Synthetic Cathinones: eutylone, 4-chloromethcathinone and dimethylpentylone

Report to the Expert Advisory Committee on Drugs

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Contents

1 EXECUTIVE SUMMARY

Eutylone, 4-chloromethcathinone (4-CMC) and N,N-dimethylpentylone (dimethylpentylone) are synthetic cathinones with evidence of harm observed both internationally and within New Zealand. These 3 synthetic cathinones are currently regulated as Class C7 controlled drug analogues under the Misuse of Drugs Act 1975. They have been recommended for classification under the Misuse of Drugs Act 1975 by the National Drug Intelligence Bureau (NDIB) and the Institute of Environmental and Science Research (ESR). Eutylone and 4-CMC have been scheduled under the United Nations Convention on Psychotropic Substances 1971. As a signatory to this convention, New Zealand is obligated to consider these substances under our domestic legislation. There are no known therapeutic uses for these substances.

As synthetic cathinones, eutylone, 4-CMC, and dimethylpentylone increase the concentrations of dopamine, serotonin, and noradrenaline to varying degrees at the synaptic cleft. This accounts for the psychostimulant effects seen with the use of these substances, which are similar to the effects seen with amphetamines and cocaine, and the empathogenic effects induced by 3,4 methylenedioxymethamphetamine (MDMA). Acute intoxication with synthetic cathinones can contribute to high blood pressure, rapid heart rate, inability to thermoregulate, appetite suppression, compulsive redosing, loss of consciousness, and death. Whilst some users use these substances for their stimulant and euphoric effects, synthetic cathinone consumption in New Zealand is commonly the result of misrepresented MDMA. In the 2020/2021 New Year period, more than half of the MDMA tested in New Zealand contained cathinones – with eutylone being the most commonly reported. Between 2018 and 2022, there were 21 coronial cases with detections of either eutylone or dimethylpentylone in New Zealand.

Synthetic cathinones are manufactured and imported from overseas. Therefore, the types of synthetic cathinone circulating within New Zealand tend to follow global trends. The recent detections of dimethylpentylone in New Zealand aligns with an increased presence of dimethylpentylone observed internationally.

2 INTRODUCTION

2.1 Purpose

This report provides an overview of 3 synthetic cathinones that are being presented to the Expert Advisory Committee on Drugs (the Committee) for their consideration and subsequent scheduling recommendations under the Misuse of Drugs Act 1975. Where available, specific information on individual substances, prepared by the World Health Organization (WHO), is provided alongside this paper.

The synthetic cathinones to be considered by the Committee are:

- eutylone
- 4-chloromethcathinone (4-CMC)
- N,N-dimethylpentylone (dimethylpentylone).

2.2 Substance classification

Eutylone is a synthetic cathinone of the phenethylamine class. It is currently regulated under the Misuse of Drugs Act 1975 as a Class C7 controlled drug analogue because it shares a structure substantially similar to methcathinone, a Class B1 controlled drug. Eutylone has been scheduled under Schedule II of the Convention on Psychotropic Substances 1971. During the 2019/2020 festival season in New Zealand, eutylone was detected frequently by drug checking service KnowYourStuffNZ (DIANZ 2020).

4-CMC is a synthetic cathinone, and an analogue of methcathinone, a Class B1 controlled drug. 4-CMC is currently regulated under the Misuse of Drugs Act 1975, as a Class C7 controlled drug analogue. 4-CMC has been scheduled under Schedule II of the Convention on Psychotropic Substances 1971. During 2015 and 2016, it was one of the most prevalent novel psychoactive substances circulating internationally (WHO 2019).

Dimethylpentylone is a synthetic cathinone. It is currently regulated under the Misuse of Drugs Act 1975 as a Class C7 controlled drug analogue as it shares a structure substantially similar to 3,4-methylenedioxymethamphetamine (MDMA), a Class B1 controlled drug. Dimethylpentylone is not currently controlled under any of the United Nations Drug Control Conventions. In December 2021, Drug Information and Alerts Aotearoa New Zealand (DIANZ) issued a notification on a detection of dimethylpentylone circulating within New Zealand (DIANZ 2021c).

2.3 Why is this substance being considered?

Eutylone, 4-CMC, and dimethylpentylone have been recommended for Committee consideration by the National Drug Intelligence Bureau (NDIB) and the Institute of Environmental Science and Research (ESR). Eutylone and 4-CMC are scheduled under the United Nations Convention on Psychotropic Substances 1971. As a signatory to this Convention, New Zealand is obligated to consider scheduling these substances under domestic legislation.

3 SUBSTANCE IDENTIFICATION AND CHEMISTRY

3.1 Identification

Eutylone

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

CAS Number: 802855-66-9

Molecular weight: 235.28g/mol

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

Appearance: neat solid (Cayman Chemical 2022a)

Solubility: hydrochloride salt is soluble in dimethyl formamide, dimethyl sulfoxide, ethanol and phosphate buffer solution (pH 7.2) (Cayman Chemical 2022a).

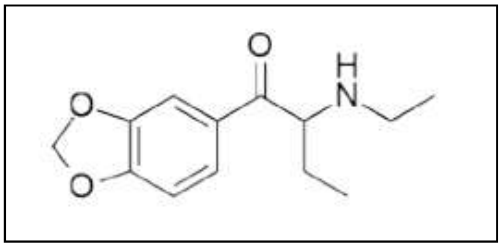


Figure 1: Chemical structure of eutylone

4-CMC

IUPAC Name: 1-(4-chlorophenyl)-2-methylamine)propan-1-one

CAS Number: 1225843-86-6

Molecular weight: 197.66g/mol

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

Appearance: crystalline solid (Cayman Chemical 2022b)

Solubility: soluble in dimethyl sulfoxide, dimethyl formamide, ethanol and phosphate buffer solution (pH 7.2) (Cayman Chemical 2022b).

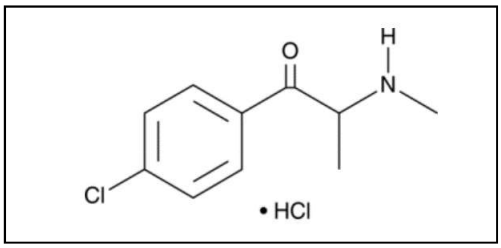


Figure 2: Chemical structure of 4-CMC

Dimethylpentylone

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

CAS Number: 17763-13-2

Molecular weight: 249.3g/mol

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

Appearance: neat solid (Cayman Chemical 2022c)

Solubility: soluble in methanol and phosphate buffer solution (pH 7.2) (Cayman Chemical 2022c).

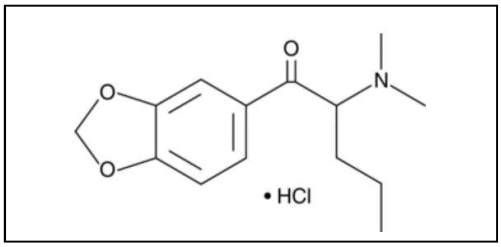


Figure 3: Chemical structure of dimethylpentylone

3.2 Therapeutic value

There are no known therapeutic uses for eutylone, 4-CMC, or dimethylpentylone in New Zealand or internationally.

3.3 Similarities to other known substances

Structural similarities

Synthetic cathinones have a β-keto phenethylamine core and share structural similarities with amphetamines. The major difference being the presence of a ketone group with synthetic cathinones. Synthetic cathinones are synthesised with different substituents added to different positions of the cathinone core structure (Almeida et al 2022).

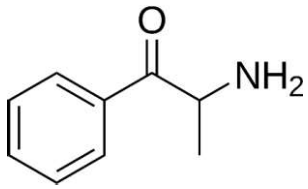
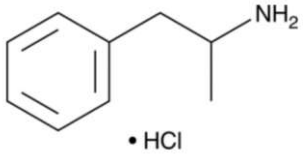
Cathinone Core	Amphetamine Core
	

Figure 4: Core structures of cathinone and amphetamine

Eutylone has a structure substantially similar to methcathinone. The structure of eutylone contains the entirety of the methcathinone structure. However, the eutylone structure contains some further additions, including:

- 3,4-methylenedioxy group fused to benzene ring
- extra methyl group at amino group to give ethylamine chain
- extra methyl group at alpha-carbon give ethyl side chain.

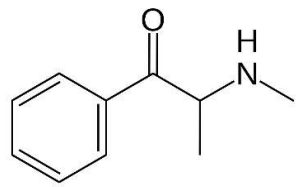
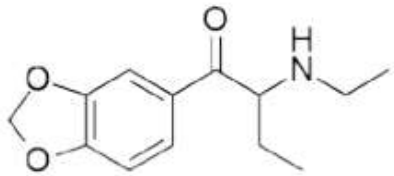
Methcathinone	Eutylone
	

Figure 5: Chemical structure of methcathinone compared to eutylone

4-CMC also has a structure substantially similar to methcathinone. 4-CMC has a chlorine added to the fourth position of the phenyl ring in methcathinone.

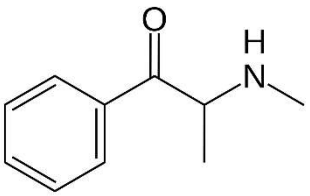
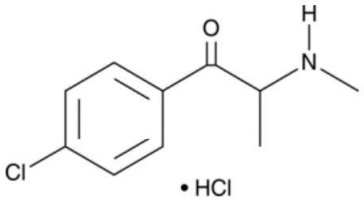
Methcathinone	4-CMC
	

Figure 6: Chemical structure of methcathinone compared to 4-CMC

Whilst containing the core cathinone structure, dimethylpentylone also shares a structure substantially similar to MDMA. The structure of dimethylpentylone contains the entirety of the MDMA structure. However, the dimethylpentylone structure contains some further additions, including:

- extra methyl group at amino group
- propyl side chain at alpha-carbon
- ketone group at beta-carbon.

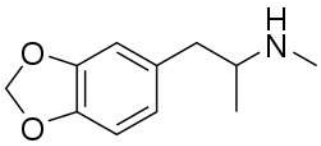
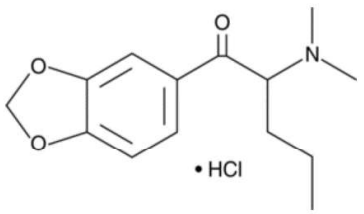
MDMA	Dimethylpentylone
	

Figure 7: Chemical structure of MDMA compared to dimethylpentylone

Pharmacological similarities

Synthetic cathinones share similar mechanisms of action to other controlled drugs such as MDMA, cocaine, and methamphetamine. Eutylone, 4-CMC and dimethylpentylone interfere with dopamine, noradrenaline and serotonin transmission to increase synaptic concentrations of these neurotransmitters. These interactions can occur through inhibition of monoamine reuptake from the synaptic cleft or by promoting monoamine release into the cleft (Almeida et al 2022).

Similarities in risk of harm

In general, synthetic cathinones can have similar effects to MDMA, cocaine, and methamphetamine. Acute intoxication of synthetic cathinones is associated with tachycardia, hypertension, chest pain, hyperthermia, insomnia, agitation, hallucinations, delusions and confusion (Zawilska and Wojcieszak 2013). Synthetic cathinones interfere with dopamine neurotransmission and may be associated with risk of addiction. Synthetic cathinones that display higher affinity and potency at dopamine transporters compared to serotonin transporters are associated with higher abuse liability (Eshleman et al 2017).

The para-substituted analogues of methcathinone, such as 4-CMC, exert a higher selectivity for serotonin transporters, suggesting a potential concomitant decrease in abuse liability compared to unsubstituted methcathinone (Eshleman et al 2017).

3.4 Methods and ease of manufacturing

The first synthesis of eutylone was published by a german pharmaceutical company (Boehringer Sohn AG and Co KG Boehringer Ingelheim GmbH 1967). The WHO reports that although it is unclear how illicit eutylone is being synthesised, the chemical synthesis of cathinones generally follows a two-step process. This two-step process involves the initial synthesis of an α-bromoketone from an arylketone, followed by a nucleophilic substitution with an appropriate amine to produce the freebase of a cathinone (WHO 2021).

WHO also states that it is not known whether eutylone or 4-CMC can be converted into another controlled substance or what the ease of conversion would be (WHO 2019; WHO 2021).

Preliminary data shows that pentylone, another known synthetic cathinone of abuse, may be a major metabolite of dimethylpentylone (NPS Discovery 2021).

4 RISK OF HARM

4.1 Likelihood or evidence of abuse in New Zealand

Internationally, eutylone, 4-CMC, and dimethylpentylone are all known drugs of abuse. 4-CMC was first reported to the European Monitoring Centre for Drugs and Drug Addiction in 2011 (WHO 2019). Eutylone was first reported to European Early Warning Systems in 2014 (EMCDDA 2015). In 2022, dimethylpentylone was identified as an emerging synthetic stimulant (NPS Discovery 2022). Synthetic cathinones are more commonly sold as misrepresented MDMA in New Zealand (DIANZ 2020).

Between April 2016 and March 2021, cathinones were detected by New Zealand drug checking services KnowYourStuffNZ on 658 occasions. On most of these occasions, the presence of a cathinone was not what the user had presumed; in most cases the presumption being that the substance being checked was MDMA. Of these users with unexpected cathinones detected, some users indicated that they still either intended to consume or might consume the substance on 150 occasions (KnowYourStuffNZ 2021a).

In 2020/2021, KnowYourStuffNZ reported that the second most commonly detected substance at events were cathinones (predominantly eutylone), sitting behind MDMA. The

rate of detection for cathinones was higher than in previous years. Mixtures of psychoactive substances were also a concern. MDMA and eutylone combinations represented over a third of detected mixed substances. This is of particular concern as reagent tests (purchased and used by users) indicate the presence of MDMA only and may not indicate the presence of other substances. Therefore, users may still unknowingly consume dangerous doses of eutylone in these combination substances even after reagent testing (KnowYourStuffNZ 2021a).

In December 2021, DIANZ issued a notification on a detection of dimethylpentylone circulating within New Zealand (DIANZ 2021d).

There is limited information on 4-CMC use in New Zealand.

New Zealand seizure data

NDIB data on seizures are shown in Table 1.

Table 1: Seizure quantities by Police and Customs of eutylone, 4-CMC and dimethylpentylone between 2017 and 2021

	Year	2017	2018	2019	2020	2021*
Eutylone	Total quantity seized (g)	0	0	6,988	12,923	5,092
	Number of Seizures	0	0	9	18	7
4-CMC	Total quantity seized (g)	0	2	22	6	0
	Number of Seizures	0	1	2	1	0
Dimethylpentylone	Total quantity seized (g)	No seizures				
	Number of Seizures					

**provisional data*

Seizures of eutylone were in powder or crystal forms, and seizures of 4-CMC were in powder form only.

More recent data reported that the first seizure of dimethylpentylone at the New Zealand border occurred in February 2022. As of May 2022, approximately 12,266g of dimethylpentylone has been seized. The monthly quantity seized has increased each month since first detection (NDIB 2022).

Detections in drug checking samples per year

ESR data on detections in drug checking samples are shown in Table 2.

Table 2: Detections in drug checking samples of eutylone, 4-CMC and dimethylpentylone between 2017 and 2022

	Year	2017	2018	2019	2020	2021	2022*
Eutylone	Number of detections	0	0	9	5	56	23
4-CMC	Number of detections	2	0	0	0	1	0
Dimethylpentylone	Number of detections	2	0	0	18	1	1

**provisional data*

4.2 General pharmacology

DIANZ reports that synthetic cathinones can cause physical effects such as stimulation, high blood pressure, rapid heart rate, anxiety, paranoia, euphoria, inability of the body to regulate temperature, appetite suppression, compulsive redosing, loss of consciousness and death (DIANZ 2021b).

Other reports from online user forums indicate that eutylone can be associated with social disinhibition, tingling sensations, insomnia, anxiety and seizures. Most of these reported effects induced by eutylone appear to occur immediately after administration and resolve in a few hours (WHO 2021).

In Poland, case reports from non-fatal cases in which 4-CMC was taken in combination with other psychoactive substances included descriptions of dilated pupils, slow or absent pupillary light reflex, slurred speech, agitation, increased drive, tachycardia, difficulty with walking, difficulty in picking up objects from the ground, lack of balance, disorientation to time, place and surroundings, drowsiness, and slow behaviour. In a single case where 4-CMC was the only detected substance, the reported effects were agitation, joyful expressions, increased drive, tachycardia, dilated pupils and difficulty picking objects from the ground (Tomczak et al 2018).

There is limited information relating to the consumption of dimethylpentylone specifically. One online user reported “feel like my liver is shutting down/extremely noticeable high heart rate and started getting visuals very slightly similar to the come of LSD,” after consuming a tablet thought to contain dimethylpentylone (Reddit 2022). DIANZ reported an individual who brought dimethylpentylone for testing had consumed the substance and reported the experience as “very unenjoyable” (DIANZ 2021d).

Routes of administration and dosage

The patent for eutylone by Boehringer Sohn AG and Co KG Boehringer Ingelheim GmbH, submitted in 1967, claims that eutylone is suitable for tablet, capsule, pill, suppositories and injectable dosage forms. Illicit eutylone is often used via oral administration in the form of tablets, capsules, crystals and pills. However, some online users have reported using eutylone via the intranasal route (WHO 2021). Some online Reddit users have reported to using eutylone intravenously (Reddit 2021). Users report to feeling the effects of eutylone from a 35mg dose, but average illicit doses range between 60 to 100mg (WHO 2021).

4-CMC is usually administered orally or intranasally, though there is potential for intravenous use. Oral dosing tends to range between 100 to 300mg. With nasal insufflation, the dose ranges between 50 to 150mg. Some tolerant users have reported consuming up to 1g of 4-CMC (WHO 2019).

There is limited information available on the doses of dimethylpentylone consumed by users.

Pharmacodynamics

Synthetic cathinones are similar to amphetamines due to interactions with membrane dopamine, noradrenaline, and serotonin transporters resulting in increased synaptic monoamine concentrations. This could be via monoamine neurotransmitter reuptake inhibition, promotion of monoamine transmitter release or both (Almeida et al 2022). Different cathinones can cause varying changes in extracellular neurotransmitter

concentrations and therefore, may account for the range of psychoactive effects, toxicity, and abuse liability observed with synthetic cathinones (Capriola 2013).

In *in vitro* experiments, eutylone inhibits neurotransmitter (dopamine, noradrenaline and serotonin) reuptake and has substrate activity at the serotonin transporter (Glatfelter et al 2021). In human embryonic kidneys cells, eutylone demonstrated higher affinity for the dopamine transporter (Ki = 640nM) compared to the noradrenaline transporter (Ki = 1,870nM) or serotonin transporter (Ki = 8,500nM). Notably, eutylone had a similar affinity to the dopamine transporter as cocaine (Ki = 750nM) but less than methamphetamine (Ki = 4,660nM) and methcathinone (Ki = 6,600nM). Eutylone is a more potent inhibitor of serotonin uptake compared to methamphetamine (14 times) and methcathinone (56 times), but less potent as an inhibitor of norephedrine uptake than methamphetamine and methcathinone (approximately 30- and 18- times respectively) (WHO 2021). *In vivo* behavioural studies using Swiss-Webster mice demonstrated subcutaneous administration of eutylone stimulated locomotion in a dose-dependent manner (ED_{50} = 2mg/kg) (Glatfelter et al 2021).

Likewise, 4-CMC binds to dopamine, noradrenaline and serotonin transporters but at lower affinities (Ki = 9410nM, 28,700nM and 19,600nM respectively). 4-CMC also stimulates dopamine, serotonin and noradrenaline release at the synaptic cleft. Compared to methamphetamine, 4-CMC released more serotonin (EC_{50} value 1,980nM vs. 27,500nM) and less noradrenaline (EC_{50} value 1,240nM vs. 152nM) (Eshelman et al 2017). *In vivo* animal behavioural models demonstrated that administration of 4-CMC (5 to 20mg/kg) resulted in potent stimulation of horizontal locomotor activity and elevated vertical activity (Wojcieszak 2020).

Dimethylpentylone binds to dopamine, serotonin and noradrenaline receptors and inhibits neurotransmitter reuptake. It demonstrates higher affinity for dopamine receptors (Ki = 354nM) compared to serotonin and noradrenaline receptors (Ki = 2270nM, Ki=2000 nM respectively). Furthermore, it is more potent at inhibiting dopamine and noradrenaline uptake at these receptors compared to cocaine (hDAT IC_{50} 233nM vs. 425nM, hNET IC_{50} 425nM vs. 382nM) (Eshleman et al 2019).

Pharmacokinetics

There is limited information on the pharmacokinetics of eutylone, 4-CMC and dimethylpentylone.

Similar to other 3,4-methylenedioxy cathinone derivatives, eutylone is predicted to undergo hepatic metabolism mediated by CYP2D6 and CYP2C19. In blood, eutylone showed a half-life of 31 days at 20˚C and 4.8 days at 32˚C (WHO 2021).

User reports for 4-CMC suggest that onset of action from oral dosing is 30 to 60 minutes and from nasal insufflation 2 to 3 minutes. 4-CMC has been associated with poor stability in human serum specimens when stored at 4°C. In a report involving a blood sample from a 27-year-old male, 4-CMC was detected at 11.5ng/mL at the time of analysis but the detected concentration dropped by 65% on the third day after the first measurement (Nowak et al 2018).

In *in vitro* models using telencephalon tissue from Sprague-Dawley rats, dimethylpentylone was detected in brain tissue following a 3mg/kg intraperitoneal dose. The reported

dimethylpentylone concentration in the brain tissue was 762ng/g (approximately 20% of the administered dose) indicating some blood-brain barrier permeability (Fabgregat-Safront et al 2020).

4.3 Toxicology

WHO reports that the toxic dose for eutylone is not known (WHO 2021). There does not appear to be a correlation between blood and urine concentrations of eutylone to severity of clinical presentation. Urine samples from 11 cases presenting in Taiwan emergency departments between January 2019 to July 2020 had eutylone concentrations ranging from 210 to 18,364ng/mL. These concentrations were unrelated to the severity of clinical presentation (Chen et al 2021). In the United States, the concentration of eutylone in post-mortem blood ranged between 1.2 to 11,000ng/mL in 67 cases (Krotulski et al 2021).

The toxic dose for 4-CMC is not known. One study analysed the blood concentration of 4-CMC in 15 forensic cases in Poland. The 4-CMC concentration in non-fatal cases ranged from 1.3 to 75.3mg/mL and in fatal cases from 56.2 to 1870ng/mL (Tomczak et al 2018).

In the United States, dimethylpentylone has been implicated in 26 post-mortem cases between August 2021 and March 2022. The dimethylpentylone concentration in post-mortem blood from 5 cases ranged between 33 to 970ng/mL (NPS Discovery 2022).

4.4 Risk to public health

Synthetic cathinones pose a notable risk to public health in New Zealand due to use as a prevalent MDMA adulterant and their associated negative effects. Unintentional synthetic cathinone use often occurs from misrepresented MDMA (NDIB 2021).

Wastewater analyses were collected from 25 sites across 10 different countries, including New Zealand, over the 2020/2021 New Year period. Eutylone was detected in wastewater samples across several countries, indicating an international presence for this substance. Eutylone levels were particularly significant in New Zealand with mass loads reported up to 52mg/day/1000 people in a single New Zealand site during the period. This was higher than observed in the other countries (Bade et al 2022). DIANZ released a media release cautioning the prevalence of eutylone as more than half of the MDMA tablets tested during the 2020/2021 New Year period were found to contain cathinones with eutylone being observed as the most common substitute (DIANZ 2021d). In February 2021, KnowYourStuffNZ reported a dangerous amount of eutylone in pink and yellow “Red Bull” tablets circulating within New Zealand. These pink tablets contained between 300 to 350mg of eutylone and contained no MDMA (KnowYourStuffNZ 2021a). DIANZ reported that the amount was “dangerous and very likely to cause harm” (DIANZ 2021a). NDIB reports that those who purchase and consume synthetic cathinones unknowingly are likely to be inexperienced and/or infrequent drug users and thus, likely to experience higher levels of harm (NDIB 2021).

Since 2018, eutylone is known to have been implicated in 2 Land and Transport Act cases in New Zealand including impaired and hospitalised drivers. Alcohol was also detected in one of these cases (ESR, personal communications, August 2022).

The negative health impacts of eutylone and 4-CMC are well documented. A retrospective study into 11 patients with eutylone-related emergency department admissions in Taiwan highlighted that agitation and delirium were common manifestations. Almost all the patients had documented tachycardia (pulse rate >100 per minute). Some patients had documented hyperthermia, hypertension, leukocytosis and rhabdomyolysis. Of the 11 cases, most recovered within 12 hours with favourable outcomes, however, one case had a fatal outcome (Chen et al 2021). Between 2015 and 2017, 4-CMC was detected in blood samples in 15 forensic cases in Poland involving driving under the influence, and in fatalities from overdoses, suicide and traffic accidents. Only one of the 15 cases had 4-CMC detected as the only psychoactive substance. This case had reported agitation, joyful expressions, increased drive, tachycardia, dilated pupils and difficulty in picking objects up from the ground (Tomczak et al 2018).

The risk of harm specifically related to dimethylpentylone is not currently known. However, the presence of the dimethylpentylone has been detected in some deaths.

4.5 Potential to cause death

Eutylone, 4-CMC and dimethylpentylone have been implicated in deaths internationally and domestically.

In Japan, there was a fatal report of intoxication from a single dose of eutylone. The 32-year-old male experienced a cardiac arrest and was pronounced dead on arrival to the hospital, approximately 50 minutes after the emergency call was made. Other clinical history and physical findings included abnormal behaviour, severe hyperthermia and elevated biochemistry (blood sodium, total protein, albumin) which suggested severe dehydration. Dehydration and renal failure are clinical features consistent with synthetic cathinone intoxication. The case was receiving regular intramuscular aripiprazole injections. However, analysis of cardiac blood and gastric contents suggested that this case involved intoxication of eutylone alone prior to death. The blood concentration of eutylone from the peripheral blood taken at the emergency department was 2500ng/g. This was lower than the concentration measured at the autopsy (4290ng/g) suggesting a possibility of post-mortem redistribution (Nakamura et al 2022).

In the United States, eutylone was detected in 343 deaths in 2020 (CDC 2022).

In Poland, there were 6 fatal cases between 2015 to 2017 involving 4-CMC alongside other psychoactive substances. These deaths were a result of either car accidents, suicides, or acute intoxication (Tomczak et al 2018).

In New Zealand coronial cases, the presence of these synthetic cathinones has been detected in post-mortem samples. Eutylone has been implicated in 19 coronial cases between 2018 and August 2022, 13 of which occurred in 2021. In 17 of these 19 cases, other substances were detected alongside eutylone. Dimethylpentylone has been implicated in 2 New Zealand coronial cases in 2022. There have been no known coronial cases involving 4-CMC in New Zealand (ESR, personal communications, August 2022).

4.6 Potential for physical or psychological dependence

Cathinones affect dopamine neurotransmission which could theoretically contribute to dependence. However, there have been no known studies on eutylone, 4-CMC or dimethylpentylone dependence in humans specifically.

WHO reported a drug discrimination study in Sprague-Dawley rats where eutylone fully substituted the discriminative stimulus effects of the training dose of 1mg/kg methamphetamine following the intraperitoneal administration of eutylone in doses between 1 to 10mg/kg (WHO 2021).

In drug discrimination assays with rats, 4-CMC substituted fully for the discriminative effects of methamphetamine (at 1mg/kg intraperitoneal), cocaine (at 10mg/kg intraperitoneal) and MDMA (at 1.5mg/kg) (Gatch et al 2019). 4-CMC also had rewarding effects in a brain stimulation model that is predictive of abuse potential (Negus and Banks 2017). In Poland, one of the fatal cases (suicide) related to 4-CMC and had a 4-CMC blood concentration of 1870ng/mL. The author suggested that the case had likely developed a degree of tolerance to 4-CMC to be able to consume the likely dose needed to achieve this concentration. Reports from online user forums have indicated that some users have used doses up to 1000mg indicating a degree of tolerance with repeated administration. However, it is not possible to verify that the substance consumed by these users was actually 4-CMC (WHO 2019).

5 CLASSIFICATION

5.1 New Zealand classification and regulation

Eutylone, 4-CMC and dimethylpentylone are currently regulated as controlled drug analogues under the Misuse of Drugs Act 1975. The Ministry of Health considers that these substances share substantial structural similarities to named substances under this Act.

As controlled drug analogues, the substances are treated as Class C7 controlled drugs.

5.2 International classification and regulation

Australia

Eutylone, 4-CMC, and dimethylpentylone are likely to be captured under Schedule 9 of the Poisons Standard as the entry “cathinones except when separately specified in these Schedules”.

Eutylone, 4-CMC and dimethylpentylone are not specified elsewhere in the schedules.

United Kingdom

Eutylone, 4-CMC and dimethylpentylone are controlled as Class B controlled drugs under the Misuse of Drugs Act 1971.

United States

Eutylone is controlled under Schedule I of the Controlled Substances Act 1970 in the United States.

4-CMC is not scheduled under the Controlled Substances Act 1970 but it is considered a Schedule I controlled substance by a number of states in the United States, such as Virginia and Florida (Virginia Law 2022; The Florida Senate 2022).

Dimethylpentylone is not listed in the schedules of the Controlled Substances Act 1970 but it could be considered an isomer of N-ethyl pentylone, a Schedule I substance.

Canada

Eutylone, 4-CMC and dimethylpentylone are controlled under Schedule I of the Controlled Drugs and Substances Act 1996 in Canada.

5.3 UN classification

In March 2020, 4-CMC was included in Schedule II of Convention on Psychotropic Substances of 1971.

In March 2022, eutylone was included in Schedule II of Convention on Psychotropic Substances of 1971.

Dimethylpentylone is not currently controlled under the United Nations Drug Control Conventions.

6 OTHER RELEVANT INFORMATION

6.1 History in New Zealand

Prevalence of synthetic cathinone related harm increased following the ban on legal highs with the introduction of the Psychoactive Substances Act 2013. As of 2021, 26 different synthetic cathinones have been detected in New Zealand (NDIB 2021).

6.2 Anticipated future trends

New Zealand's synthetic cathinone market reflects international trends as these substances are manufactured overseas and imported into New Zealand. As one synthetic cathinone is brought under international control, a new analogue is introduced to the illicit market to avoid regulation. Eutylone was first detected in New Zealand in 2019, at the same time as it first appeared in the United States. The increase of domestic dimethylpentylone seizures in 2022 aligns with the current increasing dimethylpentylone prevalence in the United States.

7 CLASSIFICATION OPTIONS

Option 1 – Maintain status quo

Eutylone and 4-CMC are captured as Class C7 controlled drug analogues of methcathinone under the Misuse of Drugs Act 1975.

Dimethylpentylone is captured as a Class C7 controlled drug analogue of MDMA under the Misuse of Drugs Act 1975.

Penalties for the Class C controlled drugs are listed in Table 3 below.

Choosing this option will mean that New Zealand is not aligned with the scheduling in the United Nations Convention on Psychotropic Substances 1971 for eutylone and 4-CMC.

Dimethylpentylone has not been reviewed by the Expert Committee on Drug Dependence (ECDD) or scheduled under the United Nations Convention on Psychotropic Substances 1971.

Option 2 – Schedule as a Class A controlled drug under the Misuse of Drugs Act 1975

Substances posing a very high risk of harm to individuals or society that are highly addictive and liable to abuse, or are easily convertible into drugs that are similarly addictive and liable to abuse.

There may be additional implications for substances that are captured as an analogue of eutylone, 4-CMC and dimethylpentylone.

The regulatory penalties for Class A controlled drugs are listed below in Table 3. For a full breakdown on the controls, please see the EACD guidelines.

Dimethylpentylone has not been reviewed by the ECDD or scheduled under United Nations Convention on Psychotropic Substances 1971.

Option 3 – Schedule as a Class B controlled drug under the Misuse of Drugs Act 1975

Substances posing a high risk of harm to individuals or society that can be highly addictive and liable to abuse, or are easily convertible into drugs that are similarly addictive and liable to abuse.

There may be additional implications for substances that are captured as an analogue of eutylone, 4-CMC and dimethylpentylone.

The penalties for Schedule 2 (Class B) controlled drugs are listed below in Table 3. For a full breakdown of the differences in control between these parts of Schedule 2, please see the EACD guidelines.

Dimethylpentylone has not been reviewed by the ECDD or scheduled under United Nations Convention on Psychotropic Substances 1971.

Option 4 – Schedule as a Class C controlled drug under the Misuse of Drugs Act 1975

Substances posing a moderate risk of harm to individuals or society and a moderate to high risk of abuse and dependency or are easily convertible into drugs that are similarly addictive and liable to abuse.

There may be additional implications for substances that are captured as an analogue of eutylone, 4-CMC and dimethylpentylone.

The penalties for Schedule 3 (Class C) controlled drugs are listed below in Table 3. For a full breakdown of the differences in control between these parts of Schedule 3, please see the EACD guidelines.

Dimethylpentylone has not been reviewed by the ECDD or scheduled under United Nations Convention on Psychotropic Substances 1971.

Table 3: Comparison of regulatory requirements and penalties under the Misuse of Drugs Act 1975

Class	Requirements	Penalties
A	Ministerial approval required for supplying, administering, prescribing, or granting licences to deal in, import or export Class A controlled drugs – except for cocaine and derivatives. All Class A controlled drugs must be kept in a controlled drugs safe.	Maximum penalty of life imprisonment for the importation, manufacture or supply (subject to presumption of supply). Up to 14 years imprisonment for conspiracy to commit an offence. Up to 6 months imprisonment or $1,000 fine or both for possession.
B1	Ministerial approval required for supplying, administering, prescribing, or granting licenses to deal in, import or export Class B1 controlled drugs – except for morphine or opium and derivatives, or a CBD product. Must be kept in a controlled drugs safe.	All Class B drugs hold the same maximum penalties for offences involving these drugs. Up to 14 years imprisonment for importation, manufacture, or supply (subject to presumption of supply) Up to 10 years imprisonment for conspiracy to commit an offence Up to 3 months imprisonment or $500 fine or both for possession
B2	Ministerial approval required for prescribing, dispensing, and administration. No Ministerial approval required for granting licences to deal in, import or export Class B2 controlled drugs. Must be kept in a controlled drugs safe.	
B3	No Ministerial approval required for supplying, administering, prescribing or granting licenses to deal in, import or export Class B3 controlled drugs. Must be kept in a controlled drugs safe.	
C1	A person who wishes to import, manufacture, and supply or administer a Class C1 controlled drug must apply for a written approval of the Minister for issuance of a licence to do so.	All Class C drugs hold the same maximum penalties for offences involving these drugs. The penalty for anyone caught in possession of a class C controlled drug for

	Class C1 drugs are required to be stored in a safe.	personal use without a prescription is the same as that for a prescription medicine (3 months imprisonment and/or a $500 fine). The penalties for anyone involved in the importation, manufacture and supply of Class C drugs is up to 8 years imprisonment, or, summarily, one year jail and/or a $1,000 fine (similar or slightly harsher than for a prescription medicine). The penalty for conspiracy to commit an offence involving Class C drugs is up to 7 years imprisonment, and up to 3 months imprisonment or a $500 fine or both for possession.
C2-5	A person who wishes to import, manufacture, and supply or administer a Class C 2-5 controlled drug must obtain a licence to do so but doesn't need the written approval from the Minister. Class C2-4 drugs are required to be stored in a safe. Class C5 drugs are not required to be stored in a safe.	

8 PRESUMPTION FOR SUPPLY

8.1 Options for presumption of supply

Option 1: Status Quo

Option 1 is to set no presumption of supply.

The default amount of **56 grams** will apply. This is likely to be approximately **560 doses** of eutylone or 4-CMC (based on 100mg oral dose).

There is currently no information on the doses used by users of dimethylpentylone.

Option 2: Proposed presumption of supply

Option 2 is to set a presumption for supply at:

5 grams or **100 doses**, whether or not contained in a substance, preparation, or mixture, or **25 flakes, tablets, capsules, or other drug forms**, each containing some quantity of the drug

From information available on reported doses, 5 grams is likely to be approximately 50 doses of eutylone or 4-CMC (based on 100mg oral dose) or 17 doses of 4-CMC (based on 300mg oral dose). There is currently no information on the doses used by users of dimethylpentylone.

This presumption of supply is consistent with the presumption of supply set for other synthetic cathinones, ethylone and N-ethyl pentylone.

9 FUTURE ACTIONS

If the Committee recommends that eutylone, 4-CMC and dimethylpentylone should be scheduled under the Misuse of Drugs Act 1975, the Secretariat will draft a letter from the Committee to the Minister of Health to progress the advice. The Secretariat may undertake targeted consultation with industry to ensure impacts on legitimate uses of eutylone, 4-CMC

and dimethylpentylone are reasonable and minimised. If the status quo is kept, no further action is required.

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