-BICA. One country in Europe described an emergency visit involving a non-fatal accidental poisoning of a 13-month-old child. Another described eight emergency presentations by people who had consumed 4F-MDMB-BICA with other substances, who had a wide range of symptoms, the most common being reduced consciousness (seven of the eight cases) and increased liver enzyme activity (suggesting abnormal liver function; five cases). One South-East Asian country reported confusion and memory loss in emergency department patients.

Deaths

Two countries (1 European, 1 Americas) reported a total of 25 4F-MDMB-BICA-related deaths between 2018 and 2020. One country (European) reported three deaths in 2020 in which another substance was also involved. One country (Americas) reported 22 4F-MDMB-BICA-related deaths in which another substance was also involved, also in 2020.

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 4F-MDMB-BICA.

Current control activities

Twenty-five countries (17 European, 4 Western Pacific, 2 Americas, 1 Eastern Mediterranean, 1 South-East Asia) responded that the availability of 4F-MDMB-BICA was currently regulated under national legislation. Table A3 shows the main reported control activities for 4F-MDMB-BICA.

Table A3. Reported activities for control of 4F-MDMB-BICA for purposes other than medical, scientific or industrial use

Activity	No. of countries
Smuggling (from other countries)	10
Trafficking	6
Internet sales (from abroad to buyers in respondent's country)	7
Internet sales (other or location of sellers and website unknown)	5

Activity	No. of countries
Internet sales (seller or website located in respondent's country)	3
Manufacture of the substance by chemical synthesis	2
Direct sales	2
Production of consumer products containing the substance	1
Manufacture of the substance by extraction from other products	1
Diversion	1
Do not know	9
Othera	3

a Includes "As there has been seizures of this substance, we know there must be activities going on, but we do not know the source", "seizures by customs" and "use for recreational purposes".

Seizures

Six countries (3 European, 1 Western Pacific, 1 South-East Asia) reported seizures in 2021. The number of seizures per country ranged from 3 to 185 and the amounts seized ranged from 7.75 g to 19 kg (Table A4). Eleven countries (8 European, 1 Western Pacific, 1 South-East Asia, 1 Americas) reported seizures in 2020. The number of seizures per country ranged from 1 to 254 and the amounts seized from 0.155 g to 23 t.

Table A4. Reported seizures of 4F-MDMB-BICA

Year	No. of countries that reported seizures	No. of seizures
2021	7	247
2020	11	537

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 4F-MDMB-BICA.

Brorphine

Of the 89 countries that agreed to provide data, 17 had information on brorphine (Table A5).

Table A5. Numbers of countries that provided information on bupropion

Region	No. of countries with no information	No. of countries with information
African	5	0
Americas	9	3
Eastern Mediterranean	8	0
European	18	12
South-East Asia	4	0
Western Pacific	10	2
Total (71)	54	17

Approved medical, scientific or industrial use

No countries reported any approved human medical products, therapeutic indications, scientific use or industrial use relating to bupropion.

Epidemiology of non-medical use

Five countries (3 European, 2 Americas) described seizures, reports from health professionals and reports from toxicology laboratories as evidence of non-medical use of bupropion in their country (use outside the medical, industrial or scientific context).

Routes of administration and formulations

The most commonly reported routes of bupropion administration were oral and injection (Table A6).

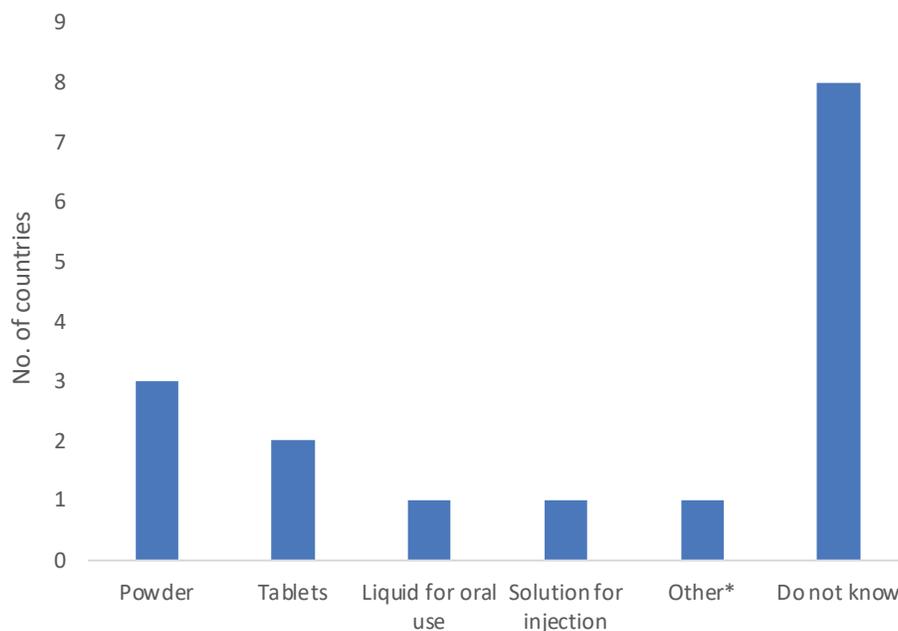
Table A6. Reported routes of bupropion administration

Route of administration	No. of countries
Oral	3
Injection	2
Sniffing	1
Smoking	1
Do not know	9
Other ^a	1

^a Rectal route of bupropion administration

The most commonly reported formulation of brorphine was powder (Fig. A3).

Fig. A3. Formulations of brorphine

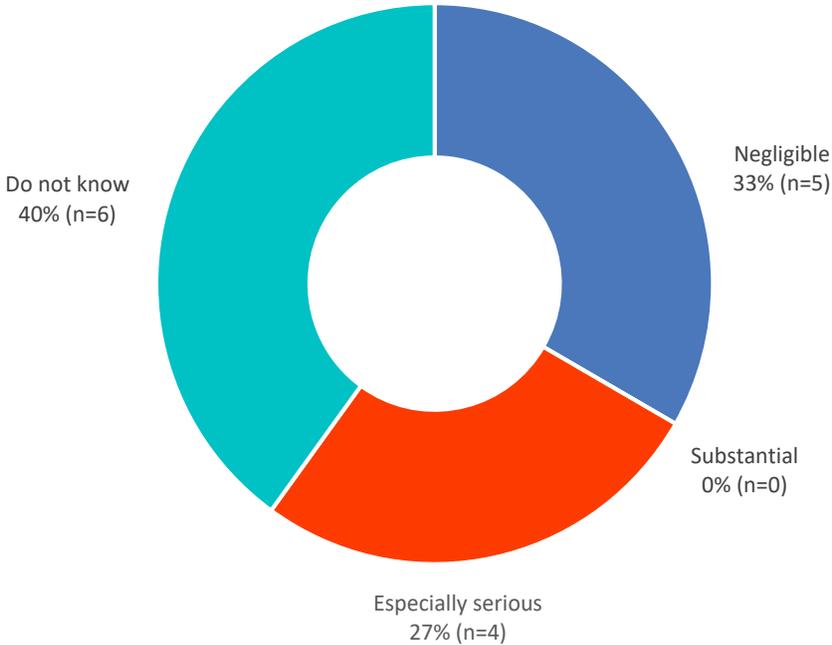


* Other brorphine formulation included “rock, capsule, unspecified liquid”.

Perceived negative health impact

Four countries (4 European, 1 Americas, 1 Western Pacific) reported the negative health impact of non-medical consumption of brorphine as “especially serious” (Fig. A4). One country (Americas) noted “Brorphine has been encounter[ed] on the illicit market and has been positively identified in over 120 toxicology cases”.

Fig. A4. Countries that reported a negative health impact of non-medical consumption of brrorphine



Emergency department visits

No countries were aware of emergency department visits related to brrorphine.

Deaths

No countries reported any deaths in which brrorphine was the only substance involved. One country (Americas) reported 120 deaths in 2020 in which brrorphine and another substance(s) were involved.

Drug dependence

Two countries (European) reported that they were aware of people presenting for drug dependence treatment due to use of brrorphine.

Current control activities

Ten countries (8 European, 2 Americas) reported the availability of brrorphine is currently regulated under national legislation. One country (European) stated brrorphine “has been placed under control as a narcotic substance due to the

potential risks posed by the opioid receptor activity and due to the documented fatalities in other countries. The assessment and control have been made and placed nationally.”

Table A6 shows the reported control activities involving buprenorphine.

Table A6. Reported control activities for use of buprenorphine for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	2
Internet sales (seller or website located in respondent's country)	2
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
Othera	1
Do not know	9

a “Other activities are present as buprenorphine has been identified in seized samples.”

Seizures

Two countries (Americas) reported 1–12 seizures of buprenorphine in 2021 (Table A7). Three countries (5 European, 2 Americas) reported 1–112 seizures of buprenorphine in 2020 in quantities of 0.05–1717 g. Two countries (Americas) reported 6–8 seizures of buprenorphine in 2019.

Table A7. Reported seizures of buprenorphine

Year	No. of countries reporting seizures	No. of seizures
2021	2	13
2020	3	117
2019	2	14

Fourteen countries (11 European, 2 Americas, 1 Western Pacific) reported that they had forensic laboratory capacity to analyse buprenorphine.

Metonitazene

Of the 89 countries that agreed to provide data, 15 had information on metonitazene (Table A8).

Table A8. Numbers of countries that provided information on metonitazene

Region	No. of countries with no information	No. of countries with information
African	4	0
Americas	9	3
Eastern Mediterranean	6	0
European	20	10
South-East Asia	4	0
Western Pacific	9	2
Total (67)	52	15

Approved medical, scientific or industrial use

No countries reported therapeutic indications, scientific use or industrial use for metonitazene.

Epidemiology of non-medical use

Four countries (2 European, 2 Americas) reported evidence from health professionals and law enforcement bodies of non-medical use of metonitazene in their country (use outside the medical, industrial or scientific context).

Routes of administration and formulations

The most commonly reported routes of administration for metonitazene were oral and injection (Table A9).

Table A9. Reported routes of metonitazene administration

Route of administration	No. of countries
Oral	2
Injection	2
Smoking	1
Do not know	9

The most commonly reported formulation of metonitazene was powder (Fig. A5).

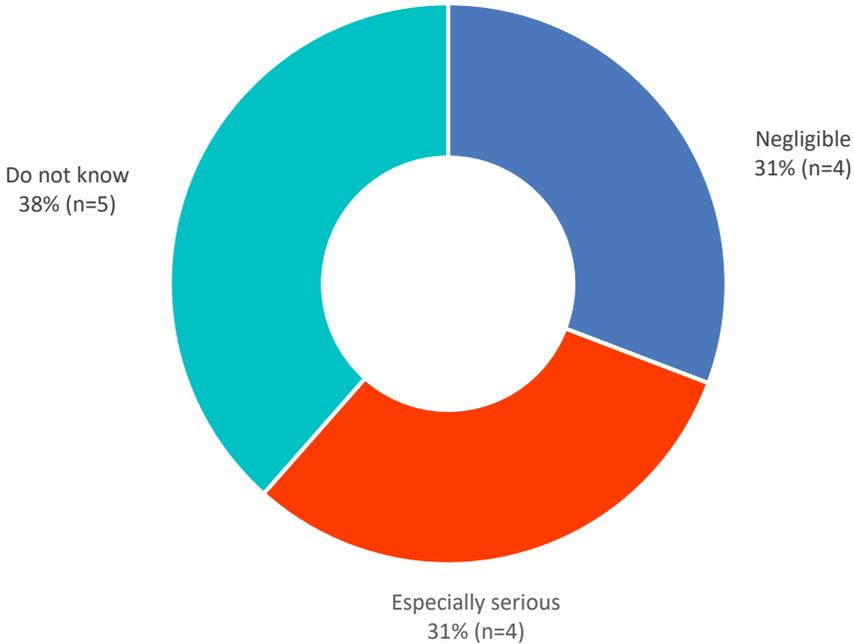
Fig. A5. Formulations of metonitazene



Perceived negative health impact

Four countries (2 European, 2 Americas) reported that the negative health impact of non-medical consumption of metonitazene was “especially serious” (Fig. A10). One country (Americas) reported that “metonitazene has been encountered on the illicit drug market and has been positively identified in 20 postmortem cases.” Another country (Americas) reported that “one death due to metonitazene was confirmed in a public health alert made by [a jurisdiction’s] chief medical examiner.” One country (European) noted that metonitazene had been identified in the femoral blood of a fatality.

Fig. A10. Countries that reported negative health impacts of non-medical consumption of metonitazene



Emergency department visits

No countries were aware of emergency department visits related to metonitazene.

Deaths

One country (Americas) reported a death in 2019 in which metonitazene was the only substance involved. Two countries (1 European, 1 Americas) reported deaths in which metonitazene and other substances were involved – 20 deaths in 2021 (Americas) and 1 death in 2020 (European).

Drug dependence

No countries reported they were aware of people presenting for drug dependence treatment in their country due to use of metonitazene.

Current control activities

Nine countries (7 European, 1 Americas, 1 Western Pacific) reported the availability of metonitazene is currently regulated under national legislation. Table A10 shows the reported control activities involving metonitazene.

Table A10. Reported control activities for use of metonitazene other than medical, scientific or industrial

Activity	No. of countries
Trafficking	1
Internet sales (from abroad to buyers in respondent's country)	1
Internet sales (other or location of sellers and website unknown)	1
Othera	1
Do not know	9

a Other metonitazene activities: "This substance has been anecdotally identified in investigations e.g. in 2018. The substance has been listed in internet markets with the involvement of known sites investigated in cases concerning other, already controlled substances".

Seizures

Two countries (Americas) reported 61–142 seizures of metonitazene in 2021 (Table A11). One country (Americas) reported 105 seizures of metonitazene in 2020.

Table A11. Reported seizures of metonitazene

Year	No. of countries reporting seizures	No. of seizures
2021	2	203
2020	1	105

Thirteen countries (9 European, 2 Americas, 2 Western Pacific) reported that they had the forensic laboratory capacity to analyse metonitazene.

Eutylone

Of the 89 countries that agreed to provide data, 32 had information on eutylone (Table A12).

Table A12. Numbers of countries that provided information on eutylone

Region	No. of countries with no information	No. of countries with information
African	6	0
Americas	8	4
Eastern Mediterranean	6	1
European	8	22
South-East Asia	3	1
Western Pacific	7	4
Total (70)	38	32

Approved medical, scientific or industrial use

No countries reported therapeutic indications, scientific use or industrial use for eutylone.

Epidemiology of non-medical use

Twenty countries (16 European, 3 Americas, 1 Western Pacific) reported evidence of non-medical use of eutylone in their country (outside the medical, industrial or scientific context). This information was primarily derived from seizures (n=11), early warning systems (n=2) and drug checking services (n=2). One country (European) noted “More seizures by the police than made by customs control, which could indicate more filtration within the country.”

Routes of administration and formulations

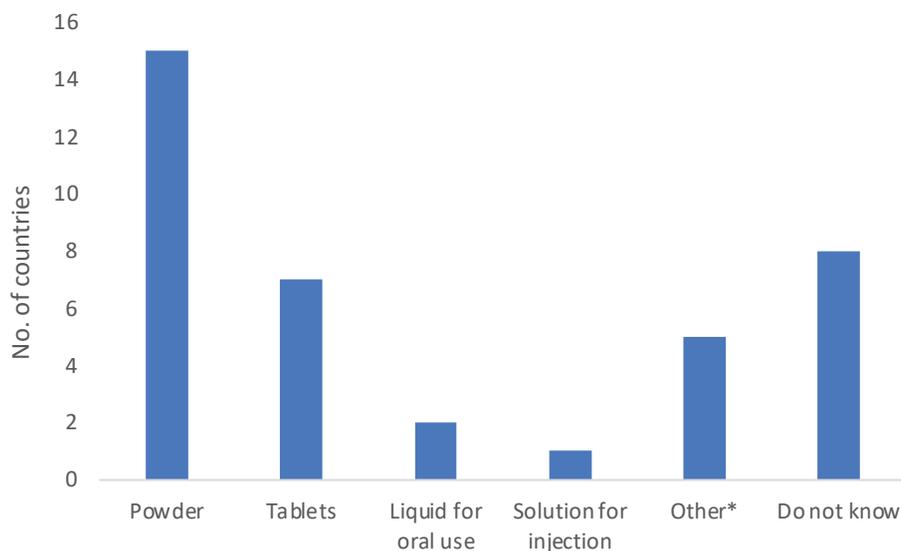
The most commonly reported routes of eutylone administration were oral and sniffing (Table A13).

Table A13. Reported routes of eutylone administration

Route of administration	No. of countries
Oral	8
Sniffing	4
Smoking	3
Injection	3
Inhalation	1
Do not know	15

The most commonly reported formulation of eutylone was powder (Fig. A6).

Fig. A6. Formulations of eutylone

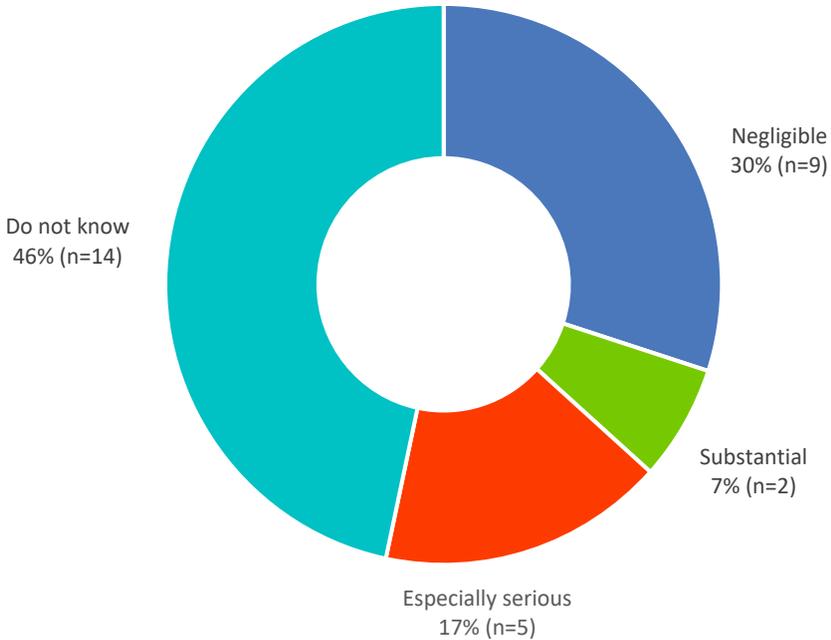


a Other eutylone formulations included crystals (n=2), plant/vegetable matter (n=2) and “rock, drug patch, unspecified liquid, capsule, paper” (n=1).

Perceived negative health impact

Seven countries (4 European, 2 Americas, 1 Western Pacific) reported that the health effect of non-medical consumption of eutylone was “substantial” or “especially serious” (Fig. A7). One country (Americas) remarked “Eutylone has been encountered on the illicit drug market and has been positively identified in over 40 toxicology cases.”

Fig. A7. Numbers of countries that reported a negative impact of non-medical consumption of eutylone on health



Emergency department visits

Two countries (2 European) were aware of emergency visits related to eutylone. One country reported symptoms of hallucinations, dysphoria, headache, tachycardia and profuse sweating. Another country reported that eutylone was detected in four cases, all in combination with other substances.

Deaths

Two countries (European) reported deaths in which eutylone was involved. It was not known whether other substances were also involved. One country reported one death involving eutylone in 2019.

Drug dependence

One country (European) reported that people presented for drug dependence treatment due to use of eutylone.

Current control activities

Twenty-three countries (15 European, 3 Americas, 4 Western Pacific, 1 South-East Asia) reported that the availability of eutylone is currently regulated under national legislation. Table A14 shows the reported control activities for eutylone.

Table A14. Reported control activities for use of eutylone for purposes other than medical, scientific or industrial

Activity	No. of countries
Internet sales (from abroad to buyers in respondent's country)	7
Internet sales (other or location of sellers and website unknown)	7
Trafficking	7
Smuggling (from other countries)	6
Manufacture of the substance by chemical synthesis	1
Internet sales (seller or website located in respondent's country)	2
Direct sales	1
Other	3
Do not know	14

Seizures

Five countries (2 European, 2 Americas, 1 Western Pacific) reported 1–3471 seizures of eutylone in 2021 in quantities of 129–19 868 g (Table A15). Sixteen countries (10 European, 3 Western Pacific, 2 Americas, 1 South-East Asia) reported 1–11 451 seizures of eutylone in 2020 in quantities of 4.12–76 613 g. Nine countries (6 European, 2 Americas, 1 Western Pacific) reported 1–5403 seizures of eutylone in 2019 in quantities of 4–37 830 g.

Table A15. Reported seizures of eutylone

Year	No. of countries that reported seizures	No. of seizures
2021	5	3532
2020	16	11 628
2019	9	5472

Twenty-nine countries (21 European, 4 Western Pacific, 3 Americas, 1 South-East Asia) reported that they had the forensic laboratory capacity to analyse eutylone.

Benzylone

Of the 89 countries that agreed to provide data, 20 had information on benzylone (Table A16).

Table A16. Numbers of countries that provided information on benzylone

Region	No. of countries with no information	No. of countries with information
African	5	0
Americas	9	3
Eastern Mediterranean	8	0
European	16	14
South-East Asia	4	0
Western Pacific	8	3
Total (70)	50	20

Approved medical, scientific or industrial use

No countries reported any approved human medical products, therapeutic indications, scientific use or industrial use related to benzylone.

Epidemiology of non-medical use

Five countries (4 European, 1 Americas) described seizures and reports from health professionals as evidence of non-medical use of benzylone in their country (outside the medical, industrial or scientific context).

Routes of administration and formulations

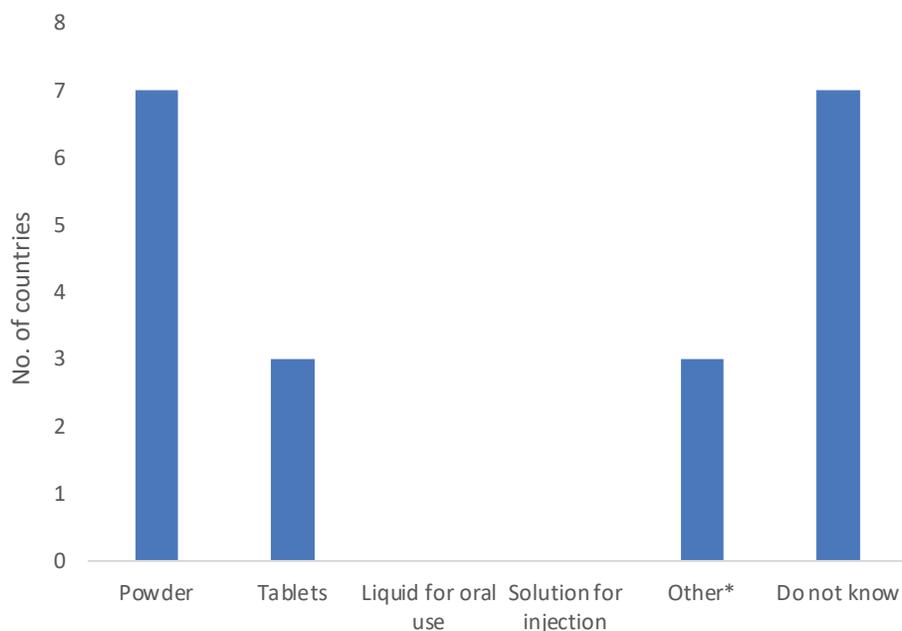
The most commonly reported routes of benzylone administration were oral and smoking (Table A17).

Table A17. Reported routes of benzyllone administration

Route of administration	No. of countries
Oral	2
Smoking	2
Inhalation	1
Sniffing	1
Injection	1
Other ^a	1
Do not know	12

^a Rectal use

The most commonly reported formulation of benzyllone was powder (Fig. A8).

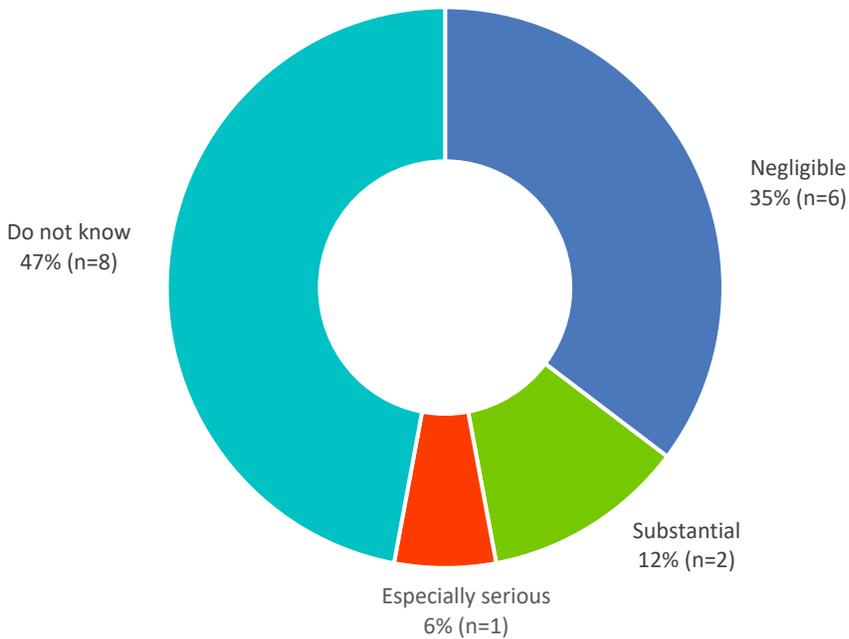
Fig. A8. Formulations of benzyllone

^a Three countries described other benzyllone formulations: “capsule and crystalline” (n=1), crystal powder (n=1) and “rock, capsule, drug patch, plant or vegetable matter” (n=1).

Perceived negative health impact

Three countries (1 Americas, 1 European, 1 Western Pacific) reported that the negative health impact due to non-medical consumption of benzylone was “substantial” or “especially serious” (Fig. A9). These countries did not specify the nature of the health impacts.

Fig. A9. Countries that reported negative health impacts of non-medical consumption of benzylone



Emergency department visits

No countries were aware of emergency department visits related to benzylone.

Deaths

No countries reported any deaths in which benzylone was the only substance involved. One country (European) reported a death in 2019 in which benzylone and another substance(s) were involved.

Drug dependence

No countries reported they were aware that people presented for drug dependence treatment due to use of benzylone.

Current control activities

Eleven countries (7 European, 2 Western Pacific, 2 Americas) responded that the availability of benzylone is currently regulated under national legislation. Table A18 shows the reported control activities for benzylone.

Table A18. Reported control activities for use of benzylone for purposes other than medical, scientific or industrial

Activity	No. of countries
Trafficking	5
Internet sales (other or location of sellers and website unknown)	4
Smuggling (from other countries)	3
Internet sales (from abroad to buyers in respondent's country)	3
Internet sales (seller or website located in respondent's country)	2
Manufacture of the substance by chemical synthesis	1
Direct sales	1
Do not know	10

Seizures

Four countries (2 Americas, 1 European, 1 Western Pacific) reported 2–105 seizures of benzylone in 2021 (Table A19). Seven countries (5 European, 2 Americas) reported 1–587 seizures of benzylone in 2020 in quantities of 0.26–3244 g. Nine countries (5 European, 2 Americas, 2 Western Pacific) reported 1–780 seizures of benzylone in 2019 in quantities of 1–1022 g.

Table A19. Reported seizures of benzylone

Year	No. of countries that reported seizures	No. of seizures
2021	4	123
2020	7	659
2019	9	859

Eighteen countries (13 European, 3 Western Pacific, 2 Americas) reported that they had the forensic laboratory capacity to analyse benzylone.

Kratom, mitragynine, 7-hydroxymitragynine

Of the 89 countries that agreed to provide data, 35 had information on kratom, mitragynine and 7-hydroxymitragynine (Table A20).

Table A20. Numbers of countries providing information on kratom, mitragynine and 7-hydroxymitragynine

Region	No. of countries without information	No. of countries with information on substance
African	5	0
Americas	7	5
Eastern Mediterranean	6	0
European	10	21
South-East Asia	2	2
Western Pacific	5	7
Total (70)	35	35

Approved medical, scientific or industrial use

No countries reported approved human or veterinary products containing kratom, mitragynine or 7-hydroxymitragynine.

Medical use

One country (South-East Asia) described use of kratom, mitragynine and 7-hydroxymitragynine in traditional medicine.

Scientific use

Three countries (2 Americas, 1 Western Pacific) reported that kratom, mitragynine and 7-hydroxymitragynine are currently used in medical or scientific research (excluding use as an analytical standard), such as in clinical trials for a human or veterinary indication. One country (Americas) reported government-sponsored research on the “basic pharmacology and potential therapeutic value of mitragynine for disorders, including opioid withdrawal syndrome”. Another country (Americas) described a “phase I trial to evaluate the safety of different

kratom-related formulations in healthy adult participants”. One country (Western Pacific) stated that “scientific research” was being conducted, with no further details.

Industrial use

One country (Americas) stated that kratom, mitragynine and 7-hydroxymitragynine were being used for industrial or other non-medical and non-scientific purposes in their country, specifically, for industrial purposes related to rubber.

Epidemiology of non-medical use

Eighteen countries (12 European, 3 Americas, 1 South-East Asia, 2 Western Pacific) reported evidence of the non-medical use of kratom, mitragynine and 7-hydroxymitragynine (outside the medical, industrial or scientific context).

Routes of administration and formulations

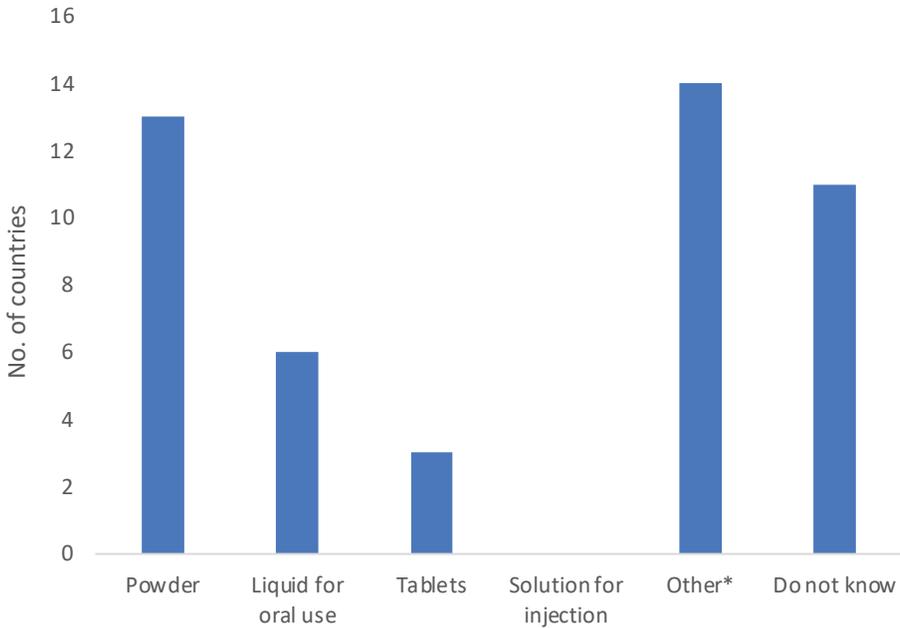
The most common routes of administration of kratom, mitragynine and 7-hydroxymitragynine reported were oral and smoking (Table A21).

Table A22. Reported routes of administration of kratom

Route of administration	No. of countries
Oral	14
Smoking	5
Inhalation	1
Sniffing	1
Injection	0
Othera	3
Do not know	13

a Other routes of administration included tea or hot-water extraction (n=3 countries) and chewing (n=1; same country that specified tea).

The most commonly reported formulations of kratom, mitragynine and 7-hydroxymitragynine were powder, herbal mixture and liquid for oral administration (Fig. A10). One country (European) specified that “the seizures have been herbal material as raw or fine powder, e.g. for infusion and capsules containing the powdered herbal material for oral use”.

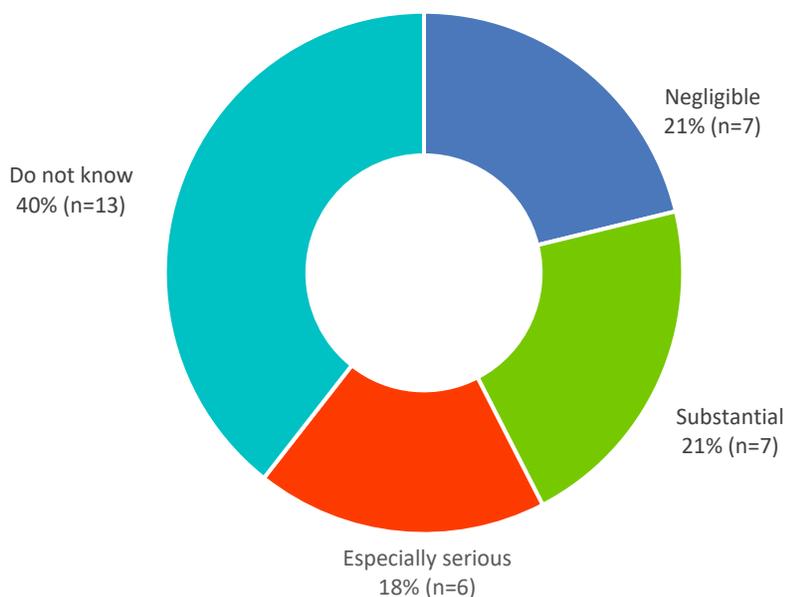
Fig. A10. Formulations of kratom, mitragynine and 7-hydroxymitragynine

a 14 countries noted other formulations, mainly herbal mixtures (n=13) and capsules (n=5).

Perceived negative health impact

Thirteen countries (6 European, 3 Americas, 1 South-East Asia, 3 Western Pacific) reported that the negative health impact of kratom, mitragynine and 7-hydroxymitragynine non-medical consumption is “especially serious” or “substantial” (Fig. A11).

Fig. A11. Countries that reported negative health impacts of the non-medical consumption of kratom, mitragynine and 7-hydroxymitragynine



One country (Americas) noted “Mitragynine has been encountered on the illicit drug market and has been positively identified in 583 postmortem cases”. Another country in the same Region noted “There has been at least one death believed to be caused by kratom intoxication”. A second country in the Americas reported that their adverse reaction database contained three hospital reports involving kratom of events (one of each) of acute hepatic failure, acute kidney injury, cholecystitis, cholelithiasis, dizziness, gastro-oesophageal reflux disease, increased hepatic enzyme activity, hepatitis, malaise, mental disorder, mental impairment, nausea, rhabdomyolysis and positive test for Salmonella.

One country (European region) reported that kratom, mitragynine and 7-hydroxymitragynine had been associated with “seizures and findings in femoral blood in cases of deaths, poison information centre calls”.

A country (Western Pacific) that noted a “substantial” negative health impact of kratom, mitragynine and 7-hydroxymitragynine in their country further remarked that “traditionally it may have been consumed for some health benefits. Based on a study on kratom users conducted by [a university in our

country] kratom consumption was found to not cause impairment in quality of life of kratom users except for severe kratom dependence which may cause deterioration in physical well-being of users. Nevertheless, we have also seen reports by [our police force] regarding seizures of concoctions of kratom mixed with other substances (i.e. Coke, cough syrup) for consumption, indicating some form of substance abuse. In addition to the fact that consumption of kratom can cause dependence, this is a significant cause for concern to public health.”

Emergency department visits

Six countries (3 European, 2 Americas, 1 South-East Asian) were aware of visits to emergency departments related to kratom, mitragynine and 7-hydroxymitragynine. Five of the countries (2 European, 2 Americas, 1 South-East Asian) expanded on the emergency visits. One country (South-East Asia) described such patients as presenting with “running nose, watery eyes, insomnia”. One country (Americas) reported data from a national poison control data system, which had noted “there have been incidence of agitation, tachycardia, drowsiness, seizure, respiratory depression, and coma”. One country (European) noted “Since 2007, at least 30 patients have presented symptoms after consumption (sic) of kratom, mitragynine, 7-hydroxymitragynine alone or in association with other substances. Use disorder, dependency, withdrawal syndrome, anorexia/weight loss, psychiatric decompensation, toxic hepatitis. Nausea, abdominal pains, respiratory depression”. Another country (European) noted that kratom had been consumed with other substances in all the presentations to an emergency department, with “Reduced consciousness, tachycardia, hypertension, agitation, hallucination, paranoid ideation, hyponatraemia, ALT/AST increased, CK increased, hypothermia, abnormal sweating, vomiting, seizure, mydriasis, epilepsy, bradycardia, depression”.

Deaths

Two countries (1 European, 1 Americas) reported deaths, one in 2018 and one in 2020, in which kratom (including the alkaloids mitragynine and 7-hydroxymitragynine) was the only substance involved.

Six countries (4 European, 2 Americas) reported a total of 590 fatalities between 2013 and 2020 in which kratom, mitragynine, 7-hydroxymitragynine and other substances were involved. One country (Americas) reported most (583) of the deaths in which kratom and other substances were involved between 2013 and 2018.

One country (European) reported a death related to kratom, mitragynine and 7-hydroxymitragynine in 2020 in which it was not known whether other substances were involved.

Drug dependence

Four countries (2 European, 1 South-East Asian, 1 Americas) reported that people presented for drug dependence treatment in their country due to use of kratom, mitragynine and 7-hydroxymitragynine.

Current control activities

Eighteen countries (14 European, 4 Western Pacific) replied that the availability of kratom, mitragynine and 7-hydroxymitragynine is currently regulated under national legislation. A country in the Americas reported that as mitragynine is an isomer a controlled drug, mitragynine is also under the control of [the list of narcotic drugs that can have medical use].

Table A23 shows the main reported control activities for kratom, mitragynine and 7-hydroxymitragynine.

Table A23. Reported control activities for kratom, mitragynine and 7-hydroxymitragynine for purposes other than medical, scientific or industrial use

Activity	No. of countries
Trafficking	9
Smuggling (from other countries)	8
Internet sales (seller or website located in respondent's country)	5
Internet sales (other or location of sellers and website unknown)	5
Internet sales (from abroad to buyers in respondent's country)	4
Production of consumer products containing the substance	2
Direct sales	2
Diversion	1

Seizures

Eight countries (4 European, 2 Western Pacific, 2 Americas) reported 1–2546 seizures of kratom, mitragynine and 7-hydroxymitragynine in 2021 in quantities ranging from 4 g to 156 891 kg (Table A24). Thirteen countries (7 European, 4 Western Pacific, 2 Americas) reported 1–4970 seizures of kratom, mitragynine and 7-hydroxymitragynine in 2020 in quantities ranging from 15 g to 298 120 kg. Nine countries (5 European, 2 Western Pacific, 2 Americas) reported 1–3882 seizures of kratom, mitragynine and 7-hydroxymitragynine in 2019, in quantities ranging from 428 g to 162 945 kg.

Table A24. Reported seizures of kratom

Year	No. of countries that reported seizures	No. of seizures
2021	8	2668
2020	13	5478
2019	9	4485

Thirty-two countries (20 European, 6 Western Pacific, 3 Americas 2 South-East Asia) have the forensic laboratory capacity to analyse kratom, mitragynine and 7-hydroxymitragynine.

Phenibut

Of the 89 countries that agreed to provide data, 22 had information on phenibut (Table A25).

Table A25. Numbers of countries that provided information on phenibut

Region	No. of countries with no information	No. of countries with information
African	5	0
Americas	8	4
Eastern Mediterranean	6	0
European	14	16
South-East Asia	5	0
Western Pacific	7	2
Total (67)	45	22

Approved medical, scientific or industrial use

Medical use

One country (European) reported approved human medical products containing phenibut: “Phenibut is used for anxiety, asthenia, trouble sleeping (insomnia), speech disorder and tics in children, Meniere’s disease, dizziness and etc.”

Scientific use

No country reported that phenibut was currently used in medical or scientific research, such as in clinical trials for a human or veterinary indication (excluding use as an analytical standard).

Industrial or other non-medical, non-scientific use

One country (European) reported that phenibut was sold on the Internet as a food supplement.

Epidemiology of non-medical use

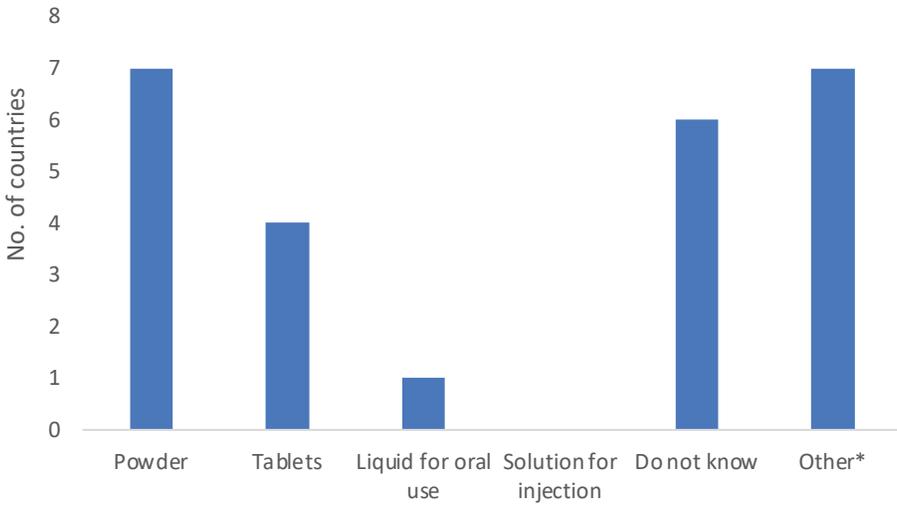
Twelve countries (9 European, 3 Americas) reported non-medical use of phenibut. Six cited evidence from seizures, and four countries reported that phenibut was sold on the Internet, sometimes as a dietary supplement.

Routes of administration and formulations

The only reported route of phenibut administration was oral (Table A26), and the most commonly reported formulations of phenibut were powder, tablets and capsules (Fig. A12).

Table A26. Reported routes of phenibut administration

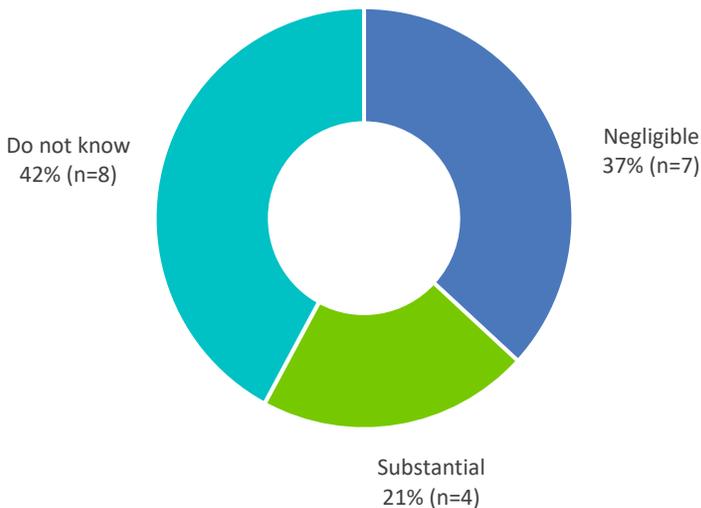
Route of administration	No. of countries
Oral	10
Smoking	0
Inhalation	0
Sniffing	0
Injection	0
Other	0
Do not know	7

Fig. A12. Formulations of phenibut

a All other formulations (n=7) were capsules.

Perceived negative health impact

Four countries (3 Americas, 1 European) reported that the negative health impact due to non-medical consumption of phenibut was “substantial” (Fig. A13).

Fig. A13. Countries that reported negative health effects of non-medical consumption of phenibut

Three countries (1 European, 2 Americas) reported further information on the extent and magnitude of public health problems and social harm caused by use of phenibut. One country (European) reported phenibut-related seizures and calls to poisoning centres. One in the Americas stated “Phenibut use and misuse can result in sedation, respiratory depression, and reduced levels of consciousness, as well as withdrawal symptoms including anxiety, agitation, and acute psychosis” and that “Phenibut has also been encountered on the illicit drug market”.

A second country in the Americas cited a hospital report from their adverse reaction database of a patient who had “consumed oral phenibut which is the suspected cause of the below adverse effects. The patient had also consumed a Red Bull energy drink, l-arginine, and omega-3”. The adverse effects were agitation, decorticate posture, drug withdrawal syndrome, hypertension, hypothermia, overdose, restlessness, tachycardia, and urinary incontinence.

Emergency department visits

Three countries (2 European, 1 Americas) were aware of visits to emergency departments related to phenibut. One country (European) further described clinical symptoms in a case in which phenibut was used in combination with other drugs: a Glasgow coma scale score of three, bradycardia, slight prolongation of QT, hypertonia, agitation, stereotyped movements, requiring intubation with sedation, fluctuating hyperthermia, encephalopathy, rhabdomyolysis, persistent vomiting and drowsiness, then transition to a state of euphoria, excitement and aggression, tremors, chills, tachycardia, hallucinations, mydriasis, insomnia, obtundation and extrasystole.

Deaths

No countries reported deaths in which phenibut was involved.

Drug dependence

Three countries (2 European, 1 Americas) reported they were aware that people presented for drug dependence treatment due to use of phenibut.

Current control activities

Eight countries (6 European, 1 Western Pacific, 1 Americas) replied that the availability of phenibut is currently regulated under national legislation. Table A27 shows reported activities for phenibut.

Table A27. Reported control activities for phenibut when used for purposes other than medical, scientific or industrial

Activity	No. of countries
Internet sales (other or location of sellers and website unknown)	6
Internet sales (from abroad to buyers in respondent's country)	3
Internet sales (seller or website located in respondent's country)	2
Smuggling (from other countries)	2
Trafficking	2
Direct sales	1
Do not know	7
Other ^a	2

^a Other: two other countries described seizures but due to an unknown or unspecified source

Seizures

Four countries (2 European, 2 Americas) reported 3–16 seizures of phenibut in 2021 in quantities of 19–911 g (Table A28). Eight countries (5 European, 1 Americas, 1 Western Pacific) reported 1–19 seizures of phenibut in 2020 in quantities ranging from 50 g to 126 kg. Seven countries (5 European, 2 Americas) reported 1–26 seizures of phenibut in 2019 in quantities ranging from 49 g to 40 kg.

Table A28. Reported seizures of phenibut

Year	No. of countries that reported seizures	No. of seizures
2021	4	26
2020	7	55
2019	7	51

Nineteen countries (14 European, 2 Western Pacific, 3 Americas) reported having the forensic laboratory capacity to analyse phenibut.

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

Wim Best, Freudenthal Instituut, Utrecht University, Netherlands

Sandra Comer, Department of Psychiatry, Columbia University, USA

Ifeoma Toyin Ekwere, Department of Anaesthesiology, University of Benin, Nigeria

Simon Elliott, Elliott Forensic Consulting, England, United Kingdom

Raka Jain, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, India

Pamela Kaduri, Department of Psychiatry, University of Toronto and adjunct faculty, Muhimbili University of Health and Allied Sciences, United Republic of Tanzania (Rapporteur)

Junichi Kitanaka, Department of Pharmacology, Hyogo College of Medicine, Japan

Antonio Pasquale Prieto, Center of Biomedical Sciences of the University of Montevideo, Uruguay

Afarin Rahimi-Movaghar, Iranian National Centre for Addiction Studies, Tehran University of Medical Sciences, Islamic Republic of Iran (Co-Chair)

Sutisa Nudmamud-Thanoi, Centre of Excellence in Medical Biotechnology, Naresuan University, Thailand

Jason White, School of Pharmacy and Medical Sciences, Division of Health Sciences, University of South Australia, Australia (Chair)

Representatives of the International Narcotics Control Board, Vienna, Austria

Stefano Berterame, Secretariat

Beate Hammond, Secretariat

Galina Korchagina, Member

Raul Martin del Campo Sanchez, Member

Representatives of the United Nations Office of Drugs and Crime, Vienna, Austria

Conor Crean, Laboratory and Scientific Division

Justice Tettey, 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

Judith Sprunken, Access to Medicines and Health Products Division

Annette Verster, Testing, Prevention and Populations

The Forty-fourth Meeting of the World Health Organization (WHO)'s Expert Committee on Drug Dependence (ECDD) was convened in a virtual format from 11 to 15 October 2021 and was coordinated from the WHO headquarters in Geneva.

WHO is mandated by the 1961 and 1971 International Drug Control Conventions to make recommendations to the UN Secretary-General on the need for and level of international control of psychoactive substances based on the advice of its independent scientific advisory body, the ECDD. To assess the appropriate control of a psychoactive substance, the WHO convenes the ECDD annually to review the potential of a substance to cause dependence, abuse and harm to health, as well as any therapeutic applications.

The Forty-fourth WHO ECDD critically reviewed five new psychoactive substances: including one synthetic cannabinoid receptor agonist (4F-MDMB-BICA), two novel synthetic opioids (bromophine; metonitazene), and two cathinones/stimulants (eutylone; benzylone). 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-fourth ECDD carried out pre-reviews of kratom, mitragynine, and 7-hydroxymitragynine; and phenibut to consider whether current information justified a critical review.

This report summarizes the findings of the forty-fourth ECDD meeting.

