



Australian Government
Department of Health and Ageing

**FINAL DECISIONS & REASONS FOR DECISIONS BY DELEGATES OF THE
SECRETARY TO THE DEPARTMENT OF HEALTH AND AGEING**

JULY 2011

Delegate's final decision on a scheduling matter considered as a delegate-only matter i.e. was not referred for advice to an expert advisory committee meeting.

**Notice under subsection 42ZCZX of the Therapeutic Goods Regulations 1990
(the Regulations)**

A delegate of the Secretary to the Department of Health and Ageing hereby gives notice of a delegate's final decision for amending the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons – SUSMP*) under subsections 42ZCZX of the Regulations. This notice also provides the reasons for the decision and the date of effect of the decision.

Matters not referred to an advisory committee

A delegate may decide not to refer a matter to an advisory committee and instead may make a final decision on the matter. Guidance for the delegate when deciding not to refer a matter to an advisory committee is set out in the Scheduling Policy Framework (SPF) accessible at www.tga.gov.au/industry/scheduling-spf.htm.

Implementation

The amendments arising from this notice will be incorporated into the SUSMP through a special amendment (SUSMP No. 1 Amendment 3). An electronic copy of SUSMP No. 1 Amendment 3 will be available on the ComLaw website, a link to which can be found at www.tga.gov.au/industry/scheduling-poisons-standard.htm. The next SUSMP consolidation (SUSMP No. 2) will also contain these amendments and hardcopies of the consolidation will be available for purchase from August 2011 from National Mailing and Marketing Pty Ltd, telephone (02) 6269 1035. A hardcopy of SUSMP No. 1 Amendment 3 will not be produced.

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GLOSSARY

<i>ABBREVIATION</i>	<i>NAME</i>
AAN	Australian Approved Name
AC	Active Constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSOM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods

CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils Of Australian Governments
CRC	Child-Resistant Closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority (NZ)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract
GP	General Practitioner
HCN	Health Communication Network
HCP	Health Care Provider
INN	International Non-proprietary Name
ISO	International Standards Organization

LC ₅₀	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD ₅₀	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MCC	Medicines Classification Committee (NZ)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee (now replaced by the Secretary of the Department of Health and Ageing [or Secretary's delegate] as scheduling decision-maker)
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCSEH	Office of Chemical Safety and Environmental Health
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (was Office of Prescription and Non-prescription Medicines)

OOS	Out of Session
OTC	Over-the-Counter
PACIA	Plastics And Chemicals Industries Association
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted Flow Insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons (now the Standard for the Uniform Scheduling of Medicines and Poisons [SUSMP])
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese Medicine

TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working Party
WS	Warning statement

FINAL DECISIONS ON MATTERS NOT REFERRED TO AN ADVISORY COMMITTEE

1. MEDICINES

1.1 SYNTHETIC CANNABINOIDS

BACKGROUND

Synthetic cannabinoids (or synthetic cannabinomimetics) comprise a number of groups of chemically unrelated structures, all of which are functionally similar to the active principle in cannabis, delta-9-tetrahydrocannabinol (THC).

Effects of synthetic cannabinoids are due to their agonist activity at the cannabinoid receptors, CB1 and CB2. CB1 is the receptor thought responsible for the euphoric and psychoactive effects of cannabis. CB2 is mainly found in the immune system and may play a role in pain control as well as mood and behaviour regulation.

The binding affinities for the CB1 and CB2 receptors vary between the various synthetic cannabinoid substances. For example, JWH-018 binds to both receptors with a higher affinity than THC and this is the likely reason for the assumption that this substance may be 4-5 times more potent than cannabis. However, the binding affinity of a substance for a receptor does not necessarily indicate strength of psychoactive effect.

Many of these synthetic cannabinoids were synthesised with the aim of using them as a laboratory tool to identify marijuana receptors and to determine the mechanism of action of cannabis. Others have been developed as part of efforts to find new drugs for nausea, glaucoma and appetite suppression, but few appear to have moved past the preliminary testing stage. Synthetic cannabinoids may also be used in pharmacological studies involving structure-activity relationships, receptor binding studies and mechanisms of action studies.

Some synthetic cannabinoids have been used for medicinal purposes:

- Rimonabant (currently in Schedule 4): A selective CB1 receptor antagonist which was used to treat obesity for some time, but was withdrawn from the market due to severe side effects.
- Nabilone (currently in Schedule 8): A synthetic cannabinoid used for treatment of anorexia and for its antiemetic effects (e.g. in cancer patients under chemotherapy); its chemical structure is closely related to THC.
- Dronabinol (currently in Schedule 8 for therapeutic use): Synthetically produced pure THC applied in multiple sclerosis and pain patients.

Recreational use

There were reports of a number of synthetic cannabinoids being used recreationally as a 'legal' substitute for cannabis. These substances appeared to be added to (sprayed onto) mixtures of dried herbs which were then smoked in order to obtain an effect similar to

cannabis. Use as a herbal tea was uncommon due to the lipophilic compounds' low solubility in water.

Due to the lack of quantitative information about the amount of synthetic cannabinoids incorporated into the herbal smoking blends, caution should be exercised when drawing any conclusions about comparison of the strength of these products with cannabis.

Recreational use of these products was reported in Europe, the US, Asia, New Zealand and Australia. Commonly used names for these products included 'Kronic' and 'Spice'. In Europe, 'Spice' was commonly used as a proprietary eponym to describe the entire class of products. In Australia and New Zealand product names included 'Karma', 'Voodoo' and 'Kaos' and in the US a commonly used brand was 'K2'.

At this time, these products were available over the Internet and through specialty stores. Websites where these herbal smoking blends could be purchased commonly promoted them as 'legal highs'. The products were also sold as 'herbal incense' and, in some countries, as 'plant foods'.

Australian jurisdictional activities

On 17 June 2011, Western Australia (WA) implemented a ban via state-specific legislation on the seven synthetic cannabinoids as listed in the WA scheduling request below. However, several days after the release of the intent to ban these substances an alternative synthetic cannabinoid formulation was being marketed claiming to circumvent these controls.

On 17 June 2011, South Australia (SA) also implemented a ban via state-specific legislation on 17 synthetic cannabinoids (including the seven prohibited by WA).

Certain other jurisdictions were also investigating alternate state-specific approaches such as capturing synthetic cannabinoids 'intended' to have a substantially similar pharmacological effect to cannabis. This outcome-based approach is also possible under the scheduling system, where substances may be scheduled based on effect rather than chemical structure (e.g. the current entry for antibiotic substances captures substances which vary widely in structure and mode of action). Inclusion of a clause "except where separately specified" in the Schedule entry would then allow for appropriate scheduling of individual substances which may have profiles different from the general class.

SCHEDULING STATUS

Apart from rimonabant, nabilone and dronabinol (as described above) there appear to be no other specific entries for synthetic cannabinoids. A limited number of cannabinoids may be captured as derivatives in accordance with Part 1 (2) of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) (e.g. HU-210 is captured as a derivative of nabilone).

Almost all of the synthetic cannabinoids under consideration (except some dibenzopyrans) have chemical structures unrelated to currently scheduled cannabinoids and were therefore not likely to be captured as derivatives by existing entries.

PART 1 - Interpretation

(2) Unless the contrary intention appears a reference to a substance in a schedule or an appendix to this Standard includes:

- (a) that substance prepared from natural sources or artificially; and
- (b) where the substance is a plant (other than a plant included in Schedule 8 or 9), that plant or any part of that plant when packed or prepared for therapeutic use; and
- (c) every salt, active principle or derivative of the substance, including esters and ethers, and every salt of such an active principle or derivative; and
- (d) every alkaloid of the substance and every salt of such an alkaloid; and
- (e) every stereoisomer of the substance and every salt of such a stereoisomer; and
- (f) every recombinant form of the substance; and
- (g) a preparation or admixture containing any proportion of the substance,

A substance is not classed as a derivative on the basis of a single, prescriptive set of criteria. Classification of a substance as a derivative of a Scheduled poison relies on a balanced consideration of factors to decide if a substance has a similar nature (e.g. structurally, pharmacologically, toxicologically) to a Scheduled poison or is readily converted (either physically or chemically) to a Scheduled poison.

SUBMISSIONS

WA Request

The WA State Drugs and Poisons Unit submitted a request for:

- A delegate-only final decision to include in Schedule 9 seven of the most commonly detected individual synthetic cannabinoids with demonstrated harmful effects or potential for significant harmful effects; and
- A referral to the Advisory Committee on Medicines Scheduling (ACMS) for advice on the inclusion in Schedule 9 of broader synthetic cannabinoid groups.

Scheduling of individual synthetic cannabinoids

The request stated that rapid scheduling of the individual actives could be justified due to the potential for significant public health risk, noting that the substances under consideration were new chemical entities not previously scheduled.

The request recommended that the substances listed in the following table be included in Schedule 9 on the basis that they are used for the purpose of obtaining a psychoactive effect; may be dependence producing; have no legitimate therapeutic uses; and have documented harmful effects which may be significant in some individuals.

Common name	CAS#	Chemical name(s) in Martindale	International Union of Pure and Applied Chemistry (IUPAC) systematic name
JWH – 018	209414-07-3	1-Naphthalenyl(1-pentyl-1 <i>H</i> -indol-3-yl)methanone	1-Pentyl-3-(1-naphthoyl)indole
JWH – 073	208987-48-8	1-Naphthalenyl(1-butyl-1 <i>H</i> -indol-3-yl)methanone JWH-018 butyl homologue	Naphthalen-1-yl-(1-butylyndol-3-yl)methanone
JWH – 122	619294-47-2	nil	1-Pentyl-3-(4-methyl-1-naphthoyl)indole
JWH – 200	103610-04-4	nil	(1-(2-morpholin-4-ylethyl)indol-3-yl)-naphthalen-1-ylmethanone
JWH – 250	864445-43-2	nil	2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone
CP 47,497	70434-82-1	(1 <i>RS</i> ,3 <i>SR</i>)-3-[2-hydroxy-4-(2-methyloctan-2-yl)phenyl]cyclohexan-1-ol	2-[(1 <i>R</i> ,3 <i>S</i>)-3-hydroxycyclohexyl]-5-(2-methyloctan-2-yl)phenol
Cannabicyclohexanol (CP 47,497 C8 homologue)	70434-92-3	(1 <i>RS</i> ,3 <i>SR</i>)-3-[2-hydroxy-4-(2-methylnonan-2-yl)phenyl]cyclohexan-1-ol	2-[(1 <i>R</i> ,3 <i>S</i>)-3-hydroxycyclohexyl]-5-(2-methylnonan-2-yl)phenol

XXXXXX recommended use of the IUPAC systematic name to identify the various chemicals. The request also suggested that for clarity it may be necessary to include both the chemical name and the more widely used abbreviated names (i.e. JWH-018 and CP 47,497) in the schedule entries and the SUSMP Index.

These substances have either been included in Schedule I of the US Federal *Controlled Substances Act* (also controlled by a number of European countries) or known to have been detected in products for sale in Australia. Some European countries have also scheduled CP 47,497 and its C6, C8 and C9 homologues. The request suggested that these particular homologues may also need scheduling to ensure appropriate restrictions.

The request also suggested an alternative outcome-based approach similar to the Norwegian drug control legislation where an entry could be included in Schedule 9 for “synthetic agonists of cannabinoid receptors or synthetic cannabinomimetics”. However,

noted that there were issues associated with this approach similar to those of scheduling the group entries.

Scheduling of groups of synthetic cannabinoids

The groups below have either been reported in smoking mixtures (both overseas and in Australia) or have been controlled in other countries. These groups were also requested for scheduling consideration and inclusion in Schedule 9:

- Dibenzopyrans ('classical' cannabinoids) – e.g. HU-210 and HU-211, THC.
(It was noted that due to their chemical structure, HU-210 and HU-211 could be captured under the derivatives clause by the Schedule 8 nabilone entry).
- Cyclohexylphenols ('non-classical' cannabinoids) – e.g. CP 47,497, Analog VII or cannabicyclohexanol.
- Naphthoylindoles – e.g. JWH-015, JWH-018, JWH-073, JWH-122, JWH-200, JWH-210, JWH-398, WIN-55,212.
- Naphthylmethylindoles.
- Naphthoylpyrroles.
- Naphthylmethylindenes.
- Phenylacetylindoles – e.g. JWH-250, JWH-251.

Clarification was requested whether the dibenzopyrans class would be captured as 'derivatives' by the existing Schedule 9 tetrahydrocannabinols entry. If it was decided that these substances were captured as derivatives, a cross reference in the SUSMP Index was suggested to clarify the scheduling status. However, if it was determined that the tetrahydrocannabinols entry did not capture this class of substances, then requested to also include dibenzopyrans in Schedule 9.

The request raised concerns that if only certain substances within each chemical group were scheduled, those manufacturing these products would move to a different compound that is similarly pharmacologically active. There is evidence that this has occurred in other countries within weeks of the prohibition of certain synthetic cannabinoids.

It was suggested that the inclusion of group entries would circumvent this issue. However, it was noted that in the UK, where this approach was used in December 2009 to control groups of chemical compounds through the *Misuse of Drugs Act 1971*, other synthetic cannabinoids have since appeared in products within the UK which were not captured by these groups.

Although there was a lack of evidence of industrial use for the compounds captured by the UK's broad scheduling approach, the submission noted that if the above group entries were included in Schedule 9, there may be potential for impact on future drug development by pharmaceutical manufacturers.

According to the SUSMP, listing a substance or class of substances in Schedule 9 would allow access to those substances for medical or scientific research or for analytical,

teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities. However, it is within the jurisdictions' means not to grant approval to these substances for access in clinical trials.

The request noted that referral of a proposal to schedule these group entries to the ACMS would be subject to public consultation which would help inform of any unintended consequences of the proposed scheduling.

The request also specifically addressed a number of matters under section 52E of the *Therapeutic Goods Act 1989* (the Act), as summarised below:

Risks and benefits (including toxicity)

- Some users of herbal smoking blends containing synthetic cannabinoids have reported similar effects to cannabis such as relaxation and sedation. Commonly reported effects included paranoia, anxiety, racing thoughts and irritability. Other effects included hallucinations, tremors, seizures, drowsiness, slurred speech, dilated pupils, elevated blood pressure, vomiting and chest pain. There have also been reports of the use of synthetic cannabinoids precipitating the redevelopment of psychosis in patients with a history of mental illness (similar rates to those associated with cannabis use).
- The smoking of any substance is likely to have an adverse effect on health and like the smoking of tobacco and cannabis, herbal smoking blends may put users at risk of developing pulmonary conditions such as chronic bronchitis and lung cancer. Another potential concern with these substances was the possibility of serotonin syndrome. The indole moiety in certain compounds in the JWH series results in a similar structure to serotonin and may increase serotonin receptor activation. (The delegate noted that if the JWH substances under consideration were scheduled, the overall structure of these substances was sufficiently different so as not to inadvertently capture serotonin as a derivative).
- Claims have also been made in the media that herbal smoking mixtures allegedly containing synthetic cannabinoids have been responsible for at least three deaths in the US. However, one of these deaths was subsequently shown to be the result of a 'mixed drug intoxication' and there was no coronial information available on the role of these products in the other two deaths.
- There was no scientific literature describing the long-term effects of either the synthetic cannabinoids themselves or the effects of smoking the herbal blends. The relatively short period of use within populations (probably since 2008) was insufficient to examine longer-term effects such as onset of mental illness and associations with cancer.
- There was a lack of peer reviewed literature of systematically conducted trials of either the toxicology or potential beneficial effects of these substances in man. There was limited animal toxicology data available for some synthetic cannabinoids. There was also little information about the potential health effects of the herbs used as carriers for the synthetic cannabinoids.

- Determining prevalence of use was hampered by difficulties in detecting both the parent compound and metabolites in urine samples and, prior to 2008, there was no mechanism for recording synthetic cannabinoid related admissions to health services. In Australia, it was likely that hospital admissions would be recorded as relating to 'cannabis derivatives' and therefore at this time it was not possible to ascertain the proportion of admissions due to these synthetic substances.

Purpose and extent of use

- None of the seven substances requested by WA have any current legitimate human therapeutic use. Although there were anecdotal claims of antidepressant, anti-nausea and pain relieving effects, the initial choice to use synthetic cannabinoids was almost always for the purpose of obtaining a psychoactive effect.
- There were claims that synthetic cannabinoids have been used as an alternative to smoking cannabis and hence should remain 'legal' as users were therefore able to remove themselves from the illicit market.
- It was also suggested that use of these products was more popular in novice drug users hoping to get a 'high' whilst avoiding breaking the law. It could be suggested that this increases risk of use by younger persons.
- In WA, consumers have indicated that they chose to use these types of preparations as an alternative to cannabis because the substances in these herbal smoking mixtures were not detected in drug screening tests used by their employers. Recent media reports from New Zealand (NZ) also indicated that employers are concerned about use of 'herbal highs' in high risk industries such as transport, civil engineering, aviation and mining.

Dosage, formulation, labelling etc

- Herbal smoking products available at this time did not indicate which synthetic cannabinoids they contained or in what quantities. Packages generally contained 1 g or 3 g of crushed dried plant matter.
- Testing has shown that a product sold under the same brand at different times may contain different synthetic cannabinoids in varying quantities (between 2.3 mg/g and 22.9 mg/g of CP 47,497-C8, JWH-018 or JWH-073).
- Some products were labelled to suggest they should not be used by those under 18 years of age. Other products were labelled as 'not for human consumption' (suggesting that they were intended to be burned as room incense rather than being smoked).

Potential for abuse / misuse

- There were reports of patients meeting the standard criteria for both withdrawal and addiction in relation to use of certain synthetic cannabinoid herbal blends, with evidence of tolerance and withdrawal symptoms. Specific reports have also suggested that JWH-018 was associated with drug tolerance, most likely due to

receptor down-regulation. This was thought to generally increase the likelihood of dependence on that drug, where the drug has psychoactive effects.

- At least three synthetic cannabinoids were detected in herbal blends purchased in WA retail outlets: JWH-073, JWH-122 and JWH-250. Products claiming to be manufactured in NZ and sold in NZ and Australia, have also been shown to contain JWH-018.

United Nations Office on Drugs and Crime (UNODC)

The UNODC released a report on synthetic cannabinoids in herbal products focusing on the substances' pharmacological activity, potential toxicity and recommendations regarding their legal handling. The report made the following points, not previously mentioned:

- Since 2004, herbal mixtures containing synthetic cannabinoids have been available in several European countries. Initially, these products were not popular and were used by only a small group of experimental users. However, numerous reports on these products surfaced in German newspapers and television in 2008 proclaiming their use as 'legal' cannabis substitutes, leading to dramatic increases in popularity.
- While these products were initially found to be popular among users of different ages and socioeconomic status, a recent survey suggested that the use of these products had dropped significantly. However, it was still increasingly popular among users who have to undergo regular urine drug screenings as current screening methods did not detect synthetic cannabinoids.
- In addition to the seven groups of synthetic cannabinoids requested by WA, the UNODC also provided details on the following synthetic cannabinoid groups:
 - Benzoylindoles – e.g. pravadoline, AM-694, RSC-4;
 - Eicosanoids – endocannabinoids (substances produced from within the body that activated cannabinoid receptors) such as anandamide, and their synthetic analogues e.g. methanandamide; and
 - Diarylpyrazoles – selective CB1 antagonists e.g. rimonabant (listed in Schedule 4).
- Noted that synthetic cannabinoids commonly used in pharmacological studies included CP-55,940 (a cyclohexylphenol), WIN-55,212-2 (a naphthoylindole) and anandamide (an eicosanoid).
- Noted the adverse effects associated with use of synthetic cannabinoids, specifically the increasing numbers of hospitalisations with severe intoxications following use of products claimed to contain JWH-122.
- Stated that there was no valid data on the toxicity of these compounds so far, however it could be speculated that some of the metabolites, particularly those carrying a naphthyl moiety, may have carcinogenic potential.

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- Stated that although cannabis has a comparatively low acute toxicity, at least some of the synthetic compounds under consideration could cause severe or life-threatening intoxications when overdosed, particularly those which act as full agonists at the CB1 receptor (HU-210, CP-55,940 or WIN-55,212-2).
 - Noted evidence which suggested that a number of synthetic cannabinoids may have a higher addictive potential compared to cannabis due to quicker development of tolerance.
 - Stated that the herbal blend phenomenon did not seem to disappear in countries which prohibited either single actives or groupings of synthetic cannabinoids, although the number of users may have been reduced due to lower availability and lesser media presence. Noted that there remained a variety of these products available on the Internet with new synthetic cannabinoids continuously appearing.
 - Noted that the use of a generic definition for controlling synthetic cannabinoids would still bear the risk of not covering all possible derivatives and may possibly hamper synthetic cannabinoid research.

International considerations

Initial reports of use appeared in Europe around 2008, with increases leading to the UN International Narcotics Control Board (INCB) expressing concern with the level of use. Although none of the synthetic cannabinoids are listed in either the *United Nations Single Convention on Narcotic Drugs, 1961* or the *United Nations Convention on Psychotropic Substances 1971*, the INCB considers the availability of herbal mixtures containing these substances to be a matter of concern. The INCB recently issued a statement in which they welcomed the timely efforts of governments to prevent the trafficking in and abuse of synthetic cannabinoids and recommended the continued monitoring of the situation and the adoption of preventative measures as necessary.

A number of jurisdictions with similar regulatory frameworks to Australia have implemented controls on access to these substances, including the UK (December 2009) and the US (March 2011).

Europe

In the UK, Schedule 1 of the Misuse of Drugs Regulations 2001 results in the most stringent controls under those Regulations, where substances are not authorised for medical use and can only be supplied, possessed or administered in exceptional circumstances under a special Home Office licence, usually only for research purposes. Class B drugs are subject to both possession and dealing offences (resulting in up to 5 years imprisonment and up to 14 years imprisonment respectively). The following substances were added to Schedule 1 and classified as 'Class B':

- 3-(1-naphthoyl)indole or 1H-indol-3-yl-(1-naphthyl)methane;
- 3-(1-naphthoyl)pyrrole;
- 1-(1-naphthylmethyl)indene;

- 3-phenylacetylindole; and
- 2-(3-hydroxycyclohexyl)phenol.

In mainland Europe, several countries have enacted controls on a number of different synthetic cannabinoids varying from prohibition of distribution to prohibition of any activities (sometimes with provision for access by authorisation for some research type activities). Certain countries have also prohibited use of any substance with cannabinoid activity.

USA

In the US, Schedule I is the most restrictive Schedule of the *Controlled Substances Act* (CSA), where possession and supply (including import and export) of a substance is illegal, except as authorised by law. From 1 March 2011, the US Drug Enforcement Administration (DEA) added five synthetic cannabinoids (JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol) to Schedule I to 'avoid an imminent hazard to the public safety'. A summary of the actions undertaken by the DEA is provided below:

- This scheduling will remain in place for at least 12 months (with the option of a 6 month extension) while the US Department of Health and Human Services further investigates whether these chemicals should be permanently controlled.
- The DEA considered a number of factors prior to making a decision including the history and current pattern of abuse, the scope, duration, and significance of abuse, and what, if any, risk there is to the public health, including actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution.
- Three reasons were given for the US DEA action:
 - Although the substances are not intended for human consumption, there has been a rapid and significant increase in abuse in the US;
 - Law enforcement agencies have seized 'synthetic cannabinoids' with controlled substances and based on self-reports to law enforcement and health care professionals, synthetic cannabinoids are abused for their psychoactive properties; and
 - Numerous state and local public health department and poisons control centres have issued health warnings describing the adverse health effects associated with synthetic cannabinoids.
- Asserted that these five substances were developed and evaluated as research tools, were not intended for human consumption and no other known legitimate uses have been identified.
- Noted that smoking these synthetic cannabinoids for the purpose of achieving intoxication and experiencing the psychoactive effects has been identified as a reason for emergency room visits and calls to poison control centres.

New Zealand (NZ)

In November 2010, the NZ Expert Advisory Committee on Drugs considered an assessment of the synthetic cannabinoids JWH-018 and JWH-073. In summary, the assessment made a number of points specific to NZ not previously mentioned:

- Noted that in March 2009, the 1,1-dimethyloctyl homologue of CP 47,497 was banned following determination that it was structurally related to THC.
- Following this ban, other synthetic cannabinoids appeared on the market, including JWH-018 and JWH-073. Noted that this trend was mirrored in other jurisdictions which had also prohibited single actives.
- Noted the lack of available evidence of prevalence of synthetic cannabinoids currently available in NZ, however identified at least 80 synthetic cannabinomimetic substances derived from naphthoylindoles, phenylacetylindoles, benzoylindoles, naphthoylpyrroles, cyclohexylphenols and classical cannabinoids. Noted that due to their structural similarity some classical cannabinoids could be captured by the restrictions on THC.
- Noted a submission recommending Class C (Controlled Drug) restrictions on the following substances:
 - JWH-018 (a naphtholindole), due to issues with toxicity and abuse potential. This compound had proved unusually problematic and had a particular tendency to cause anxiety and serious adverse reactions, even when diluted in herbal smoking blends.
 - HU-210 (a classical cannabinoid), due to significant potency, severe side effects and very long duration of action.
 - AM-694 (a benzoylindole), due to toxicity concerns relating to its chemical structure.
- Noted that the increase in media attention on synthetic cannabinoids may have led to an increase in use. Also noted an increase in marketing of these products to young people.
- Noted the significant rates of use of these products in secure inpatient mental health services. Noted anecdotal evidence that these high use patterns were mostly due to a lack of proper detection techniques.
- Stated that there was no peer reviewed literature on the toxicological effects of the JWH compounds, however noted an anonymous study available on the internet claiming data on fluorescent cytochrome P450 inhibition; cytotoxicity; genotoxicity; QT interval prolongation; rat pharmacokinetics; and repeat rat toxicity for JWH-018.
- Noted a submission which stated that naphthoylindoles JWH-018 and JWH-073 may have a greater tendency to produce anxiety and paranoia than THC.
- Stated that the NZ Ministry of Health was not aware of any research into the effect on driving performance of the substances JWH-018 or JWH-073. However, given the

sedating and hallucinatory effects expected of substances which act as a CB1 agonist, it was likely that a person could become significantly impaired following the use of these substances.

- Noted that apart from anecdotal reports, there was no officially recognised therapeutic use of JWH substances. Stated that as certain therapeutic aspects of cannabis may be reproduced more strongly by synthetic cannabinomimetic drugs with a higher affinity for the CB1 and CB2 receptor than cannabis, these substances may have efficacy in treating certain conditions. Noted however, no pharmaceutical preparations containing the JWH compounds have been brought to market.
- Noted a submission which stated that the UK approach to restricting class entries missed a number of substances, such as AM-694 (1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole), which has since been brought to the market in these jurisdictions.

The minutes of the NZ EACD meeting provided the following additional points, summarised below:

- The EACD agreed that it was not only the delivery of these substances (via smoking) that may be harmful, but the substances themselves. It was noted that there still existed a lack of robust scientific data on these substances and regulation of these substances as restricted would ensure that accessibility controls would be in place to mitigate some risks while allowing for the substances to be monitored more closely.
- EACD members discussed the potential appeal to vulnerable populations and it was acknowledged that marketing for these products would continue to grow. Also noted the possibility that such regulation could increase aggressive marketing techniques as their restricted status might inadvertently convey a sense of government endorsement.
- A common concern was that other synthetic cannabinomimetic substances may emerge in place of JWH-018 and JWH-073 once these were restricted. Alternative grouping entries such as “naphthoylindole derivatives” were considered as these were currently the most widely available and cheapest on the chemical market and therefore the most likely to be incorporated into smoking products by the industry.
- It was concluded that the most effective measure would be to try to capture new emerging cannabinomimetic substances by recommending that “all synthetic substances with cannabinomimetic effects” be included in the *Misuse of Drugs Act 1975* as restricted substances. In the event that this approach was not legally possible under NZ legislation, decided to include the naphthoylindole derivatives individually as restricted substances to capture the most potent, easily available and therefore most likely substances to be utilised by this industry.
- In NZ, classifying a substance as restricted allows access to that substance subject to stipulated conditions and restrictions.

Unsolicited stakeholder input

Although an invitation for submissions was not published, several unsolicited comments were received, likely in response to the jurisdictions' implementation of state-specific controls and resulting media attention. The delegate was under no legislative obligation to consider these comments.

Intergovernmental Committee on Drugs (IGCD)

The Chair of the IGCD supported the WA request for inclusion of synthetic cannabinoids in Schedule 9 and requested an accelerated consideration. A number of comments were also provided, as summarised below:

- At the May 2011 IGCD meeting, members noted the emergence of new and existing synthetic analogue drugs (analogues) that mimic the effects of illegal drugs, particularly substances in herbal blends which mimic the effects of cannabis.
- Noted the reported wide use of these substances, particularly in the mining industry. Raised concerns over health and safety, particularly for employees operating machinery. Also raised concerns about the risk to public health and safety from the continued sale of herbal blends with synthetic cannabinoids, as the ingredients, purity and pharmacological potency of such products were largely unknown.

Department of Health, Victoria

Victoria Health supported the urgent consideration and restriction of synthetic cannabinoids and submitted for consideration the following points not previously mentioned:

- In May 2011 there was limited data on the extent of the use of these herbal blends in Victoria, however there were anecdotal reports of open promotion and sale through a variety of stores and the internet.
- Regular Alcohol & Other Drug (AOD) monitoring reports have not at this time detected harms from any analogue drug, or significant levels of use of this category of drug amongst AOD service users.
- Supported regulation of analogues to:
 - in the short term, allow the temporary prohibition of new analogues until risks could be properly assessed and longer-term regulation put in place; and
 - in the longer term, be flexible enough to ensure that new and harmful psychoactive substances would be captured by regulations without continual need for updating.
- Requested that options for addressing issues relevant to analogues be explored, including in the context of the Customs (Prohibited Imports) Regulations.
- Is currently awaiting advice from the IGCD on mechanisms to identify emerging psychoactive substances as soon as they appear on Australian markets; assess the harms; develop regulatory and administrative responses; and disseminate timely warning information to agencies and the public.

XXXXX

XXXXX submitted a request to align with the NZ decision to restrict synthetic cannabinoids such as JWH-018 and JWH-073 instead of banning. The request asserted that a number of states had existing restrictions on the supply of non-tobacco smoking substances.

XXXXX

XXXXX objected to prohibiting synthetic cannabinoids, specifically in relation to JWH-018, and suggested an alternate regulatory approach similar to NZ's classification. Suggested inclusion in Schedule 6 as the closest to the NZ classification or alternatively the creation of a sub-class of Schedule 7 reserved for 'social inebriants'. Suggested mandatory training for licensed vendors and their staff.

The majority of the input's comment related to the potential revenue of regulating synthetic cannabinoids and where this revenue would be diverted should these substances be prohibited.

The input also asserted that in concentrations of less than 10 mg per gram of carrier substance, JWH-018 was relatively safe and only mildly inebriating, and did not induce paranoia or anxiety. Asserted that the negative reactions reported in Australia to date were due to use of higher concentrations of the product.

DELEGATE'S DISCUSSION

In accordance with section 52E(4) of the *Therapeutic Goods Act 1989* (the Act) the delegate sought verbal advice on this matter from representatives of Australian jurisdictions with expertise in drugs and poisons regulation.

The delegate agreed that for this consideration the relevant matters under section 52E(1) of the Act included (a) risks and benefits of use; (b) purpose and extent of use; and (e) the potential for abuse of a substance.

The delegate agreed that this matter required a two-phased approach:

- The consideration of restrictions to a number of individual synthetic cannabinoids to address the immediate risks to public health; and
- The development of a longer-term solution to appropriately capture related substances.

Individual substances

The delegate noted the factors listed in the Scheduling Policy Framework for inclusion of substances in Schedule 9. The delegate noted that there was currently no evidence of established therapeutic value for the seven synthetic cannabinoids identified in the WA request (JWH-018, JWH-073, JWH-122, JWH-200, JWH-250, CP47,497, and cannabicyclohexanol). The delegate also noted the risks associated with these substances, including their potential for dependency, abuse and misuse.

The delegate additionally noted current reports of abuse and misuse of AM-694 (a benzoylindole). The delegate agreed that although this substance was not identified in the WA request its profile also aligned with the factors for inclusion in Schedule 9. The delegate further noted that this substance was already specifically prohibited in SA via state-specific legislation, along with a number of other benzoylindoles.

The delegate noted input from stakeholders suggesting alternative approaches to inclusion in Schedule 9, including alignment with NZ restrictions or the creation of a prohibitive category for specific Australian sub-populations. The delegate decided that such an approach was not appropriate for Australia and noted that such controls were also not possible under the current Australian scheduling arrangements.

The delegate also noted claims of alleged benefits of revenue from use of synthetic cannabinoids. The delegate clarified that scheduling decisions are made to protect public health and Schedule 9 controls for synthetic cannabinoids would assist in reducing harm associated with these substances.

On balance, the delegate agreed that the dangers of use of these eight synthetic cannabinoids were such as to warrant limiting use to strictly controlled medical and scientific research. The delegate agreed to specifically list these substances in Schedule 9, using their IUPAC names to ensure clarity and assist enforcement. The common names of these substances would also be cross-referenced to these entries in both Schedule 9 and the SUSMP Index. For clarity, the delegate also agreed that a cross-reference in the SUSMP Index from the C6 and C9 homologues of CP 47,497 to 2-[(1R,3S)-3-hydroxycyclohexyl]-5-(2-methylnonan-2-yl)phenol (i.e. cannabicyclohexanol) would be appropriate.

The delegate noted that the decision to include these eight substances in Schedule 9 was a final decision initiated by the delegate (by request) and as such was not subject to further submissions. The delegate also noted that under the SUSMP derivatives clause, the Schedule 9 entries for the eight individual substances would also capture many similar substances.

Implementation date

The delegate noted that due to the potential of the use of these substances to cause harm a shorter implementation period would be required than those reserved for routine scheduling decisions. The delegate agreed that an implementation date of 8 July 2011 would be appropriate for this decision.

Synthetic cannabinoid classes

The delegate noted the request for the scheduling of classes of cannabinoids to limit potential future abuse of substances replacing those which have been prohibited.

Although some cannabinoids would be captured as derivatives of the eight substances detailed above, this clause may not extend to all substances within those classes. The delegate also noted the risk of users potentially moving onto substances within other synthetic cannabinoid classes not currently captured by these restrictions. The delegate

noted that listing all the known classes of synthetic cannabinoids in Schedule 9 as group entries could address these two potential issues.

The delegate also noted that new classes of synthetic cannabinoids could be created for misuse purposes. The delegate noted other jurisdictions' approaches to address this issue by inclusion of an outcome-based class entry either for all synthetic agonists of cannabinoid receptors or substances intended to have a substantially similar pharmacological effect to cannabis.

The delegate noted that according to the SUSMP, class entries do not capture substances which are individually listed (for example the existing Schedule 9 class entry for tetrahydrocannabinols does not capture nabiximols as it is separately listed). However, other substances within those classes which are not specifically scheduled would then be captured.

The delegate agreed that due to the complexity of any group entry approach and the potential for inadvertent impact on substances not currently scheduled, this matter would benefit from advice from the ACMS. The delegate noted that referral of this matter to the ACMS also allows for public consultation, with an invitation for public submissions on the delegate's proposal to be published on the TGA's scheduling website on 10 August 2011.

DELEGATE'S FINAL DECISION

The delegate decided to include in Schedule 9 the following synthetic cannabinoids together with reference to their common names, noting that many analogues of these substances would also be captured as derivatives:

- (1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole) (common name AM-694);
- 2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone (common name JWH – 250);
- (1-(2-morpholin-4-ylethyl)indol-3-yl)-naphthalen-1-ylmethanone (common name JWH – 200);
- Naphthalen-1-yl-(1-butylindol-3-yl)methanone (common name JWH – 073);
- 1-Pentyl-3-(4-methyl-1-naphthoyl)indole (common name JWH – 122);
- 1-Pentyl-3-(1-naphthoyl)indole (common name JWH- 018);
- 2-[(1R,3S)-3-hydroxycyclohexyl]-5-(2-methylnonan-2-yl)phenol (common name Cannabicyclohexanol or CP 47,497 C8 homologue); and
- 2-[(1R,3S)-3-hydroxycyclohexyl]- 5-(2-methyloctan-2-yl)phenol (common name CP 47,497).

For clarity, the delegate also decided that in addition to the usual SUSMP Index cross-referencing of the common names to the Schedule 9 listing, to also include a cross-reference in the Index from the C6 and C9 homologues of CP 47,497 to 2-[(1R,3S)-3-hydroxycyclohexyl]-5-(2-methylnonan-2-yl)phenol (cannabicyclohexanol).

The delegate decided on an implementation date of 8 July 2011.

Schedule 9 – New Entries

(1-(5-FLUOROPENTYL)-3-(2-IODOBENZOYL)INDOLE) *(AM-694).

2-(2-METHOXYPHENYL)-1-(1-PENTYLINDOL-3-YL)ETHANONE
*(JWH – 250).

(1-(2-MORPHOLIN-4-YLETHYL)INDOL-3-YL)-NAPHTHALEN-1-
YLMETHANONE *(JWH – 200).

NAPHTHALEN-1-YL-(1-BUTYLINDOL-3-YL)METHANONE *(JWH – 073).

1-PENTYL-3-(4-METHYL-1-NAPHTHOYL)INDOLE *(JWH – 122).

1-PENTYL-3-(1-NAPHTHOYL)INDOLE *(JWH - 018).

2-[(1R,3S)-3-HYDROXYCYCLOHEXYL]- 5-(2-METHYLOCTAN-2-YL)PHENOL
*(CP 47,497).

2-[(1R,3S)-3-HYDROXYCYCLOHEXYL]-5-(2-METHYLNONAN-2-YL)PHENOL
*(Cannabicyclohexanol or CP 47,497 C8 homologue).