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Critical Review Report:
EUTYLONE

Expert Committee on Drug Dependence

Forty-fourth Meeting

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Executive Summary

Eutylone (chemical name: 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)butan-1-one, also known as bk-EBDB) is a synthetic cathinone of the phenethylamine class, presenting a chemical structure and pharmacological similarities to Schedule I and II amphetamines and cathinones, like 3,4-methylenedioxymethamphetamine (MDMA), methylone, and pentylone. The synthesis of eutylone was described in a patent issued by Boehringer Sohn AG and Co KG Boehringer Ingelheim GmbH. The patent documented the synthesis of a series of substituted phenyl- α -amino ketones. In this patent, this substance was claimed to be suitable for pharmaceutical compositions like tablets, capsules, pills, injectable solutions and suppositories, but up to this date, no medical use has been reported for eutylone. Eutylone has not been previously reviewed by the WHO Expert Committee on Drug Dependence.

Reports on seized materials indicate that eutylone is mostly distributed as tablets, capsules, crystals, and pills, suggesting oral administration as the intended route of eutylone administration. Nevertheless, nasal administration has also been reported in online user forums. Eutylone has been identified, for example, in "Red Bull" and "Blue Playboys" tablets, as well as eutylone in cases of suspected "Ecstasy," "Molly," or "MDMA". Evidence indicates that eutylone, like other schedule I synthetic cathinones, is used for its psychoactive, namely stimulant, effects.

No detailed information could be identified on the pharmacokinetics of eutylone. However, based on the structural similarities shared with pentylone, it is expected that the β -ketone moiety of eutylone is firstly reduced to form hydroxyl metabolites. The demethylenation of the 3',4'-methylenedioxy moiety to a dihydroxy metabolite followed by its O-methylation is also expected. All these metabolites are usually then metabolized by phase II metabolism, like glucuronidation and/or sulfation. In addition, eutylone, along with other methylenedioxy substituted cathinones, has been found to be more stable in urine and blood than other structural classes of cathinones, denoting the stabilizing effect of the methylenedioxy group.

Eutylone was identified in 83 forensic investigations from 13 US states between January 2019 and April 2020. The mean concentration of eutylone was 1020 ± 2242 ng/mL (range=1.2-11000 ng/mL, n=67) in postmortem blood and 942 ± 1407 ng/mL (range=17-3600 ng/mL, n=7) in drug-driving blood samples.

Eutylone has been shown to inhibit the reuptake of dopamine, norepinephrine and serotonin in Human Embryonic Kidney (HEK) cells expressing cDNA for the human dopamine transporter (HEK-hDAT cells), the human serotonin transporter (HEK-hSERT cells), and the human norepinephrine transporter (HEK-hNET cells), with a preference for dopamine. Animal studies have further showed that eutylone increased locomotor activity of male mice in a time- and dose-dependent manner, and exhibited higher potency and efficacy than its isomers pentylone and dibutylone.

No reports on the toxic doses of eutylone could be identified. A retrospective chart review study containing data collected from emergency department cases involving eutylone use in Taiwan between January 2019 and July 2020, revealed no apparent correlation between eutylone concentrations in the urine of admitted patients and the severity of clinical manifestations.

Reported adverse effects include euphoria, insomnia, anxiety, tachycardia, hypertension, hyperthermia, delirium, paranoia, visual hallucinations, rhabdomyolysis, social disinhibition, warm tingling sensations, nausea, vomiting and in most extreme cases, seizures and even death. Unconfirmed online reports also describe bruxism, and irritation of the mucous membranes after nasal administration.

No studies on its dependence potential have been carried out in animals or humans. In drug discrimination studies performed in animals, eutylone fully substituted the discriminative stimulus effects of methamphetamine, suggesting its potential for abuse. Although no studies on the abuse potential of eutylone have been carried out in humans, its structural similarities with other synthetic cathinones (e.g., methylone, pentylone) and controlled substances (e.g., cocaine, methamphetamine, MDMA), which have high potential for abuse, it is expected that eutylone has potential for abuse in humans, which is supported by descriptions in online reports from people who used eutylone.

There are not known any therapeutic or industrial uses for eutylone, nor any marketing authorizations. However, it is used as a reference material for scientific research.

Eutylone has been primarily identified in forensic toxicology cases, including post-mortem and driving under the influence of drugs (DUID) cases. Since 2019 it has become prevalent in the US, Europe, Australia and New Zealand. For example, in the US, preliminary and projected data from the Office of National Drug Control Policy (ONDCP) suggested the involvement of eutylone in about 23000 independent seizure events domestically and/or at US points of entry in 2019 and 2020. The Center for Forensic Science Research and Education (CFSRE) trend reports showed 63 instances of eutylone since 2018, recently issuing a public health alert on the increasing prevalence of eutylone in forensic casework in the US.

In addition, it is currently listed by the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) as one of the new psychoactive substances (NPS) under intensive monitoring, as of 23 March 2021. Eutylone was also detected in wastewater from Australia collected bimonthly from October 2017 - June 2018 and October 2019 - February 2020. In New Zealand, eutylone has been found in a large number of products sold as MDMA/"Ecstasy" in festivals, further suggesting that users may be unaware of the presence of eutylone or the exact dose taken, which could contribute to adverse effects.

Eutylone is not currently controlled under the 1961, 1971 or 1988 United Nations Conventions. However, as a positional isomer of pentylone, eutylone is controlled in Schedule I of Controlled Substances Act in the US. It is also controlled under Schedule I of the Controlled Drugs and Substances Act in Canada, as Class B by the United Kingdom Misuse

of Drugs Act, and listed in Sweden as a product that is harmful to health in accordance with the Ordinance banning certain products that are harmful to health. In Germany, the use of eutylone is authorized only for industrial and scientific purposes.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not available.

B. *Chemical Abstract Service (CAS) Registry Number*

(802855-66-9 free base
17764-18-0 hydrochloric salt

C. *Other Chemical Names*

1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)-1-butanone (ACI)
Butyrophenone, 2-(ethylamino)-3',4'-(methylenedioxy)- (8Cl)
1-(2H-1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one
 β -keto-Ethylbenzodioxolylbutanamine
bk-EBDB
 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, during 2021, eutylone was found in "Red Bull" and "Blue Playboys" tablets (KnowYourStuffNZ, 2021). The presence of eutylone has also been detected in cases of suspected "Ecstasy," "Molly," or 3,4-methylenedioxymethamphetamine ("MDMA") (Krotulski et al., 2020).

F. *Physical Appearance*

The hydrochloride salt of eutylone has been described as a crystalline solid (Cayman Chemical). No reports on its odor have been identified, but from its structure, in its pure form, it is expected to be odorless

For recreational use, eutylone is mostly distributed as crystals, capsules, or tablets. Pink, yellow and blue tablets containing eutylone have been detected (KnowYourStuffNZ, 2021).

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

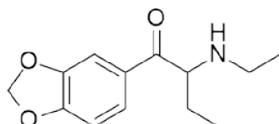
A. *Chemical Name*

IUPAC Name: 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)butan-1-one

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

B. *Chemical Structure*

Free base:

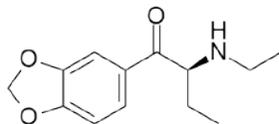


Molecular Formula: C₁₃H₁₇NO₃

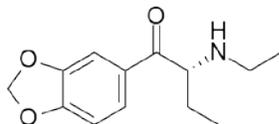
Molecular Weight: 235.28 g/mol

C. *Stereoisomers*

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



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



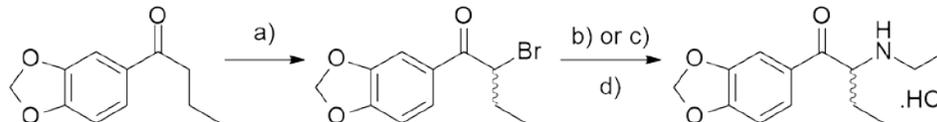
(2*R*)-1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1-one.

D. *Methods and Ease of Illicit Manufacturing*

There is no specific information available about the routes of synthesis employed for the eutylone products circulating on the market. The first synthesis of eutylone was described in a 1960's patent by a German pharmaceutical company (Glatfelter et al., 2021, C.H. Boehringer Sohn AG & Co. KG, 1967). However, 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 freebase of the cathinone.

The cathinones are generally isolated as their salts due to the instability of the freebase (UNODC, 2020). In the case of eutylone (scheme 1), the procedure includes the α -

bromination (a) of the 1-(2H-1,3-benzodioxol-5-yl)butan-1-one precursor and formation of the 1-(2H-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 employed for the preparation of eutylone analogs. 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) (C.H. Boehringer Sohn AG & Co. KG, 1967).

Boiling point

No information could be identified.

Solubility

Hydrochloride salt is soluble in water, methanol, ethanol, DMF and DMSO (NFL, 2017, Cayman, 2021b).

F. Identification and Analysis

Eutylone hydrochloride salt and eutylone-d5 hydrochloride salt are available as reference material from commercial suppliers to assist with the implementation of routine methods of analysis associated with forensic and clinical investigations (Cayman, 2021a).

Analytical methodologies for the identification and quantification of eutylone in seized and biological sample matrices have recently published and include various chromatographic, spectroscopic and mass spectrometric methods. Analysis for identification of eutylone in seized sample were conducted employing gas chromatography-mass spectrometry (GC-MS), infrared spectroscopy (IR), liquid chromatography-mass spectrometry (LC-MS), ion chromatography (IC) (NFL, 2017).

Analysis for identification and quantification of eutylone was conducted in postmortem and driving under the influence of drugs cases (Krotulski et al., 2021). Matrix types included blood, urine, and tissue. Eutylone was identified through a comprehensive

drug screening protocol using liquid chromatography–time-of-flight mass spectrometry (LC-TOF-MS) under non-targeted acquisition parameters. Quantitative analysis of eutylone was performed by liquid chromatography–tandem mass spectrometry (LC-MS/MS). The blood concentration of eutylone in forensic cases ranged from 1.2 to 11,000 ng/mL (Krotulski et al., 2021).

3. Ease of Convertibility Into Controlled Substances

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

4. General Pharmacology

A. *Routes of administration and dosage*

A patent issued by Boehringer Sohn AG and Co KG Boehringer Ingelheim GmbH (1967) included the synthesis of eutylone and other analogs. In this patent eutylone was claimed to be suitable for pharmaceutical compositions like tablets, capsules, pills, injectable solutions and suppositories, which is in accordance with the general notion that synthetic cathinones can be administered by oral, parenteral, and rectal routes of administration. Reports on seized materials indicate the presence of eutylone in tablets, capsules, crystals, and pills, suggesting oral administration as the intended route of eutylone administration. Nevertheless, nasal administration has also been reported in online user forums (“Ekstasis-//7”, 2020; “Nick”, 2021; “xammy”, 2021). Some users have reported experiencing effects at 35 mg, with an average dose reported as 60-100mg. Nevertheless, eutylone has been found in “Red Bull” tablets (containing no MDMA) at 300-350 mg (KnowYourStuffNZ, 2021). Information published in online user forums suggest the administration of 50 mg eutylone by snorting (“Nick”, 2021) or between 100-200 mg orally (““Ekstasis-//7””, 2020; ““Nick””, 2021).

B. *Pharmacokinetics*

No detailed information could be identified regarding the pharmacokinetics of eutylone. Based on its chemical structure, and considering the structural similarities shared with pentylone, it is expected that the β -ketone moiety of eutylone is firstly reduced to form hydroxyl metabolites. In 3',4'-methylenedioxyphenyl cathinone derivatives, like eutylone, the demethylenation of the 3',4'-methylenedioxy moiety to a dihydroxy metabolite (mediated by CYP2D6 and CYP2C19), followed by its O-methylation (mediated by catechol O-methyl transferase) represent the major metabolic pathways. Both hydroxyl, 4'-methoxy-3'-hydroxyl, and 3'-methoxy-4'-hydroxyl metabolites are usually then metabolized by phase II metabolism, like glucuronidation and/or sulfation (Zaitso, 2018).

The stability of twenty-two synthetic cathinones, including eutylone, was studied in urine and blood (Kerrigan and Glicksberg, 2017). In these studies, cathinones were added to urine and blood samples and examined using liquid-chromatography/quadrupole-time of flight-

mass spectrometry (LC-Q/TOF-MS) (Kerrigan and Glicksberg, 2017). Cathinone stability was evaluated in preserved blood (pH 7) and urine (pH 4 and 8) at two concentrations (100 and 1,000 ng/mL) and four storage temperatures (-20°C, 4°C, 20°C, and 32°C). This study concluded that methylenedioxy substituted cathinones, like eutylone, were significantly more stable than other structural classes of cathinones, denoting the stabilizing effect of the methylenedioxy group. Eutylone showed a half-life ($t_{1/2}$) of 31 and 4.8 days in the blood at 20°C and 32°C, respectively, a $t_{1/2}$ of 13 days in the urine (pH 4.0) at 32°C, and a $t_{1/2}$ of 6.2, 11 and 3 days in the urine (pH 8.0) at -4°C, 20°C, and 32°C, respectively. No degradation of eutylone was observed at lower temperatures in each case.

Between January 2019 and April 2020, eutylone was quantitatively identified in 83 forensic investigations, including postmortem and DUID cases from different US states. The mean concentration of eutylone in postmortem blood was $1,020 \pm 2,242$ ng/mL (range=1.2-11,000 ng/mL, n=67). The mean concentration of eutylone in blood from DUID cases was $942 \pm 1,407$ ng/mL (range=17-3,600 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 (Krotulski et al., 2020).

C. Pharmacodynamics

In vitro data:

The interaction of eutylone with monoamine transporters was determined by testing the effects of eutylone on radioligand ([125I]RTI-55) binding and [3H]neurotransmitter (i.e., dopamine, serotonin, norepinephrine) uptake by HEK cells expressing cDNA for the human dopamine transporter (HEK-hDAT cells), the human serotonin transporter (HEK-hSERT cells), and the human norepinephrine transporter (HEK-hNET cells). Eutylone presented higher affinity for DAT ($K_i = 640$ nM) than NET ($K_i = 1,870$ nM) or SERT ($K_i = 8,500$ nM) and was confirmed to be an inhibitor of monoamine neurotransmitter uptake with a potency rank order of DAT ($IC_{50} = 281$ nM) > SERT ($IC_{50} = 640$ nM) > NET ($IC_{50} = 8,800$ nM), (Table 1). As also shown in Table 1, comparison of the effects of eutylone on binding and uptake with other stimulants indicated that eutylone presented an affinity to DAT more similar to cocaine than to methamphetamine (METH) or methcathinone. Eutylone further showed to be a more potent inhibitor of serotonin uptake than METH and methcathinone (about 14- and 56-fold higher, respectively), but less potent inhibitor of norepinephrine uptake than these two stimulants (about 30- and 18-fold, relatively to METH and methcathinone, respectively).

Table 1 – Effects of eutylone, in comparison with cocaine, methamphetamine (METH) and methcathinone on [125I]RTI-55 binding and [3H]neurotransmitter uptake by HEK-hDAT, HEK-hSERT, and HEK-hNET cells (mean \pm SEM). Adapted from Janowsky, 2019.

HEK-hDAT	Eutylone	Cocaine	METH	Methcathinone
[125I]RTI-55 binding: K_i (nM)	640 ± 71	750 ± 130	$4,660 \pm 660$	$6,600 \pm 130$
[125I]RTI-55 binding: IC_{50} (nM)	651 ± 72	-	-	-

Hill Slope	-0.94 ± 0.02	-1.04 ± 0.08	-0.97 ± 0.08	-0.99 ± 0.09
[3H]DA uptake: IC50 (nM)	281 ± 80	366 ± 51	177 ± 30	450 ± 130
HEK-hSERT				
[125I]RTI-55 binding: Ki (nM)	$8,500 \pm 2500$	734 ± 60	$145,000 \pm 44,000$	$237,000 \pm 61,000$
[125I]RTI-55 binding: IC50 (nM)	$8,800 \pm 2700$	-	-	-
Hill Slope	-1.38 ± 0.22	-0.97 ± 0.09	-1.12 ± 0.08	-1.09 ± 0.10
[3H]5-HT uptake: IC50 (nM)	640 ± 160	270 ± 47	$9,200 \pm 2,400$	$36,000 \pm 3,900$
HEK-hNET				
[125I]RTI-55 binding: Ki (nM)	$1,870 \pm 550$	$1,560 \pm 340$	$1,340 \pm 270$	$3,110 \pm 190$
[125I]RTI-55 binding: IC50 (nM)	$1,880 \pm 560$	-	-	-
Hill Slope	-0.55 ± 0.17	-0.80 ± 0.18	-0.89 ± 0.10	-1.08 ± 0.19
[3H]NE uptake: IC50 (nM)	700 ± 100	390 ± 100	23.1 ± 5.4	38.3 ± 7.7

These data were supported by other monoamine transporter studies performed in rat brain synaptosomes that showed that eutylone is a hybrid transporter compound with uptake inhibition properties at DAT and NET (with effects at DAT being 10-fold more potent than the effects 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 further observed that eutylone displayed weak partial releasing actions at serotonin transporters that reached 50% of maximal response (Glatfelter et al., 2021).

In vivo data:

Treatment with eutylone (ED50 = 4.87 mg/kg) resulted in a time- and dose-dependent stimulation of locomotor activity of male Swiss-Webster mice (Hsd:ND4, aged 2-3 months) following intraperitoneal administration of 1 to 25 mg/kg (in assays conducted according to the DEA locomotor activity studies time course protocol). At 10 and 25 mg/kg, the stimulant effects of eutylone occurred within 10 minutes following administration of eutylone and lasted for 70 min (Gatch, 2020b).

These data were supported by other studies showing that eutylone stimulated locomotion in a dose-dependent manner, following its subcutaneous administration to mice (ED50 = 2mg/kg). In terms of locomotor activity stimulation, eutylone showed higher potency and efficacy than its isomers pentylone and dibutylone (Glatfelter et al., 2021).

5. Toxicology

No reports on the toxic doses of eutylone could be identified. A retrospective chart review study collected data from emergency department cases involving eutylone use in Taiwan (Chen et al., 2021). The cases, collected between January 2019 and July 2020, documented urine concentrations of eutylone in 11 cases, including one fatal case. Concentrations ranged from 210 to 18,364 ng/ml, with no apparent correlation with the severity of clinical manifestations.

Data retrieved from the UNOCD Early Warning Advisory (ToxPortal, 2021) [indicates one occurrence in which eutylone was found contributory to a clinical admission in Australia in 2020. No details on this occurrence were available.](#)

6. Adverse Reactions in Humans

In a retrospective review study of 11 emergency department cases, including a fatal case, involving eutylone use in Taiwan between January 2019 and July 2020, all patients presented pronounced sympathomimetic effects (Chen et al., 2021). All patients (excluding one who presented an out-of-hospital cardiac arrest) showed tachycardia (pulse rate > 100/min), four presented with hyperthermia (body temperature above 38°C) and three had hypertension (systolic blood pressure >140 mmHg). Other common clinical manifestations included delirium (5 cases), agitation (5 cases), and visual hallucinations (2 cases). Five patients developed leukocytosis (white cell counts >11 K/L) and one patient presented rhabdomyolysis (CK > 1,500 U/L). Nausea and vomiting were reported in one case (Chen et al., 2021). Effects such as agitation, hypertension, tachycardia, and death are consistent with those generally reported for synthetic cathinones (Drug Enforcement Administration, 2020).

In addition to these adverse effects, reports found in online user forums also disclose euphoria and social disinhibition (“nervewing”, 2021), and tingling sensations (“xammy”, 2021). Adverse events from unverified online forums include bruxism, irritation of the mucous membranes after nasal administration (“Ektasis-//7”, 2020; “xammy”, 2021), insomnia, anxiety, paranoia, and seizures (KnowYourStuffNZ, 2021). Most of the effects induced by eutylone seem to occur almost immediately after administration and disappear in a few hours.

The presence of eutylone in several post-mortem cases suggests that it may also cause or contribute to death (Chen et al., 2021; Krotulski et al., 2020). In 2020, acute eutylone intoxication was listed as the official cause of death of a man following an accidental drug overdose (AP News, 2020).

7. Dependence Potential

A. *Animal Studies*

No studies on eutylone dependence carried out in animals could be identified.

B. Human Studies

No studies on eutylone dependence carried out in humans could be identified.

8. Abuse Potential

A. Animal Studies

In drug discrimination studies (two-lever choice methodology), eutylone fully substituted the discriminative stimulus effects of the training dose of 1 mg/kg methamphetamine (ED50 = 2.83 mg/kg) following the intraperitoneal administration of eutylone to Sprague-Dawley rats in the dose range of 1 to 10 mg/kg. The response rate of eutylone increased to 139% of vehicle control following administration of 5mg/kg. The potency ratio of eutylone to methamphetamine (ED50 test compound/ ED50 reference compound) was 10.89. Eutylone and methamphetamine were also found to be equi-efficacious, as the relative efficacy of eutylone to methamphetamine [(Emax test compound/Emax reference compound)*100] was 113% (Gatch, 2020a).

B. Human Studies

No studies on the abuse potential of eutylone carried out in humans could be identified. Nevertheless, based on its structure, eutylone is expected to cause stimulant-related psychological and somatic effects similar to Schedule I (under the Controlled Substances Act in the US) synthetic cathinones (e.g., methylone, pentylone) and other Schedule I and II (under the Controlled Substances Act in the US) substances (e.g., cocaine, methamphetamine, MDMA), which have high potential for abuse (Drug Enforcement Administration, 2020).

In addition, the potential for nonmedical use of eutylone is described in online user forums (“Gaffy”, 2020; “Nick”, 2021).

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Eutylone seems to have been initially explored for use in pharmacological formulations (Boehringer Sohn AG and Co KG Boehringer Ingelheim GmbH, 1967), but it is not known to have any therapeutic uses.

10. Listing on the WHO Model List of Essential Medicines

Eutylone is not listed 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 the US, Europe, Australia and New Zealand. For example, between 2019-2020 eutylone was identified in about 23000 seizures in the US or at US points of entry.

In New Zealand, eutylone has been found in a large number of products sold as MDMA/"Ecstasy", so it is possible that in some cases users may be unaware that they have consumed eutylone, or the dose taken, which could contribute to adverse effects, especially if consumed in combination with other substances. A review of case reports in Taiwan suggests that people who use eutylone seem to self-medicate with benzodiazepines, as these drugs were detected along eutylone in biological fluids of people admitted to hospital emergency rooms following eutylone use (Chen et al., 2021).

Abuse and dependence potential has not been studied in humans, and there are only a few self-reports of intentional eutylone use in online user forums (e.g., Erowid, Bluelight). Nevertheless, two people have reported features of craving ("Gaffy", 2020; "Nick", 2021), describing a need to take more eutylone over a few days. It has been suggested that the mild euphoria effects (in contrast with MDMA) may contribute to taking additional doses after a short time period, leading to insomnia which may last 48 hours (KnowYourStuffNZ, 2021).

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

No specific information on the nature and magnitude of public health problems associated with the use of eutylone was identified. The detection of eutylone in biological fluids has been mostly described in postmortem and driving under the influence of drugs cases.

Eutylone has frequently been also detected in products thought to represent MDMA/"Ecstasy", mephredrone, methyline, alprazolam, or Spice, suggesting that most people who use eutylone may be unaware that they are using it (KnowYourStuffNZ, 2021; Wedinos, 2021). Some products tested were found to contain very high doses (i.e., 300-350 mg) (KnowYourStuffNZ, 2021). Adverse effects experienced by people who have taken eutylone have been detailed in section 6 of this document.

15. Licit Production, Consumption and International Trade

Eutylone is used as a reference material for scientific research, being available for "research use only".

16. Illicit Manufacture and Traffic and Related Information

Eutylone was first detected in Europe in March 2014 in Poland (EMCDDA, 2015) and is currently listed as one of the new psychoactive substances (NPS) under intensive monitoring by the European Monitoring Center for Drugs and Addiction (EMCDDA), as of 23 March 2021.

It is also among the most prevalent NPS identified in the US by the ONDCP across leading law enforcement datasets since 2019. Preliminary and projected data suggested the involvement of eutylone in about 23,000 independent seizure events domestically and/or at US points of entry in 2019 and 2020 (ONDCP, 2021). The Center for Forensic Science Research and Education (CFSRE) trend reports showed 63 instances of eutylone since 2018 (CFSRE, 2021). The CFSRE recently issued a public health alert on the increasing prevalence of eutylone in forensic casework in the US in response to its prevalence and contributions to mortality, following the scheduling of N-ethylpentylone in the US in August 2019 (CFSRE, 2021).

Reports from the National Forensic Laboratory Information System (NFLIS) indicate that eutylone emerged on the United States' illicit drug market in 2014, with 29, 182, and 3,958 reports for eutylone in 2017, 2018, and 2019, respectively (Drug Enforcement Administration, 2020).

Eutylone was also detected in wastewater from Australia collected bimonthly from October 2017 - June 2018 and October 2019 - February 2020 (Bade et al., 2020).

Drug checking by KnowYourStuffNZ has also identified the presence of eutylone in festivals around New Zealand in 2021. This substance was present in about 40% of the tested tablets, and 45% of those had been bought as being MDMA (KnowYourStuffNZ, 2021).

17. Current International Controls and Their Impact

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

18. Current and Past National Controls

As a positional isomer of pentylone, eutylone is controlled under Schedule I of the Controlled Substances Act in the US (Drug Enforcement Administration, 2020).

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 (Public Health Agency of Sweden, 2019).

Eutylone is controlled under Schedule I of the Controlled Drugs and Substances Act in Canada.

Eutylone is controlled as Class B by the United Kingdom Misuse of Drugs Act. In Germany, eutylone is classified as “Neue-psychoaktive-Stoffe-Gesetz (NpSG)”, which authorizes its use only for industrial and scientific purposes.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

As eutylone has been identified in products sold as MDMA/“Ecstasy” (KnowYourStuffNZ, 2021), it is reasonable to expect that the prevalence of eutylone and eutylone-related intoxications may be under-reported. There have been cases where samples sold as MDMA contained potentially harmful amounts of eutylone (KnowYourStuffNZ, 2021). .

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Data were obtained from 98 Member States (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) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire was 9 (1 African Region, 2 Eastern Mediterranean Region, 2 European Region, 2 Region of the Americas, 1 South-East Asia Region and 1 Western Pacific Region), leaving 89 countries that agreed to provide data.

Of the 89 countries who agreed to provide data, 32 countries had information on eutylone (Table 1).

Table 1. Numbers of countries providing information on eutylone

Region	Number of countries without information	Number of countries with information on substance
African	6	0
Eastern Mediterranean	6	1
European	8	22
Region of the Americas	8	4
South-East Asia	3	1
Western Pacific	7	4
Total (70)	38	32

APPROVED MEDICAL, SCIENTIFIC OR INDUSTRIAL USE

One country (European) reported approved human medical products containing eutylone being available in their country. No countries reported therapeutic indications, scientific use or industrial use relating to eutylone.

EPIDEMIOLOGY OF NON-MEDICAL USE

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

Routes of administration and formulations

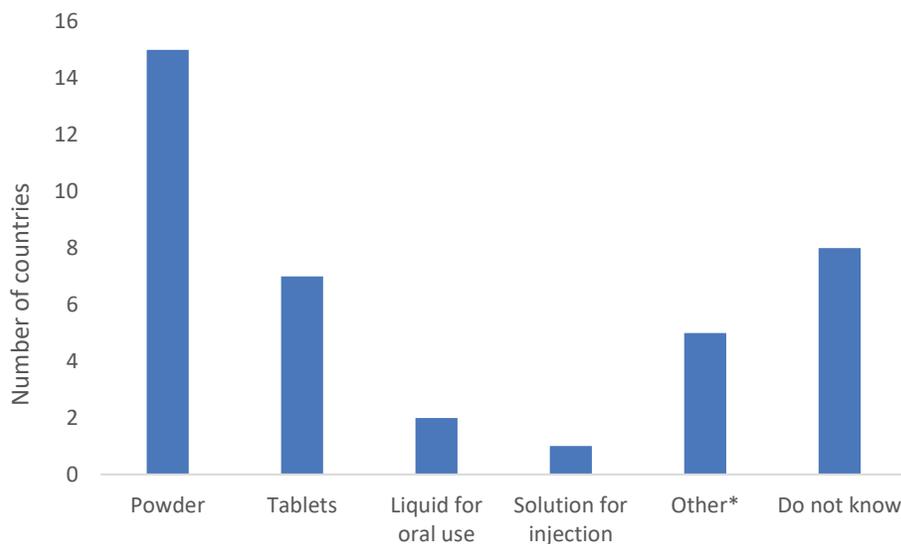
The most commonly reported routes of eutylone administration was oral and sniffing (Table 2).

Table 2. Reported routes of eutylone administration

Route of administration	Number 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 (Figure 1).

Figure 1. Formulations of eutylone

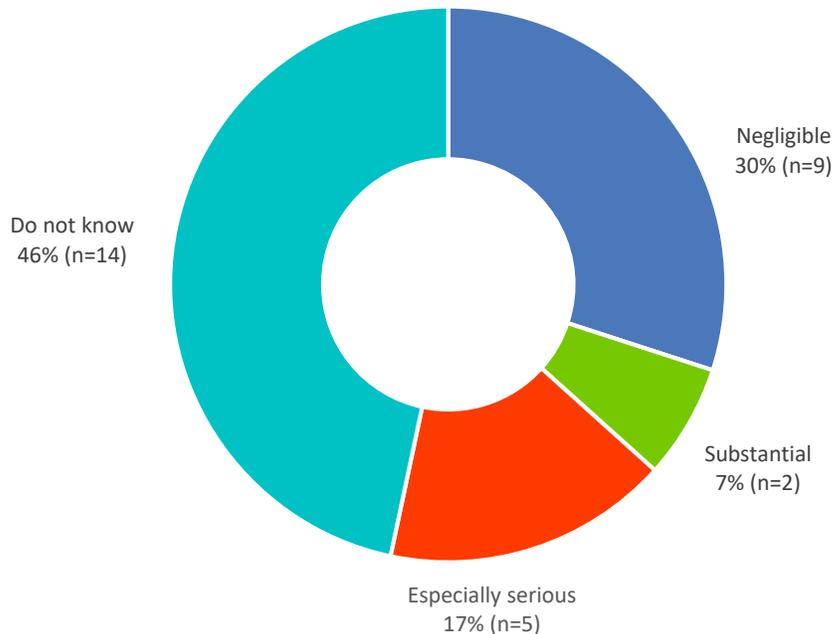


* Other eutylone formulations included crystals (n=2), plant/vegetable matter (n=2), and "rock, drug patch, unspecified liquid, capsule, paper" (n=1).

Perceived negative health impact

Seven countries (4 European, 2 Region of the Americas, 1 Western Pacific) reported the level of negative health impact due to eutylone’s non-medical consumption as “substantial” or “especially serious” (Figure 2). One country (Region of the Americas) remarked “Eutylone has been encountered on the illicit drug market and has been positively identified in over 40 toxicology cases”.

Figure 2. Countries reporting negative health impact of the non-medical consumption of eutylone



Emergency Department visits

Two countries (2 European) were aware of emergency room/department visits related to eutylone. One country reported the symptoms of hallucinations, disphoria, headache, tachycardia, and profuse sweating. Another country noted that eutylone was detected in four cases, all in combination with other substances.

Deaths

Two countries (2 European) reported deaths where eutylone was involved. It was unknown whether other substances were also involved in these deaths. One country reported 1 death in 2019. One country reported 243 deaths in 2019.

Drug Dependence

One country (European) reported they were aware of people presenting to drug dependence treatment in their country due to use of eutylone.

CURRENT DRUG CONTROL

Twenty three countries (15 European, 3 Region of Americas, 4 Western Pacific, 1 South-East Asia) reported eutylone is currently controlled under national legislation to regulate its availability. Table 3 shows reported activities involving eutylone.

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

Activity	Number 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 Region of Americas, 1 Western Pacific) reported seizures of eutylone in 2021. Seizure numbers ranged from 1 to 3471, and seizure quantities ranged from 129 to 19868 grams (Table 4).

Sixteen countries (10 European, 3 Western Pacific, 2 Region of Americas, 1 South-East Asia) reported seizures of eutylone in 2020. Seizure numbers ranged from 1 to 11451, and seizure quantities ranged from 4.12 to 76613 grams.

Nine countries (6 European, 2 Region of the Americas, 1 Western Pacific) reported seizures of eutylone in 2019. Seizure numbers ranged from 1 to 5403 and seizure quantities ranged from 4 to 37830 grams.

Table 4. Reported seizures of eutylone

Year	Number of countries reporting seizures	Number of seizures
2021	5	3532
2020	16	11628
2019	9	5472

Twenty nine countries (21 European, 4 Western Pacific, 3 Region of the Americas, 1 South East Asia) reported having the forensic laboratory capacity to analyze eutylone.