



Synthetic cannabinoids:
ADB-5Br-INACA, MDMB-5Br-INACA and
MDMB-INACA
Report to the Expert Advisory Committee on
Drugs

Prepared by the Ministry of Health
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1 EXECUTIVE SUMMARY

ADB-5Br-INACA, MDMB-5Br-INACA, and MDMB-INACA are synthetic cannabinoids which are not listed in the Schedules of the Misuse of Drugs Act 1975, nor are they regulated as psychoactive substances under the Psychoactive Substances Act 2013. They are also not regulated under the Medicines Act 1981.

However, since December 2022, ADB-5Br-INACA, MDMB-5Br-INACA, and MDMB-INACA have been subject to a temporary class drug order (TCDO). While controlled under a TCDO, the Expert Advisory Committee on Drugs (EACD) must review these substances and recommend their appropriate classification to the Minister of Health. Under the TCDO, these three substances are treated as Class C1 controlled drugs under the Misuse of Drugs Act 1975.

None of these substances have been considered by the World Health Organization Expert Committee on Drug Dependence.

ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA are novel synthetic cannabinoids detected internationally and within New Zealand.

There is currently limited evidence that these three cannabinoids are cannabinoid receptor agonists, or novel psychoactive substances of abuse. These substances have been detected and/or seized in New Zealand. None of these substances have any known therapeutic value.

The unknown potency of these synthetic cannabinoids and inconsistency in finished products may pose a risk of accidental poisoning in users. These substances may appeal to, or be used by, vulnerable populations within New Zealand.

2 INTRODUCTION

2.1 Purpose

This report provides an overview of three synthetic cannabinoids for the Expert Advisory Committee on Drugs (the Committee) to consider and make a scheduling recommendation under the Misuse of Drugs Act 1975.

The synthetic cannabinoids to be considered by the Committee are:

- ADB-5Br-INACA
- MDMB-5Br-INACA
- MDMB-INACA.

2.2 Substance classification

ADB-5Br-INACA, MDMB-5Br-INACA, and MDMB-INACA were placed under a temporary class drug order (TCDO) on 23 December 2022. This temporarily specifies the three substances as Class C1 controlled drugs under the Misuse of Drugs Act 1975 for one year (unless otherwise renewed or revoked). This TCDO was renewed for one year effective on 23 December 2023. Prior to the TCDO, the three synthetic cannabinoids were not controlled under either the Misuse of Drugs Act 1975 or the Psychoactive Substances Act 2013. None of these substances are medicines controlled under the Medicines Act 1981.

2.3 Why is this substance being considered?

These three synthetic cannabinoids are being considered by the Committee because they are currently subject to a temporary class drug order (TCDO). As required under section 4E of the Misuse of Drugs Act 1975, the Minister must seek advice about the appropriate classification of a drug while a TCDO is in place.

3 SUBSTANCE IDENTIFICATION AND CHEMISTRY

3.1 Identification

ADB-5Br-INACA

IUPAC name: N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-5-bromo-1H-indazole-3-carboxamide

CAS number: Not available

Molecular weight: 353.2 g/mol

Molecular formula: C₁₄H₁₇BrN₄O₂

Appearance: Crystalline solid, off-white powder (Cayman Chemical 2022a, HIFS 2021)

Solubility: Soluble in dimethylformamide (3 mg/mL), dimethyl sulfoxide (2 mg/mL) and ethanol (2 mg/mL); insoluble in phosphate buffer solution (pH 7.2) (Cayman Chemical 2022a).

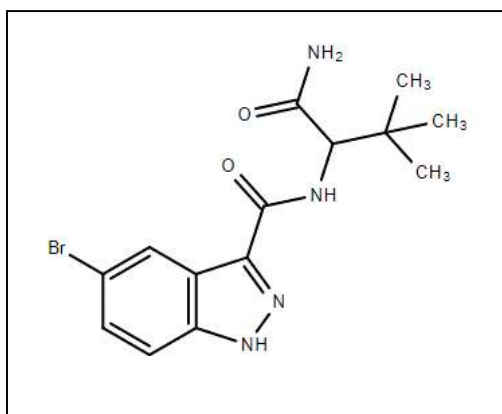


Figure 1: Chemical structure of ADB-5Br-INACA

MDMB-5Br-INACA

IUPAC name: Methyl 2-[(5-bromo-1H-indazole-3-carbonyl)amino]-3,3-dimethylbutanoate

CAS number: Not available

Molecular weight: 368.2 g/mol

Molecular formula: C₁₅H₁₈BrN₃O₃

Appearance: A solid, white powder, off-white or brown powder (Cayman Chemical 2022b; DIANZ 2022a; DrugsData 2022a)

Solubility: Soluble in dimethylformamide (14 mg/mL), dimethyl sulfoxide (14 mg/mL), and ethanol (14 mg/mL), partially soluble in phosphate buffer solution (pH 7.2) (0.20 mg/mL) (Cayman Chemical 2022b).

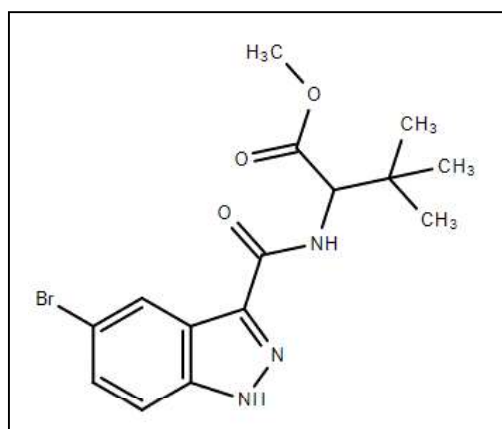


Figure 2: Chemical structure of MDMB-5Br-INACA

MDMB-INACA

IUPAC name: N-(1H-indazol-3-ylcarbonyl)-3-methyl-L-valine, methyl ester

CAS number: 2709672-58-0

Molecular weight: 289.3 g/mol

Molecular formula: C₁₅H₁₈BrN₃O₃

Appearance: A crystalline solid, white powder (Cayman Chemical 2023; National Forensic Laboratory Slovenia 2019)

Solubility: Soluble in dimethylformamide (12.5 mg/mL), dimethyl sulfoxide (10 mg/mL), and ethanol (3 mg/mL), partially soluble in dimethyl formamide:phosphate buffer solution (1:1) (pH 7.2) (0.50 mg/mL) (Cayman Chemical 2023).

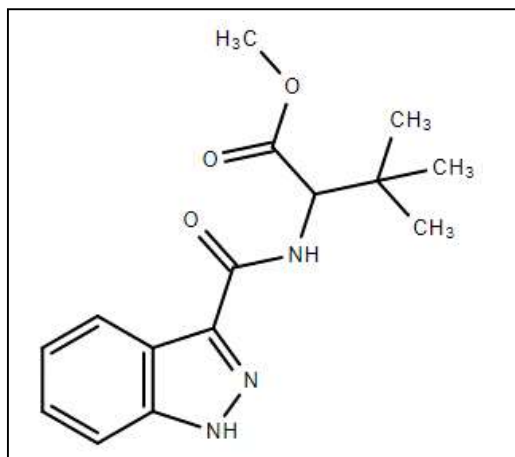


Figure 3: Chemical structure of MDMB-INACA

3.2 Therapeutic value

There are no known therapeutic uses for ADB-5Br-INACA, MDMB-5Br-INACA or MDMB-INACA.

3.3 Substance Classification

Both ADB-5Br-INACA and MDMB-5Br-INACA are classified as synthetic cannabinoids. They belong to an emerging group of synthetic cannabinoids with brominated indole cores and no tail group (CFSRE 2022a, b; EEWS 2022).

MDMB-INACA is a synthetic cannabinoid precursor which may also be being consumed as a synthetic cannabinoid (Cayman Chemical 2023; NDIB, personal communication, February 2023).

3.4 Similarities to other known substances

Structure and structural similarities to other known substances

Structurally, these three synthetic cannabinoids are indazole-3-carboxamides. The structure of synthetic cannabinoids is defined in terms of the core, tail, linker and linked group components, see Figure 4. These three synthetic cannabinoids are each missing the tail component (EMCDDA 2017).

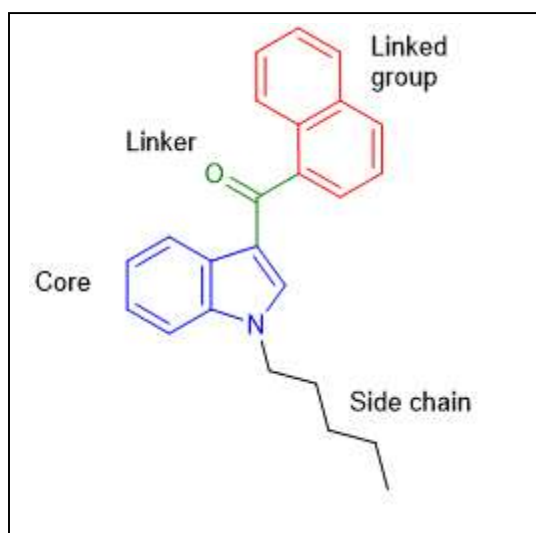


Figure 4: Example of the general synthetic cannabinoid structure

The missing tail component is the only major difference between these three substances and other structurally similar synthetic cannabinoids (eg, 5F-ADB, AB-FUBINACA) which are Class A or Class B1 controlled drugs under the Misuse of Drugs Act 1975. See Figure 5 for the structures of 5F-ADB and AB-FUBINACA. Additionally, there are further minor differences.

- A bromine substitution on the indazole structure for ADB-5Br-INACA and MDMB-5Br-INACA.
- Additional methyl groups in the linked group for MDMB-5Br-INACA and MDMB-INACA.

It is not yet known how the lack of a tail group affects the pharmacological activity of these compounds (Andrews et al 2022).

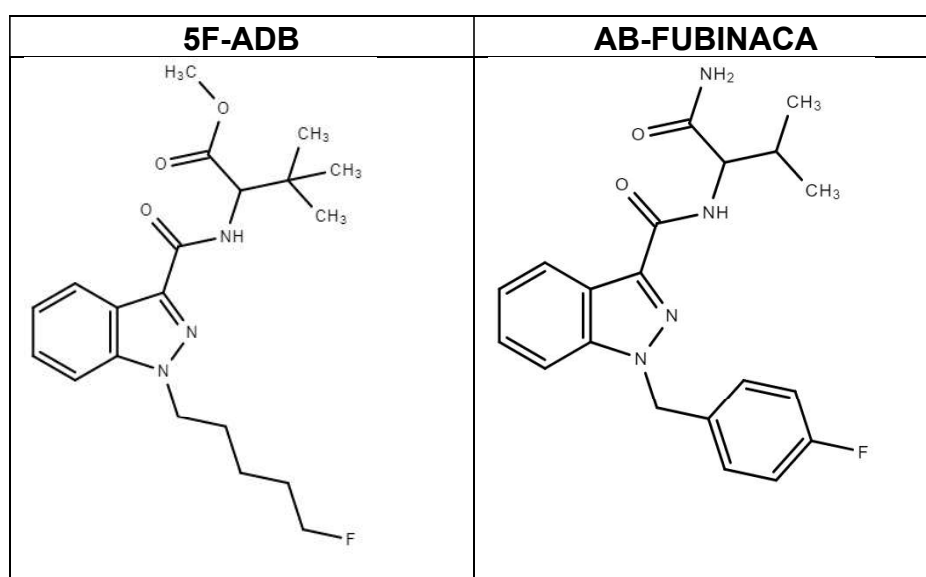


Figure 5: Structure of 5F-ADB and AB-FUBINACA

Pharmacological similarities

Pharmacologically, only ADB-5Br-INACA is reported (in unpublished data) to have cannabinoid receptor one (CB1) activity (CFSRE 2022a). This is likely to have a lower potency when compared to the CB1 agonism of other synthetic cannabinoids scheduled under the Misuse of Drugs Act 1975.

Neither MDMB-5Br-INACA nor MDMB-INACA have any data available on CB1 receptor activity.

3.5 Methods and ease of manufacturing

Specific information on the synthesis of each synthetic cannabinoid was not available in a literature search, however, chemical synthesis of indazole synthetic cannabinoids could follow a 2-step route which may be modified to manufacture ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA, using cheap and readily available reagents (Cannaert et al 2020; EMCDDA 2022a).

Synthesis of an indazole synthetic cannabinoid may involve:

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

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 2022b). Smoking mixtures are generally 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 2022b). Other synthetic cannabinoid preparations are outlined in the WHO reports provided.

3.6 Possible use as synthetic cannabinoid precursors

MDMB-INACA is described as a synthetic cannabinoid precursor (Cayman Chemical 2023). Co-detections of MDMB-INACA with 4F-MDMB-BINACA and MDMB-3en-BUTINACA have been reported (DrugsData 2021; Z6 Drogen Arbeit 2021). These co-detections suggest MDMB-INACA may be present as an impurity (eg, from unreacted starting material) following use as a precursor.

Similarly, ADB-5Br-INACA has been reported as part of a kit for people to finish synthesis of synthetic cannabinoids, this may have contributed to ADB-BUTINACA detection in Scottish prisons in early 2022 (Norman et al 2022).

Online forums have speculated on the use of ADB-5Br-INACA and MDMB-5Br-INACA as synthetic cannabinoid precursors (Reddit 2022). There is no evidence of any of these

substances being used as precursors for other synthetic cannabinoids in New Zealand (NDIB, personal communication, February 2023).

4 RISK OF HARM

4.1 Likelihood or evidence of abuse in New Zealand

ADB-5Br-INACA and MDMB-5Br-INACA were first identified in New Zealand in June 2022. MDMB-INACA was first identified in New Zealand in October 2022 (NDIB 2022a).

ADB-5Br-INACA was identified by New Zealand Customs Service as a 1,004g seizure of synthetic cannabinoid powder. This seizure is equivalent to approximately 300,000 common doses. The quantity seized means it was likely imported with the intention of supply (NDIB 2022a).

MDMB-5Br-INACA was identified by a drug checking service in July 2022 in a small capsule filled with powder. The substance was presented as a suspected 3,4-methylenedioxymethamphetamine (MDMA) sample and was accompanied by a user report of “extreme and rapid anxiety” after consuming the substance (NDIB 2022a). MDMB-5Br-INACA was also detected at the New Zealand border, in November 2021, by the Institute of Environmental Science Research (ESR) in the Customs-ESR screening laboratory (ESR, personal communication, October 2022).

There were two MDMB-INACA seizures between September 2022 and December 2022 (NDIB, personal communication, February 2023). MDMB-INACA was also identified in October 2022 in a seizure of 1,008g of cannabinoid powder by the New Zealand Customs Service (NDIB 2022a). For reference, 1,008g of cannabinoid powder is equivalent to approximately 300,000 common doses. An additional seizure, estimated to be between 500g to 1,000g has been recorded (NDIB, personal communication, February 2023). In 2023 there were 6 seizures by the New Zealand Customs Service, totalling 4,300g (NDIB, personal communication, January 2024).

All data provided above is provisional and subject to change. Please note that the drug checking detections reported are only samples submitted by drug checking providers to ESR for further confirmation. Not all samples tested by drug checkers are submitted to ESR for further analysis so it is likely that this is under reporting the prevalence of presentations to drug checking services (NDIB, personal communication, January 2024).

These types of detections suggest the substances are likely in wider circulation. Seized synthetic cannabinoid smoking mixtures are rarely tested for specific cannabinoid content, and drug checking providers struggle to analyse synthetic cannabinoids due to equipment limitations (NDIB 2022a). After a ban of most common synthetic cannabinoid backbones in China in 2021 there was a significant reduction in harm. However, Drug Information and Alerts Aotearoa New Zealand (DIANZ) has noticed an increase in synthetic cannabinoid harm in the six months prior to March 2023 (NDIB 2022a; NDIB, personal communication, February 2023).

To date, there have been no detections of ADB 5Br-INACA, MDMB-5Br-INACA or MDMB-INACA in forensic toxicology cases in New Zealand (ESR, personal communication, October

2022; ESR, personal communication, March 2023). There have been no known deaths associated with the use of these substances (NDIB, personal communication, February 2023; ESR, personal communication, February 2023).

ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA are not currently controlled under any legislation in New Zealand. If this became publicly known the importation and distribution of these substances may increase (NDIB 2022a).

ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA may become more prevalent in New Zealand due to a 2021 class wide ban in China. ADB-5Br-INACA, MDMB-5Br-INACA or MDMB-INACA are not captured by this ban, and they may replace imports of banned compounds into New Zealand. Synthetic cannabinoid users are likely to consume ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA as replacements to these banned compounds (NDIB 2022a). MDMB-5Br-INACA has been detected in Scottish prisons and deduced to be the result of circumventing the ban (Norman 2022).

The National Poisons Centre has not received any calls related to ADB-5Br-INACA or MDMB-5Br-INACA exposure. However, they believe that both substances will likely be potent cannabinoid receptor agonists and capable of causing acute harms (morbidity and mortality) (NDIB 2022a). The National Poisons Centre was not asked about MDMB-INACA at the time.

For further information on synthetic cannabinoids in New Zealand, see the Appendix – Section 11.1: Likelihood or evidence of abuse in New Zealand.

4.2 General pharmacology

Many of these new synthetic cannabinoids are unstudied with the pharmacological and effects in humans undetermined (CFSRE 2022a, b).

Little information is currently known about the activity, potency, and/or toxicity of ADB-5Br-INACA. However, in vitro studies (in unpublished data) have shown ADB-5Br-INACA to exhibit cannabinoid (CB) receptor activity, but overall potency is expected to be low (CFSRE 2022a).

Currently, little is known about the activity, potency, and/or toxicity of MDMB-5Br-INACA (CFSRE 2022b). MDMB-5Br-INACA is reported as producing “extreme and rapid anxiety” in an individual, where presence of MDMB-5Br-INACA was analytically confirmed by drug checking service KnowYourStuffNZ (KnowYourStuffNZ 2022). No further information was available.

A literature search was unable to find further information on the activity, potency, and/or toxicity of MDMB-INACA.

For further information on general pharmacology of synthetic cannabinoids, see the Appendix – Section 11.2: General pharmacology.

Routes of administration and dosage

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

MDMB-5Br-INACA has been found in capsules misrepresented as MDMA (DIANZ 2022a; KnowYourStuffNZ 2022). This presentation is a departure from the usual administration route for synthetic cannabinoids. Misrepresentation as MDMA could result in larger doses of the synthetic cannabinoid being consumed (common dosage of MDMA ranges between 80 to 120mg). Synthetic cannabinoids are typically active at lower dosages than MDMA (DIANZ 2022b; Gatch and Forster 2019).

Internationally, MDMB-INACA has been found to be present in vaping liquids (DrugsData 2021; Z6 Drogen Arbeit 2021).

ADB-5Br-INACA has also been found on adulterated cannabis in Austria (DrugsData 2022b).

There is no reliable dosage information available for any of the substances presented in this paper.

For further information on routes of administration and dosage of synthetic cannabinoids, see the Appendix – Section 11.3: Routes of administration and dosage.

Pharmacodynamics

Unpublished data suggests ADB-5Br-INACA has CB1 activity, though with low potency (CFSRE 2022a). This information is not available for the other two substances.

Pharmacokinetics

Information on the pharmacokinetics of all three substances is unavailable.

4.3 Toxicology

Information on toxicological risks of all three substances is unavailable.

4.4 Risk to public health

DIANZ released an alert on the presence of MDMB-5Br-INACA relating to the KnowYourStuffNZ detection reported in Section 4.2: General pharmacology, identifying it as a risk to public health (DIANZ 2022a).

Both ADB-5Br-INACA and MDMB-5Br-INACA were detected in late 2021 in Scottish prisons, following the ban in China of a wide variety of synthetic cannabinoid structures. These structures may have been designed to circumvent the legislation in China (Norman et al 2022).

No further information is available on MDMB-INACA.

For further information on risk to public health of synthetic cannabinoids, see the Appendix – Section 11.4: Risk to public health.

4.5 New Zealand Drug Harm Index

The 2020 Drug Harm Index assigns \$78.35 million in personal harm, and \$2.13 million in social harm to synthetic cannabinoids, with an estimated total harm of \$80.47 million (McFadden et al 2020).

4.6 Potential to cause death

Specific information on the ability of these three substances to cause death is unavailable.

Synthetic cannabinoids have been implicated in at least 70 deaths in New Zealand (DIANZ 2022d). 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).

4.7 Potential for physical or psychological dependence

Specific information on the ability of these three substances to cause physical or psychological dependence is unavailable.

For further information on the potential for physical or psychological dependence of synthetic cannabinoids, see the Appendix – Section 11.5: Potential for physical or psychological dependence.

5 CLASSIFICATION

5.1 New Zealand classification and regulation

In New Zealand, ADB-5Br-INACA, MDMB-5Br-INACA, and MDMB-INACA are not controlled under either the Misuse of Drugs Act 1975 or the Psychoactive Substances Act 2013. They are also not controlled under the Medicines Act 1981.

5.2 International classification and regulation

Australia

Controlled under the Schedule 9 entry for synthetic cannabinomimetics (Poisons Standard 2023).

United Kingdom

Currently not scheduled substances under the Misuse of Drugs Act 1971. Likely not controlled under the Psychoactive Substances Act 2016 due to the limited evidence of producing a psychoactive effect (Legislation.gov.uk 2023a,b).

United States

Currently, MDMB-5Br-INACA, ADB-5Br-INACA, and MDMB-INACA are not scheduled substances in the United States (CFSRE 2022a, b; DEA 2023).

Canada

Currently, MDMB-5Br-INACA and ADB-5Br-INACA are not controlled by the Controlled Drugs and Substances Act 1996. MDMB-INACA is controlled under schedule II of the Controlled Drugs and Substances Act 1996 (laws-lois.justice.gc.ca 2023).

5.3 UN classification

None of these three synthetic cannabinoids are scheduled under the Single Convention on Narcotic Drugs 1961, the Convention on Psychotropic Substances 1971, or the United

6 OTHER RELEVANT INFORMATION

6.1 Anticipated future trends

New synthetic cannabinoids continue to emerge among the recreational drug supply internationally. A synthetic cannabinoid class-wide ban was implemented in China in July 2021 which included most traditional indole and indazole structural scaffolds (CFSRE 2022a, b). It is possible that the prevalence of these new synthetic cannabinoids is a result of methods to circumvent this ban.

For further information on anticipated future trends of synthetic cannabinoids, see the Appendix – Section 11.6: Other relevant information.

7 CLASSIFICATION OPTIONS

Due to the possible use of these substances as synthetic cannabinoid precursors, in addition to use as synthetic cannabinoids without further reaction, the option of classifying these substances as precursors has been included here.

Though the options for ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA are presented alongside each other in this paper, the classification and presumption of supply recommendations should be considered separately for each substance.

Option 1 – Maintain status quo

ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA would return to being uncontrolled by either the Misuse of Drugs Act 1975 or the Psychoactive Substances Act 2013. Note that status quo is referring to the classification prior to the controls imposed by the TCDO.

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 ADB-5Br-INACA, MDMB-5Br-INACA or MDMB-INACA.

The penalties for Schedule 1 (Class A) controlled drugs are listed below in Table 2. For a full breakdown on the controls, please see the EACD guidelines.

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 ADB-5Br-INACA, MDMB-5Br-INACA or MDMB-INACA.

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

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 ADB-5Br-INACA, MDMB-5Br-INACA or MDMB-INACA.

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

Table 2: 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

Option 5 – Schedule as a precursor substance under the Misuse of Drugs Act 1975

If scheduling these substances under Schedule 4 of the Misuse of Drugs Act 1975 is recommended, penalties for supply, manufacture and knowingly committing an offence for these substances will be incurred as outlined in Section 12AB and 12AC of the Misuse of Drugs Act 1975. This includes penalties, outlined in Table 3, for the import or export of a precursor substance knowing that the precursor substance is going to be used to commit an offence, and penalties for the import and export of a precursor substance without a reasonable excuse.

There are three parts of Schedule 4 where these substances could be scheduled.

- Part 1 of Schedule 4 of the Misuse of Drugs Act 1975 contains substances in Table I of the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances 1988, with narrow uses and traded in limited volumes on the international market.

- Part 2 of Schedule 4 of the Misuse of Drugs Act 1975 contains substances in Table II of the 1988 Convention, with a wide range of uses and traded in large quantities.
- Part 3 of Schedule 4 of the Misuse of Drugs Act 1975 contains substances with narrow uses and a high risk of diversion.

Substances commonly used as ingredients in the manufacture of illicit substances should generally mirror the precursors in the 1988 Convention.

Table 3: Penalties for precursor substances under the Misuse of Drugs Act 1975

Schedule 4 – Precursor Substances
Up to 7 years imprisonment for importation, exportation, manufacture, production, or supply know the substance is to be used for the commission of an offence.
Up to 1 year imprisonment, or \$1,000 fine, or both, for importing or exporting a precursor substance without a reasonable excuse.
Up to 5 years imprisonment for possession.

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. State approximately how many doses of your substance this would be.

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.

Note, if these substances were to be scheduled as Class B1 drugs Option 2 for presumption of supply will automatically be applied. If a different presumption of supply, other than Option 2, is recommended for a Class B1 an exemption under the Act will be required.

9 FUTURE ACTIONS

If the Committee recommends that ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA 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 ADB-5Br-INACA, MDMB-5Br-INACA and MDMB-INACA is reasonable and minimised. If the status quo is kept, no further action is required.

10 REFERENCES

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11 Appendix

11.1 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 2022b; 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 2022b). Synthetic cannabinoid users tend to be male, across the age spectrum. Māori are disproportionately affected by use of synthetic cannabinoids (NDIB 2022b; 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 2022b; NZ Drug Foundation 2022). The vulnerability of the user demographic means they use them as a coping mechanism for life circumstances (NDIB 2022b). 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 2022b).

The low price allows people who use synthetic cannabinoids to access them regularly. Synthetic cannabinoids may have a higher potency than similarly priced cannabis – this too may cause preferable consumption over cannabis (NDIB 2022b). In New Zealand, synthetic cannabinoid smoking mixtures cost approximately \$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, July 2022). Typically, 1kg of synthetic cannabinoid powder can produce up to 10,000 bags of smoking mixture (sprayed plant material) (NDIB 2022b). 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, and psychiatric and long-term health harms in New Zealand (NZ Drug Foundation 2022). Table 1 displays hospitalisation numbers for years 2017- 2020 where synthetic cannabinoids were the primary diagnosis (NDIB 2022b).

Table 1: Hospitalizations with synthetic cannabinoids as the primary diagnosis between 2017 to 2021 (NDIB, personal communications, July 2022)

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

**provisional data*

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.

Other data related to the period of 2015-2020 found an 11% reduction in the number of hospitalisations and a 25% reduction in calls to drug help lines (NDIB 2022b). In 2013 the Psychoactive Substances Act 2013 was introduced, and all interim approvals under this act were revoked in 2014. This, coupled with scheduling specific synthetic cannabinoids identified to be causing harm under the Misuse of Drugs Act 1975 in 2019, has likely contributed to this reduction.

Since 2020, synthetic cannabinoids have been the subject of seven DIANZ warnings issued (DIANZ 2022c, 2021a, 2021b, 2020a, 2020b, 2020c, 2020d). Two warnings referenced hospitalisations, and three warnings referenced deaths (four deaths in total). Notification locations were from across different regions in New Zealand (Christchurch, Taranaki, and the lower North Island) (DIANZ 2022c, 2021a, 2021b, 2020b). The DIANZ warnings note that the total harm is likely greater than the specific instances reported (DIANZ 2021a, b; 2020a, b, c). Some harms may not be captured due to a lack of reporting, or because some symptoms considered harmful (such as loss of consciousness) may be the desired effect for the user (NDIB 2022b). One reference noted people using and suffering harm from synthetic cannabinoids have likely been using these substances for a long time (NZ Drug Foundation 2022).

11.2 General pharmacology

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

References have stated that acute 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, and 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).

11.3 Routes of administration and dosage

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 inhomogeneous. The above factors make it difficult to predict the magnitude of effects and

increases the risk of accidental poisoning. The risks can be exacerbated by the route of administration as 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 (Somerville et al 2017).

Specifically for newer generation synthetic cannabinoids, like those reported in this paper, concentrations of 44 to 120g/kg are reported internationally. The variation within samples is significant from 10% up to 141% (Somerville et al 2017).

11.4 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 2022b; 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 2022b; NZ Drug Foundation 2022). Increased use of synthetic cannabinoids by incarcerated or homeless people 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 cannabis users 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 2021, 2022b). Synthetic cannabinoids pose a risk from their specific effects, resultant behaviours, and additional situational risks (DIANZ 2021a; 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 also 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 communication, August 2022; WHO 2021a).

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

11.5 Potential for physical or psychological dependence

Synthetic cannabinoid dependence has been identified as a reason 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 2022b). Heavy use of synthetic cannabinoid receptor agonists has been associated with problematic withdrawal symptoms (WHO 2019b).

11.6 Other relevant information

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 2022b). 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 2022b). This aligns with a downward trend in amount of seized synthetic cannabinoid finished product smoking mixtures in New Zealand see Section 4.1: Likelihood or evidence of abuse in New Zealand.