Synthetic cannabinoids: MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F-MDMB-BINACA, 4F-MDMB-BICA, ADB-BUTINACA

Report to the Expert Advisory Committee on Drugs

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Contents

EXECUTIVE SUMMARY

MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA are synthetic cannabinoids regulated in New Zealand either as controlled drug analogues under the Misuse of Drugs Act 1975, or as psychoactive substances under the Psychoactive Substances Act 2013.

Schedule II of the Convention on Psychotropic Substances 1971 places MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, and 4F-MDMB-BINACA under international control. As a signatory to this convention, New Zealand is obliged to review the classification of these substances under domestic legislation.

In 2021, 4F-MDMB-BICA was considered, but not recommended for scheduling under the Convention on Psychotropic Substances 1971 by the World Health Organization (WHO), Expert Committee on Drug Dependence (ECDD).

ADB-BUTINACA is a novel synthetic cannabinoid detected internationally and is the subject of a critical review for the 45th WHO ECDD meeting. The National Drug Intelligence Bureau (NDIB) recommended 4F-MDMB-BICA and ADB-BUTINACA for consideration by the Expert Advisory Committee on Drugs) due to evidence of their harm in New Zealand.

International evidence has demonstrated these 6 synthetic cannabinoids are cannabinoid receptor agonists, and notable, novel, psychoactive substances of abuse. These substances have been detected and seized in New Zealand. None of the substances in this paper have any therapeutic value.

In general, synthetic cannabinoids (and specifically MDMB-4en-PINACA and 4F-MDMB-BICA) have been the subject of 6 notifications by Drug Information and Alerts, Aotearoa New Zealand (DIANZ). They have been identified as contributing to many hospitalisations and deaths, both domestically and internationally. The high potency of synthetic cannabinoids and inconsistency in finished product poses a high risk of accidental poisoning. These substances appeal to and are used by vulnerable populations within New Zealand.

INTRODUCTION

2.1 Purpose

This report provides an overview of 6 synthetic cannabinoids which 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 prepared by the World Health Organization (WHO) on the individual substances, is provided alongside this paper.

The synthetic cannabinoids to be considered by the Committee are:

- MDMB-4en-PINACA
- 5F-AMB-PINACA
- CUMYL-PEGACLONE
- 4F-MDMB-BINACA
- 4F-MDMB-BICA
- ADB-BUTINACA.

2.2 Substance classification

The Ministry of Health (the Ministry) considers MDMB-4en-PINACA, 5F-AMB-PINACA, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA to be substantially structurally similar to the Class A controlled drug 5F-ADB. Controlled drug analogues are controlled as Class C7 controlled drugs under the Misuse of Drug Act 1975.

The Ministry considers CUMYL-PEGACLONE to be psychoactive. Depending on their intended use, substances that are psychoactive may be controlled by the Psychoactive Substances Act 2013.

2.3 Why are these substances being considered?

As part of New Zealand's obligations as a signatory to the UN Convention on Psychotropic Substances 1971, the following substances are being considered for scheduling by the Committee:

- MDMB-4en-PINACA
- 5F-AMB-PINACA
- CUMYL-PEGACLONE
- 4F-MDMB-BINACA.

Following assessment and recommendation for scheduling by the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD), the above substances have been scheduled under Schedule II of the UN Convention on Psychotropic Substances 1971 (UN 2022).

In 2021, the ECDD assessed 4F-MDMB-BICA and recommended that it be kept under surveillance by the WHO Secretariat. 4F-MDMB-BICA was not recommended for scheduling at the time (WHO 2021b).

As a novel synthetic cannabinoid, recently detected internationally, ADB-BUTINACA was recommended to the Committee for consideration by the National Drug Intelligence Bureau (NDIB) (CFSRE 2020; NDIB, personal communications, 2022). A critical review of ADB-BUTINACA was prepared for the 45th ECDD meeting this year on 10 October to 14 October (WHO 2022).

SUBSTANCE IDENTIFICATION AND CHEMISTRY

3.1 Identification

MDMB-4en-PINACA

IUPAC Name:

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

CAS Number: 2504100-70-1

Molecular weight: 357.4g/mol

Molecular formula: $C_{20}H_{27}N_3O_3$

Appearance: a white, yellow, brown or tan powder (WHO 2020b)

Solubility: soluble in chloroform, methanol, ethanol, dimethylformamide and dimethyl sulfoxide (Cayman Chemical 2022a; WHO 2020b)

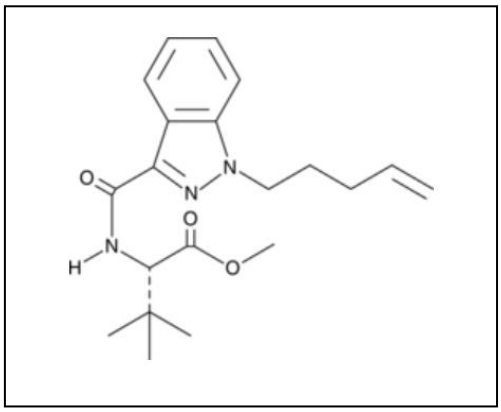

Figure 1: Chemical structure of MDMB-4en-PINACA

5F-AMB-PINACA

IUPAC Name: methyl (1-(5-fluoropentyl)-1H-indazole-3-carbonyl)valinate

CAS Number: 1801552-03-3

Molecular weight: 363.4g/mol

Molecular formula: $C_{19}H_{26}FN_3O_3$

Appearance: crystalline solid, powder (Cayman Chemical 2022c)

Solubility: soluble in dimethylformamide, dimethyl sulfoxide and ethanol (Cayman Chemical 2022c)

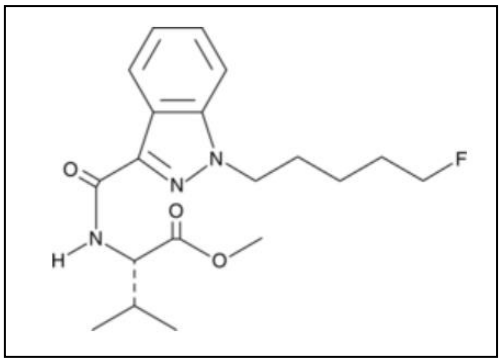

Figure 3: Chemical structure of 5F-AMB-PINACA

CUMYL-PEGACLONE

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

CAS Number: 2160555-55-3

Molecular weight: 372.5g/mol

Molecular formula: $C_{25}H_{28}N_2O$

Appearance: crystalline solid, white powder (Cayman Chemical 2022d; WHO 2020a)

Solubility: soluble in dimethylformamide, partially soluble in methanol (Cayman Chemical 2022d)

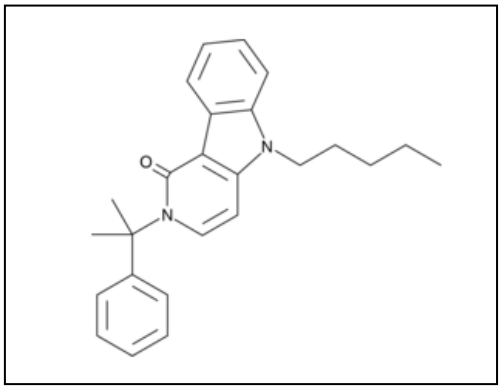

Figure 4: Chemical structure of CUMYL-PEGACLONE

4F-MDMB-BINACA

IUPAC Name:

methyl 2-(1-(4-fluorobutyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate

CAS Number: 2390036-46-9

Molecular weight: 363.4g/mol

Molecular formula: $C_{19}H_{26}FN_3O_3$

Appearance: off-white or white solid, a neat solid (Cayman Chemical 2022e; WHO 2019b)

Solubility: soluble in dimethylformamide, ethanol, dichloromethane and methanol; partially soluble in water (Cayman Chemical 2022e)

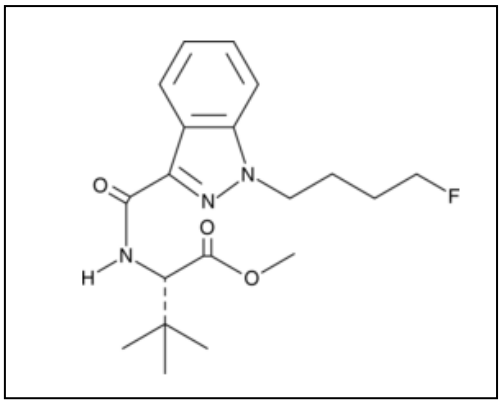

Figure 5: Chemical structure of 4F-MDMB-BINACA

4F-MDMB-BICA

IUPAC Name:

methyl 2-({[1-(4-fluorobutyl)-1H-indol-3-yl]carbonyl}amino)-3,3-dimethylbutanoate

CAS Number: not yet assigned at time of writing

Molecular weight: 362.4g/mol

Molecular formula: $C_{20}H_{27}FN_2O_3$

Appearance: a white crystalline solid; white, off-white, brown or orange powders (Cayman Chemical 2022b; EMCDDA 2022a; WHO 2021a)

Solubility: soluble in chloroform, dimethylformamide and ethanol; partially soluble in dimethyl sulfoxide (Cayman Chemical 2022b; EMCDDA 2022a)

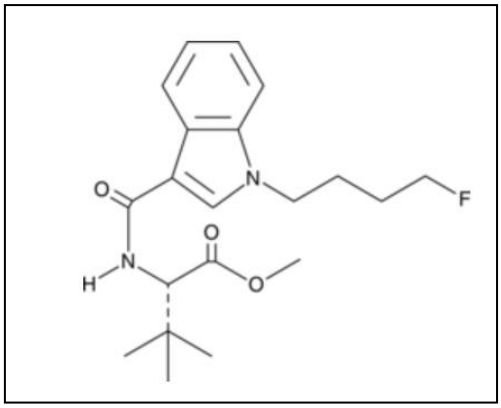

Figure 2: Chemical structure of 4F-MDMB-BICA

ADB-BUTINACA

IUPAC Name: 1-butyl-N-(1-carbamoyl-2,2-dimethyl-propyl)indazole-3-carboxamide

CAS Number: 2748155-93-1

Molecular weight: 330.4g/mol

Molecular formula: $C_{21}H_{24}N_4O_2$

Appearance: crystalline solid (Cayman Chemical 2022f)

Solubility: soluble in dimethylformamide, dichloromethane and methanol, less soluble in dimethyl sulfoxide, and partially soluble in water (Cayman Chemical 2022f; CFSRE 2020)

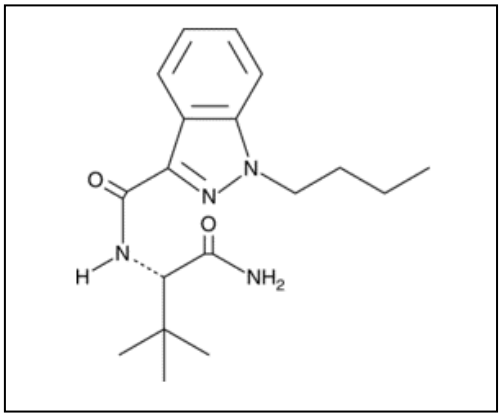

Figure 6: Chemical structure of ADB-BUTINACA

3.2 Therapeutic value

There are no known therapeutic uses for MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F-MDMB-BINACA and 4F-MDMB-BICA, (WHO 2019a, 2019b, 2020a, 2020b, 2021a). Additionally, a literature search found no therapeutic uses for ADB-BUTINACA.

3.3 Similarities to other known substances

The Ministry considers MDMB-4en-PINACA, 5F-AMB-PINACA, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA to be substantially structurally similar to the Class A controlled drug 5F-ADB. The Ministry does not consider CUMYL-PEGACLONE to be substantially structurally similar to any substance currently scheduled under the Misuse of Drugs Act 1975. These substances are all structurally and pharmacologically similar to other synthetic cannabinoids.

Structural similarities

Structurally, these 6 synthetic cannabinoids belong to either indazole-3-carboxamide, indole-3-carboxamide or carboline-1-one groups. The structure of these synthetic cannabinoids can be defined in terms of the core, tail, linker and linked group components (EMCDDA 2017). See Figure 7 for how these elements combine. MDMB-4en-PINACA, 5F-AMB-PINACA, 4F-MDMB-BINACA and ADB-BUTINACA are indazoles with substitutions at the 1- and 3-positions. 4F-MDMB-BICA is an indole with substitution at the 1- and 3- positions. CUMYL-PEGACLONE is a based on a gamma-carboline-1-one structure.

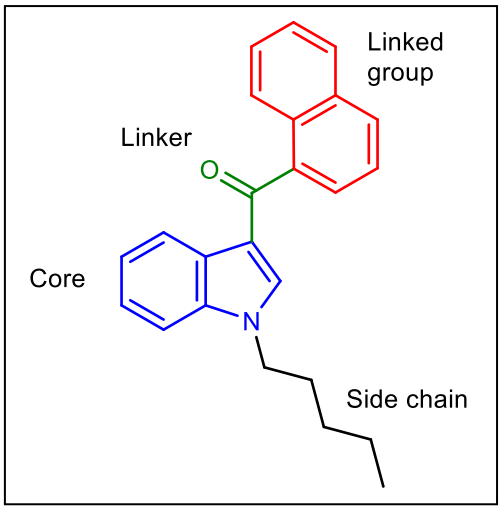

Figure 7: Example of the general synthetic cannabinoid structure.

Similarity to 5F-ADB

MDMB-4en-PINACA, 5F-AMB-PINACA, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA are structurally similar to 5F-ADB, shown in Figure 8, but they differ as follows:

- MDMB-4en-PINACA replaces the tail group with a pent-4-ene moiety
- 5F-AMB-PINACA has one less methyl group in the linked group
- 4F-MDMB-BINACA replaces the tail group with a 4-fluorobutyl group
- 4F-MDMB-BICA replaces the core with an indole structure, and the tail group with a 4-fluorobutyl moiety
- ADB-BUTINACA replaces the tail group with a butyl group and replaces the linked group with a 3,3-dimethylbutanamide group.

CUMYL-PEGACLONE does not share substantial structural similarity to 5F-ADB, though both have a 5F-pentyl tail group.

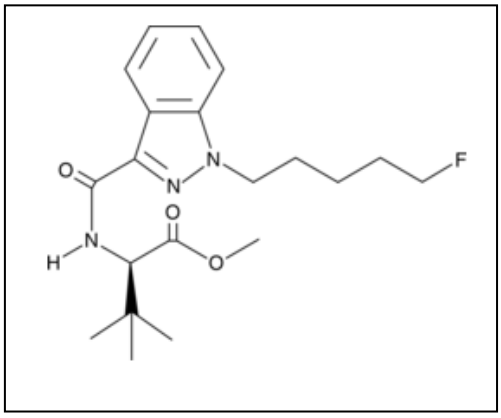

Figure 8: Chemical structure of 5F-ADB

Pharmacological similarities

Pharmacologically, all 6 substances are reported to be cannabinoid receptor one (CB1) agonists (Cannaert et al 2020; WHO 2019a; WHO 2020a). This is similar to the CB1

agonism of other synthetic cannabinoids scheduled under the Misuse of Drugs Act 1975, though the degree of receptor agonism may vary.

Similarities in risk of harm

The risk of harm for these substances is similar to other synthetic cannabinoids currently scheduled in the Misuse of Drugs Act 1975. There may be differences in the potency of these synthetic cannabinoids but generally, when compared to cannabis or tetrahydrocannabinol (THC), they represent a higher risk of harm (EMCDDA 2021). Noting the risk in relation to cannabis is important for synthetic cannabinoids, as synthetic cannabinoid smoking mixtures, may be positioned as alternatives to cannabis (NDIB 2022).

3.4 Methods and ease of manufacturing

Various published synthesis methods exist for the substances in this report, including the following:

- Synthesis of MDMB-4en-PINACA, 4F-MDMB-BICA, and ADB-BUTINACA has been described by Cannaert et al 2020)
- Synthesis of 4F-MDMB-BINACA can follow the same Cannaert et al (2020) synthesis or existing routes for related synthetic cannabinoids, such as 5F-ADB or 5F-MDMB-PICA (EMCDDA 2022a; WHO 2019b).
- Synthesis of 5F-AMB-PINACA has been published by Banister et al (WHO 2019a).
- Synthesis of CUMYL-PEGACLONE has been published by Janssens et al and may follow the synthesis pathway of CUMYL-PICA (WHO 2020a).

Chemical synthesis of indole or indazole synthetic cannabinoids generally follow a 3-step route which may be modified to manufacture a range of synthetic cannabinoids using cheap and readily available reagents (Cannaert et al 2020; EMCDDA 2022a).

The 3 step synthesis routes as described by Cannaert et al are described below.

Synthesis of an indazole may involve:

1. alkylation of a 3-carboxy indazole ester with the tail group
2. hydrolysis of ester in the linker
3. amide formation between the linker and the linked group (Cannaert et al 2020; WHO 2019a).

Synthesis of an indole may involve:

1. alkylation of the indole with the tail group and treatment with trifluoroacetic anhydride forming a N-alkyl-3-(trifluoroacetyl)indole
2. hydrolysis of this new linker
3. amide formation between the linker and the linked group (Cannaert et al 2020).

Manufacture by these processes is straight-forward but requires chemical laboratory equipment and knowledgeable personnel (WHO 2019b). The magnitude of illicit manufacture is not known for any of these substances. Illicitly manufactured substances have no quality control resulting in heterogeneous products with inconsistent strengths. They may also contain harmful residues including solvents, pesticides or toxins (EMCDDA 2022b).

Following synthesis, synthetic cannabinoid powders are shipped to the destination country where smoking mixtures are prepared and used (NDIB 2022). Smoking mixtures are prepared by dissolving synthetic cannabinoid in a solvent which is then sprayed onto inert plant material and dried (EMCDDA 2022a). This is the most common method of manufacture in New Zealand (NDIB 2022). Other synthetic cannabinoid preparations are outlined in the WHO reports provided.

RISK OF HARM

4.1 Likelihood or evidence of abuse in New Zealand

Synthetic cannabinoids appeal to and are used at higher rates by vulnerable and low-socioeconomic populations (NDIB 2022; NZ Drug Foundation 2022). People who use synthetic cannabinoids often have complex support needs and are disengaged from support services. Many are homeless or in emergency temporary housing and may also be experiencing mental illness (NZ Drug Foundation 2022). Anecdotal evidence suggests that where numbers of people in temporary housing rise, this may contribute to increases in synthetic cannabinoid use and harm (NDIB 2022). Synthetic cannabinoid users tend to be male, across the age spectrum. Māori are disproportionally affected by use of synthetic cannabinoids (NDIB 2022; NZ Drug Foundation 2022).

Dissociation is the primary motivator for use of synthetic cannabinoids. They are cheap, easy to access and make people feel “completely out of it” (NDIB 2022; NZ Drug Foundation 2022). The vulnerability of the user demographic means they use them as a coping mechanism for life circumstances (NDIB 2022). Despite being aware of the risk of harm, some consumers continue to use synthetic cannabinoids either due to addiction or to “escape daily reality” (NZ Drug Foundation 2022). Treatment providers find that synthetic cannabinoid users are most likely to change use behaviours when harm occurs to someone close to them. The motivations for use may mean people consider the benefits associated with synthetic cannabinoids (dissociation), outweigh the risk of harm (NDIB 2022).

The low price allows people who use synthetic cannabinoids to access them regularly, and likely motivates use. Synthetic cannabinoids may have a higher potency than similarly priced cannabis – this too may motivate consumption (NDIB 2022). In New Zealand, synthetic cannabinoid smoking mixtures cost $20 per 1-3g bag, similar to the cost for the same amount of cannabis. The cost internationally is around $6,100 per kg of synthetic cannabinoid powder (NDIB, personal communications, 2022). Typically, 1kg of synthetic cannabinoid powder can produce up to 10,000 bags of smoking mixture (sprayed plant material) (NDIB 2022). Based on the cost of powder compared to smoking mixtures, there is a high profit margin which incentivises supply and distribution of synthetic cannabinoids, especially compared to cannabis.

Synthetic cannabinoids have resulted in hospitalisations, psychiatric and long-term health harms in New Zealand (NZ Drug Foundation 2022). Since 2020, synthetic cannabinoids have been the subject of 6 Drug Information and Alerts Aotearoa New Zealand (DIANZ) warnings issued (DIANZ 2021a, 2021b, 2020a, 2020b, 2020c, 2020d). One warning referenced hospitalisations, and 3 warnings referenced deaths (4 deaths in total). Instances of harm and deaths were linked to 2 of the 6 substances being reviewed in this report (4F-MDMB-BICA and MDMB-4en-PINACA), as well as 2 other named synthetic cannabinoids

(5F-MDMB-PICA and MMB-2201), and a further unknown synthetic cannabinoid (DIANZ 2021a, 2020b). Notification locations were Christchurch, Taranaki and the lower North Island (DIANZ 2021a, 2021b, 2020b). The harm is likely greater than the specific instances reported (DIANZ 2021a, 2021b, 2020a, 2020b, 2020c). Some harm may not be captured due to a lack of reporting, or because some symptoms considered harmful (such as loss of consciousness) may actually be the desired effect of the user (NDIB 2022).

People using and suffering harm from synthetic cannabinoids likely have been using these substances for a long time (NZ Drug Foundation 2022). New Zealand hospitalisation data often cannot distinguish the specific synthetic cannabinoid involved. High proportions of Māori and Pasifika are hospitalised due to synthetic cannabinoids. In 2020, Māori, despite making up 16.5% of the general population, represented 56% of hospitalisations with synthetic cannabinoids as the primary diagnosis. Table 3 displays hospitalisation numbers for years 2017- 2020 where synthetic cannabinoids were the primary diagnosis (NDIB 2022).

Table 3: Hospitalizations with synthetic cannabinoids as the primary diagnosis between 2017 to 2021 (NDIB, personal communications, 2022)

Year	2017	2018	2019	2020	2021*
Number of Hospitalisations	67	81	26	16	12

**provisional data*

Other data reporting on the period 2015-2020 found an 11% reduction in the number of hospitalisations and a 25% reduction in calls to drug help lines (NDIB 2022).

New Zealand toxicology detections of the 6 synthetic cannabinoids in this report (excluding deaths referred to the coroner see section 4.6) is displayed in Table 4 (ESR, personal communications, July 2022). Toxicology samples are classified by 3 different case types:

- criminal forensic cases
- Unidentified Substances from Emergency Departments (USED), a program operating in limited hospitals for patients presenting with drug use symptoms
- Land Transport Act 1998 (LTA) cases which include impaired and hospitalised drivers. In some cases, these 6 substances are detected alongside other drugs.

Common co-detections included detection alongside each other and other synthetic cannabinoids (eg, MDMB-4en-PINACA has been detected alongside ADB-BUTINACA, 4F-MDMB-BINACA, 4F-MDMB-BICA, as well as alongside 5F-ADB, MMB-2201, 5F-MDMB-PICA, and AMB-FUBINACA in separate cases). The synthetic cannabinoids in this report were also detected alongside alcohol and cannabis, and less commonly alongside other drugs such as depressants like benzodiazepines, ketamine, tramadol, and zopiclone, as well as stimulants such eutylone and methamphetamine (ESR, personal communications, August 2022).

Table 4: Detections in toxicology samples between 2017 to 2021

Year	Case type	2018	2019	2020	2021	2022*
MDMB-4en-PINACA	Criminal	0	0	2	2	0
	USED	0	0	5	1	0
	LTA	0	0	1	1	1
5F-AMB-PINACA	Criminal					
	USED			No cases		
	LTA					
CUMYL-PEGACLONE	Criminal					
	USED			No cases		
	LTA					
4F-MDMB-BINACA	Criminal	0	0	1	2	0
	USED	0	0	1	0	0
	LTA	0	0	0	0	0
4F-MDMB-BICA	Criminal					
	USED			No cases		
	LTA					
ADB-BUTINACA	Criminal					
	USED			No cases		
	LTA					

**provisional data*

ESR have advised the following detections by drug checking services in Table 5 (ESR 2022a).

Table 5: Detections in drug checking samples between 2017 to 2021 (ESR 2022a)

	Year	2017/2018	2019	2020	2021	2022*
	MDMB-4en-PINACA	0	0	18	25	0
Number of detections	5F-AMB-PINACA	0	0	0	0	0
	CUMYL-PEGACLONE	0	0	0	0	0
	4F-MDMB-BINACA	0	11	13	1	1
	4F-MDMB-BICA	0	0	0	4	1
	ADB-BUTINACA	0	0	0	25	3

**provisional data*

New Zealand seizure data

New Zealand Customs Service (Customs) synthetic cannabinoid seizures are mainly of powders whereas, New Zealand Police (Police) mainly seizes finished synthetic cannabinoid plant material (NDIB 2022). Data from Police seizures (Table 7) indicate a declining trend for synthetic cannabinoids generally. This may be the result of many factors (NDIB 2022).

Synthetic cannabinoid presence, use and harm differs across New Zealand regions. 30% and 19% of Police seizures occurred in Auckland and Christchurch respectively. Police seizure data suggests synthetic cannabinoids are more prevalent in the North Island. In the South Island, Christchurch and Ashburton are the only seizure locations reported (NDIB 2022). Marked changes over time and regional splits in the specific synthetic cannabinoids present in finished smoking mixtures have been noted (ESR, personal communications, 2021). In 2020-2021, analysis of Police seizures showed MDMB-4en-PINACA at 40%, as

the primary synthetic cannabinoid in circulation, with 4F-MDMB-BICA at 8%, and both 4F-MDMB-BINACA and ADB-BUTINACA at 2% (NDIB 2022).

Seizure data for Police and Customs is found in tables 6 and 7 below. Note that seizures by Police do not usually get tested for specific cannabinoid content, and where specific substances were identified through testing, none related to the 6 substances being the subject of this report.

Table 6: Seizure quantities by Customs between 2017 and 2021

	Year	2017/2018	2019	2020	2021*
MDMB-4en-PINACA	Total quantity seized (g of powder)	0	0	910	0
	Number of Seizures	0	0	3	0
5F-AMB-PINACA	Total quantity seized (g of powder)	no seizures			
	Number of Seizures				
CUMYL-PEGACLONE	Total quantity seized (g of powder)	0	7	0	0
	Number of Seizures	0	2	0	0
4F-MDMB-BINACA	Total quantity seized (g of powder)	0	0	0	5
	Number of Seizures	0	0	0	1
4F-MDMB-BICA	Total quantity seized (g of powder)	0	0	516	0
	Number of Seizures	0	0	1	0
ADB-BUTINACA	Total quantity seized (g of powder)	no seizures			
	Number of Seizures				

**provisional data*

Table 7: Seizure quantities by Police of synthetic cannabinoids finished product between 2017 and 2021

Year		2017	2018	2019	2020	2021*
Synthetic Cannabinoid finished product	Plant Material (g)	49,897	37,551	13,229	9,062	2,676

**provisional data*

ESR advised of detections in the Customs-ESR Screening Laboratory (CESL) (Table 8) and of detections in Police and Customs evidential samples (Table 9).

In addition to the data in these tables below, there were 9 detections of 5F-AMB-PINACA in Police and Customs samples between November 2015 and March 2016, and a further detection in a Customs sample in June 2016. Since 2016 no further detections have been noted.

Table 8: ESR detections in the Customs-ESR Screening Laboratory between 2017 and 2021

	Year	2017/2018	2019	2020	2021	2022*
Number of detections	MDMB-4en-PINACA	0	0	6	0	0
	5F-AMB-PINACA	0	0	0	0	0
	CUMYL-PEGACLONE	0	1	0	0	0
	4F-MDMB-BINACA	0	4	0	0	0
	4F-MDMB-BICA	0	0	2	0	0
	ADB-BUTINACA	0	0	0	0	0

**provisional data*

Table 9: ESR detections in Police and Customs evidential samples

	Year	2017 / 2018 / 2019	2020	2021	2022*
Number of detections	MDMB-4en-PINACA	0	2	2	1
	5F-AMB-PINACA	0	0	0	0
	CUMYL-PEGACLONE	0	0	0	0
	4F-MDMB-BINACA	0	0	0	0
	4F-MDMB-BICA	0	0	2	0
	ADB-BUTINACA	0	0	0	0

**provisional data*

4.2 General pharmacology

All 6 substances in this paper are synthetic cannabinoids which demonstrate agonism of the CB1 receptor. They likely share the profile of centrally mediated effects such as THC-like intoxication, with other synthetic cannabinoids (WHO 2019a).

Acute physiological symptoms seen with synthetic cannabinoid use may include blood shot eyes, cognitive impairment, slowed movement, verbal slur, incoordination, somnolence or lethargy, mydriasis, nausea, vomiting (including hyperemesis), and impaired motor performance (EMCDDA 2022a; WHO 2019a).

More serious clinical symptoms include severe central nervous system depression, cardiovascular effects (tachycardia, hypertension, acute myocardial infarction, sudden cardiac death), acute kidney failure, loss of consciousness and seizures or convulsions (DIANZ 2020b; EMCDDA 2022a).

Acute psychological effects range from relaxed and unfocused euphoria, to feelings of distress. This may include confusion, agitation, delusions, catatonia, anxiety, acute psychosis. (DIANZ 2020b; EMCDDA 2022a; WHO 2019a).

However, these lists of symptoms and effects are not exhaustive.

Reasons for serious effects, and severe and fatal poisoning, are poorly understood, but may be due to high potency and exposure to unintentionally high doses (EMCDDA 2022a).

Reported effects (including clinical reports and user reports) for the substances in this report align with those outlined above (Tokarcyk et al 2022; WHO 2020a, 2020b, 2021, 2019b).

Routes of administration and dosage

Internationally, the primary route of administration for synthetic cannabinoids is inhalation (via smoking or vaping), primarily of smoking mixtures. Pure powder could be consumed either by the oral or sublingual route or by smoking or vaping, but this is not common. Vaping solutions containing synthetic cannabinoids are also used (WHO 2019a; 2020a, 2020b; 2021). Paper impregnated with synthetic cannabinoids has been reported as being vaped in prisons (for MDMB-4en-PINACA, and 4F-MDMB-BICA specifically) (WHO 2020b; WHO 2021).

In New Zealand, synthetic cannabinoids are primarily sold as a smoking mixture (NDIB 2022).

There is no reliable dosage information available for any of the substances presented in this paper (WHO 2019a, 2019b, 2020a, 2020b, 2021). Typical dosages are difficult to determine and depend on the tolerance of the user, other substances being used and the desired effect (EMCDD 2022b). Anecdotal dosage information has been summarised below:

- MDMB-4en-PINACA – 400µg reported as a strong oral dose, vaping 1.5mg/mL solution reported as a very strong effect (Reddit 2020a, 2021a)
- 5F-AMB-PINACA – likely active at less than 1mg (inhalation – smoking) possibly as low as 25 to 50µg (Bluelight 2015)
- CUMYL-PEGACLONE – oral ingestion of 0.6mg did not result in noticeable symptoms, may be active in a dosage of 50-75ug (unknown route of administration – likely inhalation) (Angerer et al 2019; Reddit 2022a)
- 4F-MDMB-BINACA – no user reports could be found
- 4F-MDMB-BICA – 50µg via inhalation reported as intoxicating with adjustments to ‘hits’ made for perceived potency, 20g/kg smoking mixture reported as having a strong effect (EMCDDA 2022b; Reddit 2020b)
- ADB-BUTINACA – 500ug/mL to 2mg/mL reported as having an effect (likely inhalation) or 75ug sublingually (Reddit 2021b; Reddit 2022b).

Dosage cannot be controlled in smoking mixtures (EMCDDA 2022b). The manufacturing process can result in varied strength, within and between, batches and may lead to “hot spots” of higher concentrations (Somerville et al 2017; WHO 2019a). Agitation of a smoking mixture can lead to further inhomogeneity. Impregnated paper can be similarly heterogenous. This makes it difficult to predict the strength of effects, increasing the risk of accidental poisoning and risks exacerbated by inhalation. Inhalation allows substances to take effect by being rapidly absorbed into the bloodstream (DIANZ 2021a; EMCDDA 2022b).

The specific synthetic cannabinoids present in smoking mixtures are frequently changed by manufacturers causing variation over time and place. Combined with differing potencies of different synthetic cannabinoids this increases the risk of accidental overdose as consumers are unlikely to be aware of these changes (EMCDDA 2022a, b; WHO 2019a).

In New Zealand there is a wide range of loadings for seized synthetic cannabinoid, smoking mixtures. Three main concentration ranges for these seized cannabinoids were found: between 5 and 100g/kg, 150 and 250g/kg, and greater than 250g/kg. Significantly more samples were found in the lower range.

Specifically, for newer generation synthetic cannabinoids, similar to those reported on in this paper, concentrations of 44 to 120 g/kg are reported internationally. The variation within samples is significant from 10% up to 141% (Somerville et al 2017). ESR have identified the average concentration of MDMB-4en-BINACA to be 43 g/kg (cannabinoid per plant matter) (NDIB 2022).

Pharmacodynamics

All studies suggested that all the substances in this report are CB1 receptor agonists, though the mechanism by which this was achieved varied.

MDMB-4en-PINACA binds to CB1 receptors as a full and potent agonist (WHO 2020b). *In vivo* studies in mice suggest a similar mechanism to other synthetic cannabinoids (EMCDDA 2022c). Unpublished pre-clinical study data on intraperitoneal administration in mice suggests it produces substantial lethargy and hypothermia at higher doses (1-10mg/kg) with some mice exhibiting seizures upon handling. Behaviour at 1mg/kg normalised within 2 hours, whilst mice dosed at 10mg/kg were still lethargic 5 hours post injection. In some mice 10mg/kg doses led to gasping and aggression which wore off by 3 hours post injection (WHO 2020b). Cannaert et al (2020) demonstrated CB1 agonism of MDMB-4en-PINACA in a live cell-based reporter assay, monitoring CB1 activation with interaction with β-arrestin2 *in vitro*. This assay considers non-canonical activation pathways (WHO 2021a). Activation of the CB1 receptor was compared to JWH-018. JWH-018 will be scheduled as a Class B1 controlled drug once the Misuse of Drugs (Classification and Presumption of Supply) Order 2022 comes into force. Based on this study, MDMB-4en-PINACA has greater potency, and significantly higher efficacy at the CB1 receptor that than JWH-018 (Cannaert et al 2020).

5F-AMB-PINACA has demonstrated highly efficacious binding to both CB1 and CB2 receptors as an agonist. The major carboxylic acid metabolite also binds as a highly efficacious agonist to both CB1 and CB2 receptors which may prolong cannabimimetic activity. At CB1 and CB2 receptors, 5F-AMB-PINACA was a full agonist with substantially greater potency than THC. In rodent *in vivo* trials, 5F-AMB-PINACA induced significant hypothermia, locomotor suppression and brachycardia in the dose range 0.1 to 3mg/kg. Reversibility with antagonist pre-treatment suggested CB1 mediated effect. 5F-AMB-PINACA substitutes for THC in drug discrimination trials in rats. In L5 neurons, intracerebroventricular infusion of 5F-AMB-PINACA elicited an anxiolytic response and impaired acquisition, but not retention, of novel object recognition memory with corresponding inhibition (WHO 2019a).

There is evidence that CUMYL-PEGACLONE binds to both CB1 and CB2 receptors and is a potent and full agonist at the CB1 receptor (WHO 2020a).

4F-MDMB-BINACA is a potent and efficacious CB receptor agonist and is a full agonist at the CB1 receptor (EMCDDA 2022b; Tokarczyk et al 2022). *In vitro* studies suggest binding and activation of human CB1 receptors at low nanomolar concentrations. A higher potency, but lower efficacy than THC was observed (WHO ECDD 2019b). Cannaert et al demonstrated CB1 agonism of 4F-MDMB-BINACA by non-canonical pathway. Based on this study, 4F-MDMB-BINACA has greater potency than JWH-018 and significantly higher efficacy (Cannaert et al 2020).

In vitro studies suggest 4F-MDMB-BICA is a full agonist with reasonably high potency (EMCDDA 2022b). Binding affinity and canonical activation of the CB1 receptor by 4F-MDMB-BICA has not specifically been assessed, though it is presumed to take that pathway. Cannaert et al demonstrated *in vitro* CB1 agonism of 4F-MDMB-BICA by non-canonical pathway. Based on this study, 4F-MDMB-BICA has lower potency than JWH-018 but has significantly higher efficacy (Cannaert et al 2020; WHO 2021a).

Cannaert et al demonstrated CB1 agonism of ADB-BUTINACA, by non-cannonical pathway. Based on this study, ADB-BUTINACA has a greater potency that than JWH-018 and have significantly higher efficacy at CB1 receptors than the JWH-018 reference (Cannaert et al 2020).

Pharmacokinetics

Studies on the pharamacokinetics are limited, where available they focused on metabolism.

Studies of the metabolism of MDMB-4en-PINACA find the parent product can be excreted unmetabolized, though the M3 metabolite is the most abundant. Studies using human liver microsomes identify metabolism by ester hydrolysis, double bond oxidation and hydroxylation (WHO 2020b). The ester hydrolysis product has a 233-fold, drop in potency in activation of the CB1 receptor (EMCDDA 2022c). *In vivo* effects in mice from intraperitoneal injection lasted from 2 to 5 hours (WHO 2020b).

5F-AMB-PINACA is metabolised rapidly and extensively by hydrolysis of the ester group, oxidative defluorination and hydroxylation. The most abundant metabolite is the ester hydrolysis product. Distribution has not been investigated systematically. One preliminary study in mice suggests *in vivo* pharmacological activity up to 60 minutes after exposure to smoke (WHO 2019a).

CUMYL-PEGACLONE is extensively metabolised. Mono- and dihydroxylation, dehydrogenation, N-dealkylations, degradation of the pentyl side chain to propionic acid or carbonyl formation at the pentyl side chain have been noted. Two mono-hydroxylated metabolites predominate in urine. In pooled human liver microsomes, the major metabolites were monohydroxylated, dihydroxylated and N-dealkylated metabolites. Thermal degradation of CUMYL-PEGACLONE has been identified. One user report describes a fast onset and effects lasting up to an hour (WHO 2020a).

In vitro studies of 4F-MDMB-BINACA show it is metabolised by one or more of the following processes: hydrolysis of the methyl ester, hydrolytic defluorination of the alkyl chain, oxidation to a butanoic acid metabolite, hydroxylation of aromatic and alkyl structures, and dehydrogenation. N-dealkylated and N-dealkylated ester hydrolysis products have also been reported (WHO 2019b).

4F-MDMB-BICA is metabolised extensively – the most prominent metabolite is the ester hydrolysis product. Absorption and distribution have not been investigated. An anecdotal report suggests a duration of action of 40 to 60 minutes when vaped and up to an hour and 45 minutes in a smoked blend (WHO 2021a).

Studies on the metabolism of ADB-BUTINACA could not be found. Anecdotal reports suggest a duration anywhere from 30 to 45 minutes and up to an hour (Reddit 2021b).

4.3 Toxicology

Preclinical evaluations have not been undertaken for any of the substances in this report. LD_{50} data and data on chronic exposure is not available.

For MDMB-4en-BINACA, one study notes mice injected with either 1 or 10mg/kg intraperitoneally were lethargic and exhibited seizures upon handling, with gasping and aggression in some mice injected with 10mg/kg (WHO 2020b).

For 5F-AMB-PINACA, one study noted that an intraperitoneal dose of 2.5mg/kg induced convulsions in 2 of 5 rats tested with it. Significant hypothermia and bradycardia was induced in rats over the dose range of 0.1-3mg/kg (WHO 2019a).

For CUMYL-PEGACLONE forensic post-mortem serum samples show concentrations from 0.38 to 34.9nM (WHO 2020a).

4.4 Risk to public health

Misuse and abuse of synthetic cannabinoids is a global issue with the potential for serious health problems. Known issues include impaired driving or operation of heavy machinery, acute psychiatric distress, death, polysubstance abuse (including abuse of a variety of synthetic cannabinoids) and increased aggression (WHO 2019a).

In New Zealand, synthetic cannabinoids are commonly used by vulnerable populations (NDIB 2022; NZ Drug Foundation 2022). Use by vulnerable populations is also noted in the European Union (EMCDDA 2022b). Vulnerable people may be specifically seeking out synthetic cannabinoids because they are cheap and have a reputation for profound intoxication (EMCDDA 2022b; NDIB 2022; NZ Drug Foundation 2022). Increased use of synthetic cannabinoids by incarcerated persons and homeless persons is noted as an explanation for increased aggression (WHO 2019a). Use by vulnerable populations may exacerbate existing health and social problems for those groups, in addition to any new problems created (EMCDDA 2022b). Synthetic cannabinoids are also used by users of cannabis and those who seek out new drug experiences (EMCDDA 2022b; WHO 2019b).

Compared to cannabis, severe and fatal poisonings appear to be more common with synthetic cannabinoids. There are no known antidotes to poisoning caused by synthetic cannabinoids (EMCDDA 2020c, 2022b). Synthetic cannabinoids can lead to people collapsing (“dropping”), foaming at the mouth, or being temporarily paralysed (DIANZ 2021a). The loss of consciousness, respiratory depression and behavioural effects outlined above may place users at risk from additional hazards such as aspiration of vomit, drowning, falling, ambient temperature related hypothermia, and self-inflicted injury (EMCDDA 2022b). Aggressive and violent behaviours may place other people at risk (DIANZ 2022a).

The effects are worsened when used in combination with alcohol or other drugs (DIANZ 2022a). Synthetic cannabinoids may be used in combination with other drugs(WHO 2019b). Fatalities and hospitalisations related to synthetic cannabinoids, both domestically and internationally, often involve multiple substances (ESR, personal communications, August 2022; WHO 2021a).

Periodic mass poisonings have been known to occur ranging from 4 or 5 victims to over 800 victims (including deaths). This risk is likely coupled to the high potency and unintentional administration of high doses. Outbreaks of mass poisoning have been reported in the United States, Russia and Europe (EMCDDA 2022b).

In the United Kingdom between January and August 2020, 11 acute non-fatal poisonings with confirmed exposure to MDMB-4en-PINACA were reported. In all cases, additional substances were identified including other synthetic cannabinoids, benzodiazepines, opioids, pregabalin, THC, cocaine, ketamine and methamphetamine (EMCDDA 2022c). In 10 of the cases, the poisonings were considered life threatening and required the patients to be hospitalised (EMCDDA 2022c). This has similarities to co-detections for MDMB-4en-PINACA in New Zealand toxicology data (see section 4.1).

MDMB-4en-PINACA has been detected as an adulterant in substances marketed as heroin, cannabis and THC. Emergency department (ED) admissions related to non-medical use of MDMB-4en-PINACA have been widely reported (WHO 2020b).

Two adolescents experienced seizures after unknowingly smoking a cigarette laced with CUMYL-PEGACLONE (WHO 2020a).

4F-MDMB-BINACA has been linked to serious adverse events, including deaths (EMCDDA 2022a). Internationally, 4F-MDMB-BINACA has been detected in toxicology data in impaired driving investigations. In some cases, multiple synthetic cannabinoids were detected. Most of these cases involved males. Two cases have been reported to WHO. One case involved clinical admission with no other substances detected (WHO 2019b).

In the United States and United Kingdom, 4F-MDMB-BICA has been reported in hospitalisations and driving under the influence of drugs cases. In the United Kingdom, between June and July 2020, 5 cases of acute intoxications with life threatening symptoms and confirmed exposure to 4F-MDMB-BICA were reported. In all cases, additional substances were identified including other synthetic cannabinoids, benzodiazepines, opioids, pregabalin, THC, cocaine, and ketamine. This aligns with common toxicology co-detections in New Zealand (see section 4.1). In all United Kingdom cases, the poisonings were life threatening and required the patient to be hospitalised. One non-fatal accidental poisoning of a 13-month-old child has been described (WHO 2021a).

4.5 New Zealand Drug Harm Index

Rankings in the 2016 Drug Harm Index gave synthetic cannabinoids a score of 3.2 with estimated total harm per dependent user of $35,900 (NZD) and the social cost per user of $42,000, and for casual users the estimated harm was given a score of 2.2, and assigned a value of $2,800 per user for estimated total harm and $2,800 per user for social cost (McFadden 2016).

The 2020 Drug Harm Index (where differing methodology means comparison with the 2016 Drug Harm Index should be treated with caution) assigns 78.35 million dollars in personal harm, and 2.13 million dollars in social harm to synthetic cannabinoids. This gives a total harm of 80.47 million dollars (McFadden et al 2020).

4.6 Potential to cause death

In New Zealand, between 2016 and 2020, the coroner reported 51 deaths (active and closed cases) where synthetic cannabinoids were a contributor to, or the cause of death (NZ Drug Foundation 2022).

With the 6 substances in this report, ESR have provided a breakdown of the number of detections of the substances in toxicology cases related to coronial cases, including deceased drivers (Table 11), (ESR, personal communications, August 2022). The extent to which these substances contributed to the deaths is unknown, and co-detections of other substances are also noted (see section 4.1).

Table 11: Detections in toxicology samples in coronial cases (ESR 2022a)

	Year	2018	2019	2020	2021	2022*
Number of Detections	MDMB-4en-PINACA	0	0	1	9	3
	5F-AMB-PINACA	0	0	0	0	0
	CUMYL-PEGACLONE	0	0	0	0	0
	4F-MDMB-BINACA	0	2	3	4	0
	4F-MDMB-BICA	0	0	0	4	0
	ADB-BUTINACA	0	0	0	3	0

**provisional data*

In the European Union between January 2019 and August 2020, at least 13 deaths with confirmed exposure to MDMB-4en-PINACA occurred. In all cases other substances were also identified. Cause of death involved substance overdose (8 cases), acute heart failure (3 cases), asphyxiation following aspirating vomit (one case), and trauma from a fall where the contribution from drugs present could not be determined (one case). In the United States MDMB-4en-PINACA has been identified in 16 post-mortem samples from May 2019 to March 2020. Most cases involved co-detection of other substances such as synthetic cannabinoids, alcohol, stimulants or other drugs (EMCDDA 2022c).

For 5F-AMB-PINACA, 3 deaths were reported (prior to 2019) where 5F-AMB-PINACA was verified in the consumed product, or in tissue or serum samples. Other substances (including other synthetic cannabinoids) were detected in 2 of the cases, and of those 2 cases a medical complication was the cause of death in one case. In the third death 5F-AMB-PINACA was the only substance detected. Use of 5F-AMB-PINACA has been associated with vehicle accidents that resulted in death. In Japan, between 2012 and 2014, it was the causal factor in 21 motor vehicle accidents. In some instances, death was to someone other than the driver (WHO 2019a).

Internationally, CUMYL-PEGACLONE has been found in post-mortem femoral blood samples from 6 individuals in 2019. In 5 of the 6 cases other drugs were present (opioids, benzodiazepines, alcohol or other synthetic cannabinoids) (WHO ECDD 2020a). In Australia, CUMYL-PEGACLONE was found in the serum of one deceased person and deemed a causal or contributary factor in 4 out of 12 reported deaths in 2020 (WHO 2020a).

4F-MDMB-BINACA has been detected in toxicology samples in the United States in cases involving deaths, between November 2018 and March 2019. There were 20 post-mortem cases which 4F-MDMB-BINACA was detected. In some cases, detections were alongside

other synthetic cannabinoids, while in one case heroin and fentanyl were also found (WHO 2019b).

In Hungary between May and August 2020, use of 4F-MDMB-BICA was associated with at least 21 deaths, and in Germany and the United States an undetermined number of deaths. Cause of death for the cases in Hungary included cardiac arrest/failure (14 cases), traumatic shock (2 cases), strangulation (one case), brain oedema (one case) and asphyxiation after aspiration of vomit (one case). Antemortem symptoms, when known, were similar to overdose for other synthetic cannabinoids (see section 4.4). The cases were all male, between the ages of 19 and 42. Nineteen of the 21 cases involved other substances. 4F-MDMB-BICA was co-detected with 5F-MDMB-PICA in 10 cases, and with MDMB-4en-PINACA in 8 cases. Note that all 3 substances may have occurred in the same case. Benzodiazepines, stimulants, alcohol and other substances were also detected in some cases (EMCDDA 2022b). In the United States, 26 blood samples from autopsies and driving under the influence cases identified 4F-MDMB-BICA (WHO 2021a).

Three coronial investigations in New Zealand detected ADB-BUTINACA. The extent to which ADB-BUTINACA contributed to the cause of death is unknown (ESR, personal communications, August 2022). In the United States, in the first quarter of 2021, there were 5 toxicology detections of ADB-BUTINACA (CFSRE 2021b). No other information on ADB-BUTINACA is available

4.7 Potential for physical or psychological dependence

Synthetic cannabinoid dependence has been identified as a motivator for use. One study found that withdrawal symptoms are common in regular users after abstinence of a single day, suggesting some users are likely to experience some level of dependence (NDIB 2022).

Heavy use of synthetic cannabinoid receptor agonists has been associated with problematic withdrawal symptoms (WHO 2019b). None of the substances in this report have been evaluated for abuse of dependence potential. No animal or human studies have been carried out (WHO 2019a, 2020b, 2021b).

Unpublished drug discrimination data showed that intraperitoneal MDMB-4en-PINACA substituted for THC in mice trained to discriminate 5.6mg/kg THC from vehicle. Prevalence of chronic use and dependence on MDMB-4en-PINACA has not been reported (WHO 2020b).

For 5F-AMB-PINACA, tests in male Sprague-Dawley rats trained to discriminate 3 mg/kg THC from vehicle, found that 5F-AMB-PINACA fully substituted for the THC. After intraperitoneal injection, full substitution occurred over a period of 60 to 120 minutes and was rimonabant reversible, suggesting CB1 receptor mediation. After injection, suppressed responding accompanied substitution in most rats at, 5 to 15 minutes. Substitution in rodents trained to discriminate THC from vehicle is predictive for drugs that produce THC-like subjective effects in humans and may be predictive of dependence potential (WHO 2019a).

CLASSIFICATION

5.1 New Zealand classification and regulation

The Ministry considers MDMB-4en-PINACA, 5F-AMB-PINACA, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA to be substantially structurally similar to the Class A controlled drug 5F-ADB. Controlled drug analogues are controlled as Class C7 controlled drugs under the Misuse of Drugs Act 1975.

The Ministry considers CUMYL-PEGACLONE to be psychoactive (Ministry of Health 2020). Substances that are psychoactive may be controlled by the Psychoactive Substances Act 2013 depending on the intent of use.

5.2 International classification and regulation

Australia

In Australia, Schedule 9 of the Poisons Standard lists synthetic cannabinomimetics as prohibited substances (Australian Government Federal Register of Legislation 2022).

CUMYL-PEGACLONE is also scheduled in Schedule 9 of the Poisons Standard, it was scheduled separately from the synthetic cannabinomimetics (Australian Government Therapeutic Goods Administration 2020).

United Kingdom

Schedule 2 of the United Kingdom Misuse of Drugs Act 1971 defines MDMB-4en-PINACA, 5F-AMB-PINACA, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA by their structural group (legislation.gov.uk 2022). CUMYL-PEGACLONE is captured by the Psychoactive Substances Act 2016 (legislation.gov.uk 2016).

United States

Under the United States Controlled Substances Act 1970, MDMB-4en-PINACA, 5F-AMB-PINACA, 4F-MDMB-BINACA, are controlled substances and are listed under schedule 1 as hallucinogenic substance 21 CFR 1308.11(d) (Code of Federal Regulations 2022).

4F-MDMB-BICA, and ADB-BUTINACA are likely controlled by isomer provisions. It is unclear if CUMYL-PEGACLONE is also covered by analogue provisions in the United States Controlled Substances Act 1970 (Code of Federal Regulations 2022). If they are not covered by these provisions, they are likely to be covered by the Synthetic Drug Abuse Prevention Act 2012 as cannabimimetics (Congress.gov 2012).

Canada

Under schedule II of the Canadian Controlled Drugs and Substances Act 1996 MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F-MDMB-BINACA and 4F-MDMB-BICA and are controlled drugs (Health Canada, personal communications, July 2022; Government of Canada 2022).

Under the Canadian Controlled Drugs and Substances Act 1996 ADB-BUTINACA is not controlled in Canada (Health Canada, personal communications, July 2022; Government of Canada 2022).

European Union

MDMB-4en-PINACA:

- controlled in Germany in Anlage II of the German Narcotics Law (BtMG 2022)
- listed in Sweden under Annex 1 of substances to be considered narcotics under the Narcotics Criminal Code (Sveriges Riksdag 2022).

5F-AMB-PINACA:

- controlled in Germany in Anlage II of the German Narcotics Law (BtMG 2022).

CUMYL-PEGACLONE:

- controlled in Germany in Anlage II of the German Narcotics Law (BtMG 2022)
- listed in Sweden under Annex 1 of substances to be considered narcotics under the Narcotics Criminal Code (Sveriges Riksdag 2022).

4F-MDMB-BINACA:

- controlled in Germany in Anlage II of the German Narcotics Law (BtMG 2022)
- listed in Sweden under Annex 1 of substances to be considered narcotics under the Narcotics Criminal Code (Sveriges Riksdag 2022).

4F-MDMB-BICA:

- controlled in Germany in Anlage II of the German Narcotics Law (BtMG 2022)
- listed in Sweden under Annex 1 of substances to be considered narcotics under the Narcotics Criminal Code (Sveriges Riksdag 2022)
- covered by Belgian Generic Legislation
- covered by the Austrian Act on New Psychoactive Substances
- covered by medicines regulations in Lithuania and Norway
- regulated by drug or medicines legislation in 13 European Union member states (WHO 2021a).

ADB-BUTINACA:

- likely controlled in Germany under the psychoactive substance legislation Neue-psychoaktive-Stoffe-Gesetz (NpSG 2021)
- listed in Sweden under Annex 1 of substances to be considered narcotics under the Narcotics Criminal Code (Sveriges Riksdag 2022).

China

In China all 6 of the synthetic cannabinoids covered by this technical report are controlled (Chinese Legislation 2021).

5.3 UN classification

MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, and 4F-MDMB-BINACA are scheduled under Schedule II of the UN Convention on Psychotropic Substances 1971, following assessment and recommendation for scheduling by the WHO ECDD (UN 2022).

4F-MDMB-BICA was assessed by the ECDD in 2021 who recommended that 4F-MDMB-BICA be kept under surveillance by the WHO Secretariat (WHO 2021b). The substance was not recommended for scheduling at the time.

A critical review of ADB-BUTINACA was prepared for the 45th ECDD meeting on the 10 October to 14 October 2014 (WHO 2022).

OTHER RELEVANT INFORMATION

6.1 Background and history

In New Zealand, prior to the Psychoactive Substances Act 2013 (PSA) coming into force, many synthetic cannabinoids were available as 'legal highs'. Both domestically and internationally, synthetic cannabinoids were linked to harm incidents, including outbreaks of mass poisonings. This led to controls being placed on these substances (EMCDDA 2021).

6.2 Anticipated future trends

The illicit synthetic cannabinoids used in smoking mixtures varies over time and place (Stansfield et al 2020). In China, in 2021 several synthetic cannabinoid backbones were banned (Chinese Legislation 2021). In the short term this will likely reduce the amount of those banned synthetic cannabinoids entering New Zealand. It may also lead to new and unknown synthetic cannabinoids being manufactured in China and seen on the New Zealand market. At present, the long-term effects on the global (and New Zealand) market are unknown (NDIB 2022). Trends in the synthetic cannabinoids are hypothesised to relate to many factors including legislative control in other countries meaning prediction of future trends is difficult (Stansfield et al 2020). A 2022 NDIB report states that it is likely the prevalence of synthetic cannabinoids in New Zealand is decreasing (NDIB 2022). This aligns with a downward trend in amount of seized synthetic cannabinoid finished product smoking mixtures in New Zealand section 4.1.

CLASSIFICATION OPTIONS

Note that, although the synthetic cannabinoids are being considered together, if the Committee considers that they have different risks of harm, different scheduling recommendations can be applied to each substance under consideration. The same applies for recommending a presumption of supply – different levels can be set if the Committee considers this appropriate.

Option 1 – Maintain status quo

Under the Misuse of Drugs Act, MDMB-4en-PINACA, 5F-AMB-PINACA, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA are likely to be captured as a Class C controlled drug analogue of 5F-ADB. Penalties for the Class C7 controlled drug analogues are listed in Table 12 below.

When used for the primary purpose of inducing a psychoactive effect, CUMYL-PEGACLONE could still be captured under the Psychoactive Substance Act 2013. Anyone caught in possession of CUMYL-PEGACLONE for personal use faces a fine not exceeding $500.

Anyone caught importing, manufacturing or supplying CUMYL-PEGACLONE faces up to 2 years imprisonment (for individuals) or a fine not exceeding $50,000 (for a body corporate).

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 MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA.

The regulatory penalties for Class A controlled drugs are listed below in Table 12. For a full breakdown on the controls, please see the EACD guidelines.

Scheduling these synthetic cannabinoids as Class A controlled drugs is in line with previous recommendations (such as 5F-ADB and AMB-FUBINACA).

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 MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F MDMB-BINACA, 4F MDMB-BICA, and ADB-BUTINACA.

The penalties for Schedule 2 (Class B) controlled drugs are listed below in Table 12. For a full breakdown of the differences in control between these parts of Schedule 2 see EACD guidelines.

Scheduling these synthetic cannabinoids as Class B controlled drugs is in line with previous recommendations (such as JWH-018, AM-2201, AB-CHMINACA, AB-FUBINACA, AB-PINACA, 5F-AKB-48, MDMB-CHMICA and AB-FUBINACA).

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 MDMB-4en-PINACA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F-MDMB-BINACA, 4F-MDMB-BICA, and ADB-BUTINACA.

The penalties for Schedule 3 (Class C) controlled drugs are listed below (Table 12). For a full breakdown of the differences in control between these parts of Schedule 3, see EACD guidelines.

Table 12: Comparison of penalties under the Misuse of Drugs Act 1975

	Schedule 1 Class A Drugs	Schedule 2 Class B Drugs	Schedule 3 Class C Drugs	Psychoactive Substances Act
Importation, manufacture, or supply	Life imprisonment (subject to presumption of supply)	Up to 14 years imprisonment (subject to presumption of supply)	Up to 8 years imprisonment	Up to 2 years imprisonment (for individuals) or a fine not exceeding $500,00 (for a body corporate)
Conspiracy to commit an offence	Up to 14 Years imprisonment	Up to 10 years imprisonment	Up to 7 years imprisonment	N/A
Possession	Up to 6 months imprisonment or $1,000 fine or both	Up to 3 months imprisonment or $500 fine or both	Up to 3 months imprisonment or $500 fine or both	A fine not exceeding $500

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 56g will apply. A default amount of **56g** of plant material sprayed with synthetic cannabinoids would be approximately equivalent to **56g** of plant material or **200 cigarettes**. A default amount of **56g** of synthetic cannabinoid pure substance would be approximately equivalent to **560g** of synthetic cannabis (assuming a loading of 100g/kg) or **2000 cigarettes**. It is not possible to determine how many doses one cigarette of synthetic cannabis contains. However, evidence suggests the number of doses of synthetic cannabis is greater than that of the equivalent weight of cannabis (MoH 2018).

If the substance is scheduled as a class B1 and no presumption of supply is set, this will default to the presumption of supply in option 2. This is due to the wording “Synthetic cannabinoids in schedule B1” used in the presumption of supply set in the Misuse of Drugs (Classification and Presumption of Supply) Order 2022. If a default of 56g, or a different presumption of supply is decided upon, the Misuse of Drugs Act 1975 will need to be amended.

Option 2: Proposed presumption of supply

Option 2 is to set a presumption for supply for:

- plant material containing synthetic cannabinoids at **28g** or **100 cigarettes** containing the drug.
- synthetic cannabinoids at **250mg**, whether or not, contained in a substance, preparation, or mixture.

It is not possible to determine how many doses a cigarette or a given number of grams of synthetic cannabis contains. However, evidence suggests the number of doses of synthetic cannabis is greater than for the equivalent weight of cannabis. These quantities for presumption of supply are set to the same level as for cannabis and for tetrahydrocannabinols. Other scheduled synthetic cannabinoids have had the same values set for their presumption of supply.

FUTURE ACTIONS

If the Committee recommends that MDMB-4en-PINACA, 4F-MDMB-BICA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F-MDMB-BINACA and ADB-BUTINACA 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 MDMB-4en-PINACA, 4F-MDMB-BICA, 5F-AMB-PINACA, CUMYL-PEGACLONE, 4F-MDMB-BINACA and ADB-BUTINACA is reasonable and minimised. If the status quo is kept, no further action is required. Note that decisions on each of the substances presented in this paper may be made independently of each other.

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