Australian Government
Department of Health

Application to Reschedule Psilocybine[1] from Schedule 9 to Schedule 8 of the Poisons Standard

14th July 2020

Mind Medicine Australia Limited

Level 1/ 10 Dorcas St
South Melbourne VIC 3006

For further guidance in using this form, refer to the *Scheduling Policy Framework for Medicines and Chemicals 1 February 2015* (SPF), in particular refer to Chapter 4: GUIDELINES FOR APPLICATIONS AND INFORMATION REQUIREMENTS, available at (https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals).

1 The SUSMP spells psilocybine with an 'e' on the end. All the literature spells psilocybin without an 'e' on the end. For the purposes of this document psilocybin will be spelt without an 'e' on the end from this point.

Contents

CONFIDENTIALITY

The Application contains no information claimed to be commercial-in - confidence.

APPLICANT'S DETAILS

1. **Applicant's Name;** Mind Medicine Australia Limited
2. **Applicant's Address;** Level 1, 10 Dorcas Street, South Melbourne, Victoria 3205
3. **Business Name;** Mind Medicine Australia
4. **Date of Submission;** 14th July 2020
5. **Contact Person;** Mr. Peter Hunt AM
6. **Email Address of Contact Person;** peter@mindmedicineaustralia.org
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8. **Phone Number of Contact Person;** 0419 271 483
9. **Fax Number of Contact Person;** Not Applicable

DECLARATION

I, Peter John Hunt, Chair of Mind Medicine Australia Limited:

- declare that the information provided in this application is true and current.
- undertake not to publicly disclose the notices of interim decision or final decision in respect of this application, until (if relevant i.e. following referral to an expert advisory committee) these documents are published pursuant to subsections 42ZCZP and 42ZCZS of the Therapeutic Goods Regulations 1990, respectively.

Signature:

Name: Peter Hunt AM
Position: Chair of Mind Medicine Australia Limited
Date: 14 July 2020

PART 1 - SUMMARY OF THE APPLICATION

A. PROPOSED RESCHEDULING OF THE POISONS STANDARD

Mind Medicine Australia Limited requests a rescheduling of psilocybine from Schedule 9 to Schedule 8 of the Poisons Standard. The SUSMP spells psilocybin with an "e" at the end (i.e. as psilocybine). All of the literature reviewed uses the spelling "psilocybin" (i.e. without an "e" at the end). For the purposes of this Application the more accepted spelling – psilocybin – will be used.

B. SUGGESTED SCHEDULING OR OTHER WORDING

Schedule 8 – Proposed New Entry/Amendment

Psilocybin for use in the treatment of medical conditions:

a. In preparation for oral use as part of psychotherapy under the authorisation of a treating psychiatrist or specialist addiction physician in a medically controlled environment

b. Manufactured in accordance with the Narcotic Drugs Act 1967; and/or

c. Imported or manufactured in Australia as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or

d. In therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989

C. SUBSTANCE SUMMARY

1. Chemistry

(source https://pubchem.ncbi.nlm.nih.gov/compound/10624)

Chemical Formula: $C_{12}H_{17}N_2O_4P$

CAS Number: 620-52-5

IUPAC Name: [3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate

Molar Mass: 248.25 g/mol

Melting Point: 220-228°C

2. Chemical structure

(source https://pubchem.ncbi.nlm.nih.gov/compound/10624)

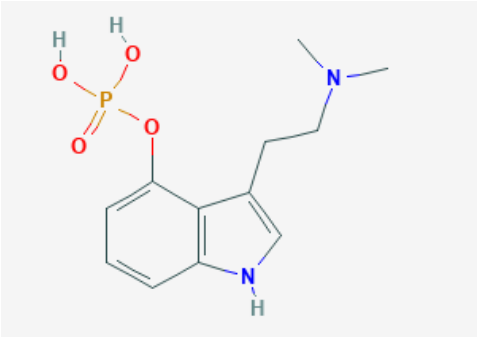

Image 1. Molecular structure of psilocybin

3. Description of substance

Psilocybin is a member of the tryptamine chemical family and presents as a white crystalline solid. It is stable over extended periods at room temperatures. It is a major psychoactive constituent in mushrooms of the Psilocybe genus**.** Psilocybin is classed as a psychedelic, sometimes called a hallucinogen, although this name is advised against in modern scientific literature as psychedelics do not generally induce true hallucinations (Nichols, 2016). Psychedelics are chemical compounds which temporarily create changes in brain function including shifts in perception, thinking, and feeling, which temporarily produces an 'altered state of consciousness'. Psilocybin is a non-chiral molecule.

4. Toxicity

The toxicity of psilocybin is very low. Based on the results of animal studies, the lethal dose of psilocybin has been extrapolated to 6 g in humans (Gable 2004, p. 690); which is 300 times the typical therapeutic dose of 20 mg. The lethal doses are below:

- LD_{50} ($mouse_{ip}$) = 285 mg/kg
- LD_{50} (rat_{ip}) = 280 mg/kg
- LD_{50} ($rabbit_{iv}$) = 12.5 mg/kg

5. Pharmacology

i. Metabolism

Psilocybin is a prodrug for its active metabolite psilocin (4-OH-DMT; 4-hydroxy-N,N-dimethyltryptamine) (Passie et al., 2002). When administered orally, psilocybin is metabolised rapidly and effectively in the liver into psilocin. The effects of psilocybin are wholly from psilocin, in fact psilocybin is 48 times less efficacious than psilocin (Dinis-Oliveira 2017, p. 87). The absorption of psilocybin is 50% (Passie et al. 2002). Psilocin is evenly distributed throughout the whole body. Psilocin is detected in plasma after 20-40min, but drug onset is generally 70-90min. Plasma C_{max} for psilocin (as psilocybin administrated in humans at a therapeutic dose of 0.3 mg/kg) is average 16 µg/L (between 14.5-17.2 µg/L) (Brown et al. 2017). The T_{max} for the respective C_{max} is average 121min

(between 69-124 min). The elimination half-life of psilocin is 163 min. The psychoactive effects of psilocybin at therapeutic dose levels can last 6-8 hours.

ii. Human Pharmacology

Psilocybin and its metabolite psilocin exert their primary psychoactive action through partial agonism of the serotonin 5-HT_{2A} receptor, a G-protein-coupled receptor (Nichols, 2016). Pre-treatment with 5-HT_{2A} receptor antagonist, ketanserin, was found to block most of the experiential effects of psilocybin. Serotonin 5-HT_{2A} receptors increase in number within the brain under conditions of depression and states of high stress, such as sleep deprivation and hypoxia (Moya & Powell, 2018). Activation of the 5-HT_{2A} receptor causes downstream effects such as changes in the expression of early growth protein 1 (ERG1) and beta-arrestin 2 (Maple et al, 2015). These findings suggest that the 5-HT_{2A} receptor is involved in processes related to adaptivity, sensitivity to context, learning and unlearning, and synaptogenesis (new neuronal connections) (Carhart-Harris & Nutt, 2017). Although 5-HT_{2A} agonism is recognised as the primary mechanism of psilocybin and other classical psychedelics, psilocybin has affinity for an array of pre and post-synaptic serotonin and dopamine receptors (Ray, 2010). For example, it has been found that classical psychedelics inhibit TNFa signalling through activation of serotonin receptor 5-HT_{2B}, a potential anti-inflammatory mechanism of classical psychedelics (Yu et al. 2008).

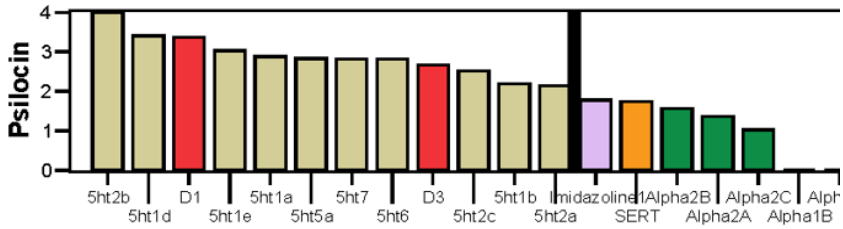

Table 1. **Receptor assay of psilocin** (Ray, 2010)
This image shows the receptor binding affinities of psilocin. The receptors before the black line contribute to the psychoactive effects.

6. Effects in Humans

i. <u>Therapeutic Psychological Effects</u>

(Carhart-Harris and Goodwin, 2017; Roseman et al., 2018; Kraehenmann, 2017; Passie et al., 2002)

- Enhancement of emotions
- Enhanced ability for introspection
- Increased awareness of sub-conscious processes
- Induction of hypnagogic experience and dream-like experiences
- Synaesthesia
- Labile brain state (see section 2.1[F]E)
- Alterations of thought and sense of time
- Enhances ‘emotional breakthroughs’

ii. Possible Adverse Effects

No drug related serious adverse events (SAE) have been reported from any previous research investigating psilocybin's effects in healthy participants (Aday, 2020). Whilst the numbers involved in clinical studies have been limited a substantial amount of further data can also be extracted from population studies (see Part 2.1[A] below). All adverse effects in the studies were appropriately managed with safeguards in a clinical setting. The most common psychological adverse experiences have been anxiety and negative mood. The most common physical adverse events are cardiovascular (mild to moderate increases in blood pressure and heart rate), occasional nausea and headache.

Table 2 - Adverse events in a study of psilocybin in healthy volunteers (Brown et al., 2017).

Adverse Event Description†	Total No. of episodes	# of participants		# per dose	
			0.3mg/kg	**0.45mg/kg**	**0.60mg/kg**
hypertension (mild) defined as SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg	22	10/12 (83%)	8	8	6
hypertension (moderate) defined as SBP ≥160 mmHg or DBP ≥100 mm Hg	5	4/12 (33%)	2	2	1
hypotension (mild) defined as SBP <90 mm Hg over DBP <60 mm Hg	1	1/12 (8%)	0	0	1
bradycardia (mild) defined as <60 BPM	22	7/12 (58%)	8	7	7
tachycardia (mild) tachycardia was defined as > 100 BPM	12	6/12 (50%)	5	1	4
headache (mild)	14	9/12 (75%)	5	5	4
fever (mild) mild fever was defined as <39.00 C	6	5/12 (42%)	0	1	5
fatigue (mild)	5	4/14 (33%)	1	1	3
nausea (mild)	4	3/12 (25%)	2	2	0
diarrhea (mild)	1	1/12 (8%)	0	0	1
dizziness (mild)	1	1/12 (8%)	0	0	1

* in all cases, the adverse effect was resolved by the end of the session day.

On December 12, 2019 Compass Pathways Limited announced the results of a randomised Phase 1 placebo-controlled study by King's College London in which psilocybin was administered to healthy adult volunteers. In this double-blind study, 89 healthy volunteers were randomised in a 1;1;1 ratio to receive 10mg of psilocybin (n= 30), 25mg of psilocybin (n=30) or placebo (n=29), with 1:1 support from a trained assistant therapist during a session lasting 6 hours. In total 25 dosing sessions were completed, with up to 6 participants per session. The study involved a 12-week follow-up period.

Key results were**:**

- There were no serious adverse events.
- The majority of adverse events seen with 10mg and 25mg doses were of the expected psychedelic nature; the most frequent were changes in sensory perception and positive mood orientation.
- There were no negative effects on cognition and emotional functioning. (COMPASS, 2018)

Psilocybin has been shown to be tolerated well even in more at-risk patient groups, such as those facing a cancer diagnosis (Griffiths et al. 2016).

Table 3 - Adverse events reported in Johns Hopkins study investigating psilocybin-assisted therapy for anxiety & depression exacerbated by recent cancer diagnosis (Griffiths et al, 2016)

Adverse Event Description*	Low Dose (N = 52)	High Dose (N = 53)
Elevated Diastolic Blood Pressure (> 100)**	1 (2%)	7 (13%)
Elevated Systolic Blood Pressure (> 160)**	9 (17%)	18 (34%)
Elevated Systolic (> 160) and/or Diastolic Blood (> 100)	10 (19%)	18 (34)
Elevated Heart Rate (> 110)**	1 (2%)	3 (6%)
Mild Headache	0	1 (2%)
Nausea/vomiting	0	8 (15%)
Paranoia	0	1 (2%)
Psychological Discomfort	6 (12%)	17 (32%)
Physical Discomfort	4 (8%)	11(21%)
Anxiety during session	8 (15%)	14. (20%)

***In all cases, the adverse effect had resolved by the end of the session day.
** In one participant, the peak blood pressure magnitude (214/114 mmHg) met the protocol criterion for pharmacological treatment, however the protocol criterion for duration of elevation for pharmacological treatment was not met as the event lasted less than 15 minutes. In all cases blood pressure returned to normal levels by the end of the session.

See also data in relation to possible adverse effects in Part 2.1[A] below (including information that can be drawn from non-clinical studies).

7. Special Considerations

Patients must undergo appropriate counselling and education in preparation for psilocybin, this normally takes 6-8 hours of therapist time. Dosing with psilocybin requires the patient to be in a safe, clinical environment and supported by at least one but ideally two treating therapists for the duration of the 6-8 medicinal session (Schenberg, 2018).

8. Range of use

The following are taken from completed or current clinical studies. An in-depth analysis will be provided in Part 2.1B with further data in Part 3.

- Major depression
- Treatment-resistant depression
- Anxiety disorders
- Addiction
- Annorexia nervosa
- Body-dysmorphic disorder
- Cluster and migraine headaches
- OCD (obsessive compulsive disorder)

D. OVERVIEW

Australia is facing a mental health epidemic with rising social, ethical and economic costs. Annually there is a ≈ $180 billion dollar cost on the Australian economy due to mental illness (Productivity Commission, 2019). 1 in 5 adults are currently diagnosed with a chronic mental illness, with 48% of all Australians experiencing a mental illness in their lifetime (Australian Bureau of Statistics, 2018). The most common mental illnesses are depression, anxiety disorders and post-traumatic stress disorder (PTSD).

With current pharmacotherapy treatments, only 35% of people diagnosed with depression experience remission from using antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) (Rush et al., 2009). Currently, 1 in 8 adults and 1 in 4 older people are being treated with antidepressants (OECD, 2015). In the last 15 years there has been a 95% increase in antidepressant prescriptions in Australia, with an 18% increase in the last 5 years. Australia is the second-highest prescriber of anti-depressants worldwide per-capita, of the 30 countries with available data. A 'more of the same' approach is not going to alleviate the high levels of mental illness in Australia.

This application supports the opportunity to expand the paradigm for the treatment of mental illness to improve the mental health outcomes of suffering Australians. Psilocybin has been granted two Breakthrough Therapy Designations by the Food and Drug Administration (FDA) in the United States - the first to Compass Pathways Limited in 2018 for psilocybin as part of therapy for treatment resistant depression (COMPASS, 2018) and the second in 2019 to Usona Institute for psilocybin as part of therapy in the treatment of major depressive disorder (Businesswire, 2019). This designation from the FDA acknowledges both the unmet medical need in these broad populations and the potential for these therapies to offer significant improvements over existing therapies. In a medically controlled environment psilocybin-assisted therapy is safe, non-addictive, and there is no increase in risk for mental ill-health in a clinically controlled environment (Passie, 2008).

Psilocybin-assisted therapy has yielded remarkable clinical results for depression and anxiety in numerous trials at leading universities internationally (Johnson & Griffiths, 2017). The proportion of participants who show positive clinical improvements, and the degree to which they improve, are substantially higher than clinical outcomes associated with currently available treatments (Schenberg, 2018). Psilocybin-assisted therapy can lead to remission in 60-80% of cases of anxiety and depression, whereas current existing treatments lead to remission in a maximum of 35-42% of cases (Griffiths et al., 2016; Ross, 2016; Carhart-Harris, 2016). There are over 40 current or recently completed clinical trials in humans (Williams, 2020). Clinical trials are underway for an increasing number of treatment indications in addition to depression, including OCD, anorexia, addiction, and dementia (Part 2.1[B] and Part 3). See section 2.1[F]D and E for therapy protocols and mechanisms.

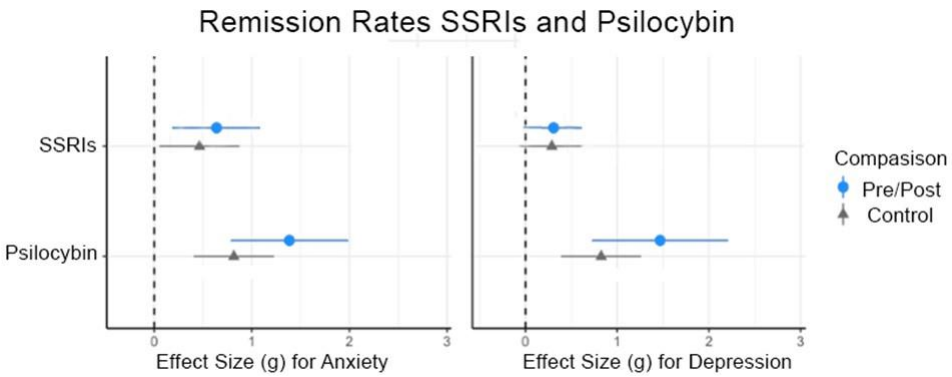

Table 4 - Forest plot of remission rates from mental illness - effect sizes as Hedges g

This data was collated from meta analyses of antidepressants (Cipriani, 2018; Locher, 2017) and psilocybin (Goldberg, 2020). The Psilocybin data combines outcomes from four studies: one uncontrolled (Carhart-Harris, 2016 and, three randomised, placebo controlled (Griffiths, 2016; Ross, 2016; Grob, 2011). Total n=117.

The rescheduling of psilocybin from Schedule 9 to Schedule 8 will make it easier for Australians suffering from depression and anxiety disorders and substance abuse (and potentially other illnesses such as anorexia nervosa and OCD) to access psilocybin-assisted therapy through their psychiatrists and specialist addiction physicians (with supporting therapists) in strictly medically controlled environments. It will also increase the ease and reduce costs of clinical research.

We believe there is sufficient evidence to justify the rescheduling of psilocybin to facilitate its use in this manner.

PART 2 - BODY OF THE APPLICATION

A. BACKGROUND - CURRENT SCHEDULING

The SUSMP currently schedules psilocybin as a schedule 9.

B. HISTORICAL CONTEXT

1. Historical Use of Psychedelic Plants

Historians and anthropologists have found that psychedelic plants have been used by humans for thousands of years in various contexts, from the medicinal to the ritualistic.

The Eleusinian Mysteries of Ancient Greece (1600 BC to 396 AD) were a ritual attended by thought leaders of the ancient world including Plato, Aristotle, and Cicero. The rites involved what is believed to be a psychedelic drink 'Kykeon', derived from fungus growing on barley (Nichols, 2016). Cicero, stoic philosopher and Roman senator, described the Eleusinian Mysteries as:

"For among the many excellent and indeed divine institutions which your Athens has brought forth and contributed to human life, none, in my opinion, is better than those mysteries. For by their means we have been brought out of our barbarous and savage mode of life and educated and refined to a state of civilization; and as the rites are called 'initiations,' so in very truth we have learned from them the beginnings of life, and have gained the power not only to live happily, but also to die with a better hope," Cicero, Laws II, xiv, 36

Psychedelic plants have been used by indigenous cultures for millennia (Johnson et al. 2008). These indigenous cultures have restricted psychedelic plant use to sacramental and healing rituals, in controlled ceremonial environments guided by shamans and healers.

2. Early Scientific Research

Psilocybin was first isolated from Psilocybe mushrooms in 1957 and then synthesised in 1958 by Albert Hoffman (Nichols, 2016). It was then marketed as Indocybin® by Sandoz for experimental and psychotherapeutic use. In the 1950s, psychedelic-assisted therapy was regarded by a large proportion of psychiatry as the next big breakthrough for treating mental illness and was used for a range of conditions in thousands of patients (Rucker, 2015).

3. Political Controversy

Although there was promising psychedelic medicine research results from 1940-1970 research came to halt in 1971 as psychedelic medicines were rescheduled by the Nixon Administration as part of the US Government's War on Drugs. This change in scheduling for psychedelic medicines occurred without any scientific or medical rational or consensus.

The American War on Drugs (which was extended to other members of the United National such as Australia) was applied without any scientific support to psychedelic medicines. Classical

psychedelics, including psilocybin, are currently Schedule 9 drugs in Australia (Schedule 1 in the USA). This category is reserved for substances considered by regulators to be without medical value, and with high abuse potential. Research has shown that psychedelics do not meet either of these criteria (Rucker, 2015). Given that psychedelic-assisted therapy was establishing itself through the 1950s and 1960s as the 'next big thing' in psychiatry, this censoring of inquiry into such a promising line of research severely restricted further research into this area for decades.

4. Psychedelic Research Profile

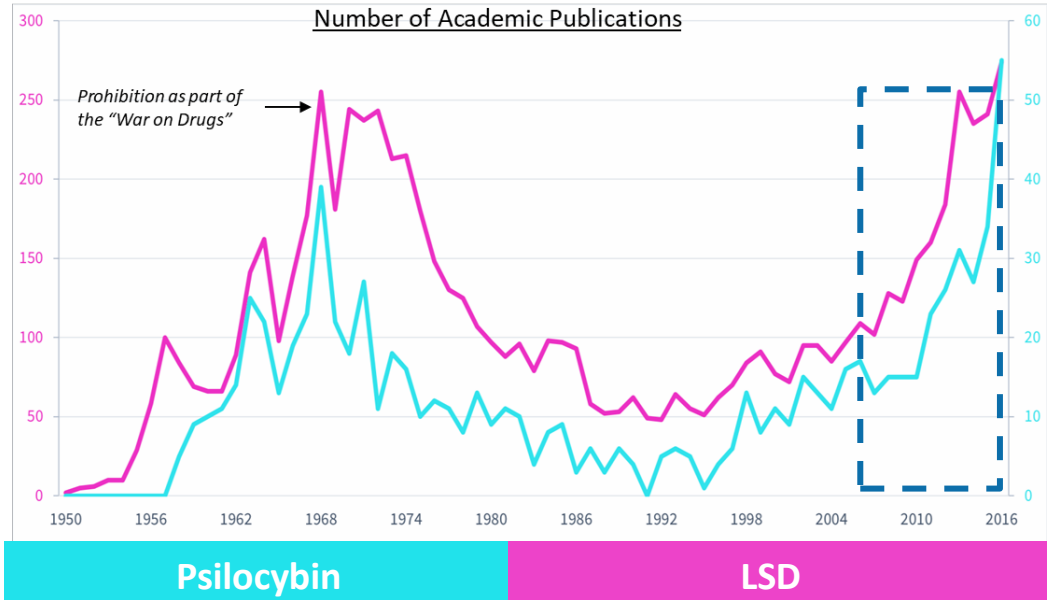

Table 5. Number of academic publications on psilocybin and LSD over time

In the last decade well-controlled clinical trials have shown impressive evidence for the clinical use of psychedelics, such as psilocybin, for inducing therapeutically beneficial behavioral change in a variety of mental health conditions. This new data shows that psilocybin-assisted therapy frequently leads to remission from certain mental illnesses within a few doses, when administered with proper psychotherapeutic support before, during and after treatments. Completed and current clinical studies as well as the range of current and future directions are summarised in Part 2.1 [B] and Part 3.

C. BASIC CHEMISTRY FACTS

1. Chemistry

(source https://pubchem.ncbi.nlm.nih.gov/compound/10624)

Chemical Formula: $C_{12}H_{17}N_2O_4P$

CAS Number: 620-52-5

IUPAC Name: [3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate

Molar Mass: 248.25 g/mol

Melting Point: 220-228°C

2. Chemical structure

(source https://pubchem.ncbi.nlm.nih.gov/compound/10624)

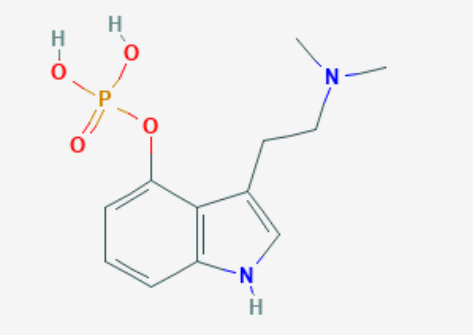

Image 1. Molecular structure of psilocybin

Psilocybin is a member of the tryptamine chemical family and presents as a white crystalline solid. It is stable over extended periods at room temperatures. It is a major psychoactive constituent in mushrooms of the Psilocybe genus**.** Psilocybin is classed as a psychedelic, sometimes called a hallucinogen, though this name is advised against in modern scientific literature as psychedelics do not generally induce true hallucinations (Nichols, 2016). Psychedelics are chemical compounds which temporarily create changes in brain function including shifts in perception, thinking, and feeling, which temporarily produces an 'altered state of consciousness'. Psilocybin is a non-chiral molecule.

DETAILED CLAIMS AGAINST THE REQUIREMENTS OF THE SCHEDULING POLICY FRAMEWORK

PART 2.1 - PROPOSAL TO CHANGE PART 4 OF THE POISONS STANDARD - SCHEDULING OR RESCHEDULING OF SUBSTANCES

PART 2.1 [A] RISKS AND BENEFITS ASSOCIATED WITH THE USE OF PSILOCYBIN

There is not much research on the risks or hazards associated with the human administration of synthetic psilocybin outside of a clinical setting, as the synthetic manufacture of psilocybin is complex and expensive. Outside of a research setting, there are no records of clandestine synthesis. However, the risks and benefits of synthetic psilocybin can also be extrapolated from the widespread use of psilocybin-containing mushrooms.

A. WHAT ARE THE BENEFITS?

Note: For an overview of therapeutic benefits see Part 2.1[B] and also Part 2.1[F]C and D.

1. Non-addictive and no dependence

Tolerance builds rapidly to psilocybin limiting the ability for it to be used regularly and there is no evidence of physical dependence (Passie, 2008). Providing psilocybin to patients in clinical studies has not resulted in reported instances of subsequent illicit abuse (Griffiths et al., 2011). The finding that psilocybin did not serve as positive reinforcers in rhesus monkeys shows that primates do not find the psychoactive effects of the $5HT_{2A}$ receptor agonists rewarding (Heal, Gosden, & Smith, 2018). All available evidence suggests psilocybin is non-addictive. Moreover, psilocybin has profound effects for facilitating remission from addiction in people with alcohol and tobacco addiction (Burdick & Adinoff 2013, p. 291), and is currently in Phase 2 clinical trials for cocaine and opioid addiction (Part 2.1[B]).

2. Historical medical use without complication

Early therapeutic use of synthetic psilocybin developed by the pharmaceutical sector (Indocybin® Sandoz) was without complication (Passie et al. 2002, p. 358). A review on psychedelic drugs (including psilocybin) found little to no adverse reactions, if used within a controlled setting (Strassman 1984, p. 590). In more recent trials there have been no significant adverse events (Dos Santos et al., 2018).

3. Safe and non-toxic

The therapeutic index of psilocybin is 1000 (Rucker 2015, p. 1). The therapeutic index is the quantitative measurement of a drug's safety; the TD_{50} (toxic dose) divided by the ED_{50} (effective dose). An index of 1000 is very high. This gives psilocybin a therapeutic index of very high efficacy to toxicity. For a comparison, the therapeutic index of other schedule 9 drugs, such as cocaine and heroin, is 15 and 6 respectively (Rucker, 2015). Psilocybin (and psilocin) does not accumulate in the body, its metabolites are non-toxic, and the body is easily able to excrete them rapidly and completely.

4. Benefits in Population Use

An analysis of information from the National Survey on Drug Use and Health showed that the use of psilocybin is associated with significantly reduced odds of (Hendricks et al. 2015, p. 282):

- Past month psychological distress
- Past year suicidal thinking
- Past year suicidal planning
- Past year suicide attempt

In 2016, a study was completed at Johns Hopkins by 1993 individuals in an online survey, in which 84% of participants endorsed psychologically benefiting from the psilocybin-containing mushroom experience (Carbonaro et al. 2016).

B. WHAT ARE THE HAZZARDS?

1. The Vital Importance of Environment and Context

There are several factors which influence psychological reactions to psilocybin. In trials, occasionally temporary anxiety can occur which alleviates as psilocybin is metabolized. Modern clinical research is undertaken in a controlled context also described as adhering to a "set and setting" protocol (Usona 2018). This approach diminishes adverse experiences and enhances trial outcomes (Carhart-Harris, 2018). For more information on set and setting protocols please see (Part 2.1[F]D).

Note: all following hazards are in an uncontrolled setting.

i. Vulnerable individuals in uncontrolled settings may experience complications from the psychological effects of psilocybin (Carhart-Harris, 2018).

ii. Analysis of harms caused by a range of psychotropic substances ranked psilocybin-containing mushrooms as among the least harmful to the user and least harmful to others in population use (Nutt et al., 2010). Current schedule 8 drugs; buprenorphine, methadone, cannabis, ketamine, amphetamine; schedule 4 drugs; anabolic steroids, benzodiazepines; and unscheduled drugs; tobacco and alcohol; all ranked as causing more harm to the user and more harm to others; when compared to psilocybin-containing mushrooms. This research was recently repeated in Australia at St Vincent's Hospital Melbourne (Nutt, D and Castle, D et. al, 2019).

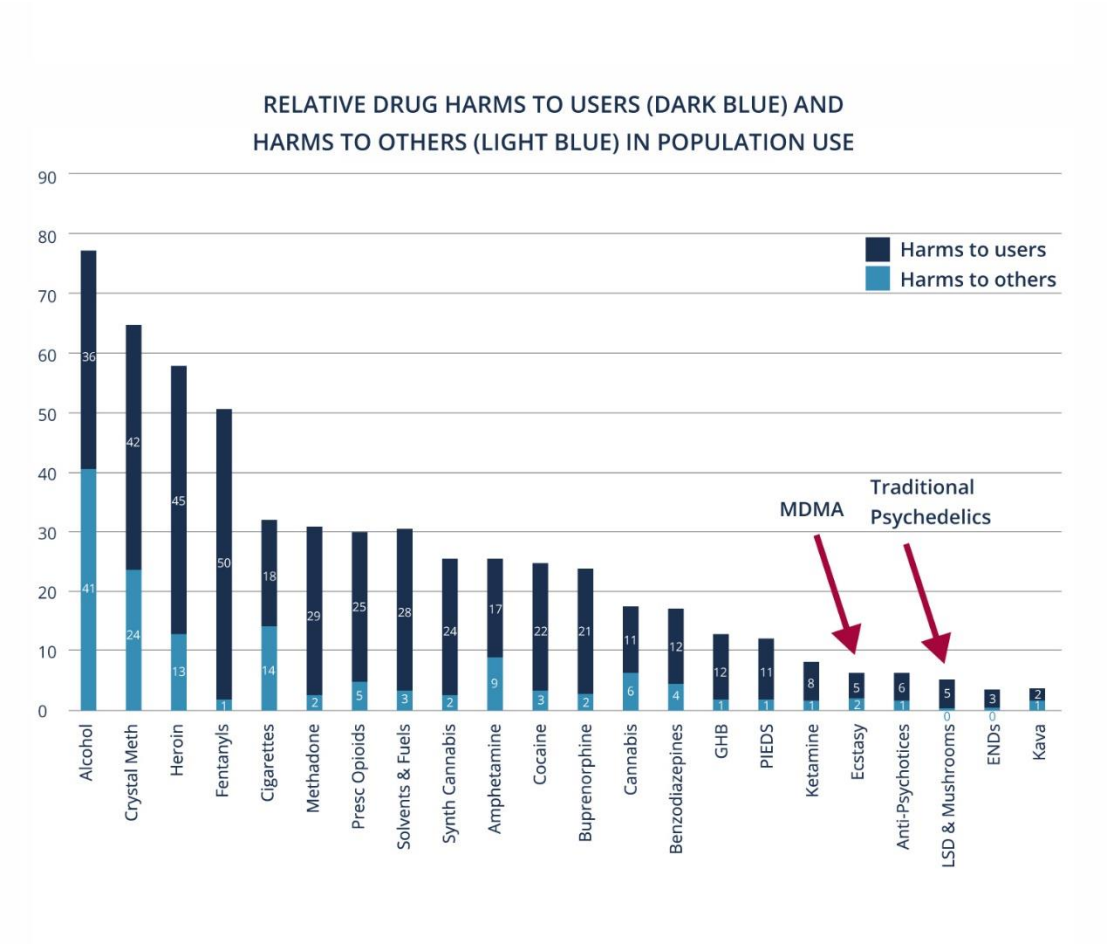

Table 6. The Australian Drug Harms Ratings Study examined the psychological, medical and social harms of substances in population use.

iii. With unexpected or accidental ingestion of psilocybin-containing mushrooms, panic reactions can occur in some cases. Reported negative effects include confusion, anxiety, violent behaviour, suicidal thoughts (Peden et al. 1982, p. 544), and temporary experiences of delusion (Vollenweider et al. 1998, p. 8). However, this only applies to non-medicinal use outside of a medically controlled environment.

2. How widespread are the hazards?

i. The uncommon hazards (Part 1 C6[ii] and Part 2.1[A]B4) are significantly more prevalent in any person who administers psilocybin in an uncontrolled setting (i.e. non-medical environment, recreational) (Carhart-Harris, 2018). **However, with the rescheduling of psilocybin to schedule 8, the limit of use of psilocybin will be in a strictly controlled medical environment**.

ii. The rare and very rare hazards (Part 2.1[A] B) are more common in vulnerable people (Part 2.1[A]B1[i]).

3. In what circumstances can the hazards arise?

i. Hazards can arise if there is unexpected or accidental psilocybin ingestion (Part 2.1[E]F); or

ii. Hazards can arise in an uncontrolled or recreational setting (Part 2.1[A]B2[i]); or

iii. Hazards can arise in vulnerable people (Part 2.1[B]1[i]).

4. What is the likelihood of the hazards occurring?

i. In 2016, a study at Johns Hopkins University involved 1993 individuals completing an online survey about their single most psychologically difficult or challenging experience after consuming psilocybin-containing mushrooms **in an uncontrolled setting**. The results were (Carbonaro et al. 2016):

Uncommon

- 11% put self or others at risk of physical harm
- 7.6% sought treatment for enduring psychological symptoms

Rare

- 2.7% received medical help
- 2.6% behaved in a physically aggressive or violent manner

Very Rare

- 0.15% associated with onset of enduring psychotic symptoms
- 0.15% attempted suicide

ii. While psilocybin is a powerful psychedelic substance, and can produce challenging experiences without appropriate support, there is no evidence that psilocybin use is linked to either mental illness or negative health outcomes. A meta-analysis found no link between psychedelic use (outside of a clinical context) and psychosis across a cohort of 135,000 (Johansen & Krebs, 2015). The researchers found that individuals who had taken psychedelics were not at increased risk of developing 11 indicators of mental-health problems, including: schizophrenia, psychosis, depression, anxiety disorders and suicide attempts.

iii. Incidence of risky behaviour or enduring psychological distress is extremely low when psilocybin is administered in a controlled setting; where participants are screened, prepared, and supported (Carbonaro et al. 2016).

5. Who is at Risk?

i. The hazards are mitigated in the clinical trials by exclusion of potential participants with schizophrenia, other psychotic disorders, bipolar I and II disorders, and first or second-degree family relations to these psychiatric disorders (Johnson et al. 2008).

ii. To date, research trials have done well to select appropriate participants and conduct trials in such a way as to produce impressive levels of safety. In order to offer these therapies to a much larger proportion of the population, we believe that the above guidelines should be followed to maintain the currently low levels of adverse events.

6. What are the consequences of the hazards in terms of severity (morbidity and mortality) and duration?

i. Fatal intoxication due to ingestion of psilocybin-containing mushrooms is extremely rare (McCawley et al. 1962; Gonmori & Toshioka 2002). The toxicity is evaluated in Part 1[C]4 and is extrapolated to be approximately 17 kg of fresh psilocybin-containing mushrooms in humans (Amsterdam et al. 2011). It would be highly unusual and very challenging to consume 17 kg of mushrooms.

ii. Ingesting psilocybin-containing mushrooms in an uncontrolled setting could theoretically cause reckless behaviour and/or panic attacks. This could lead to public nuisance and/or violation of traffic rules.

These hazards have been shown to be minimal in a medically controlled environment (see Part 1C6[ii])

PART 2.1 [B] PURPOSE AND EXTENT FOR WHICH THE SUBSTANCE IS TO BE USED

A. TREATMENT CONDITIONS

i. Treatment Resistant Depression

The US Food and Drug Administration (FDA) has granted psilocybin-assisted therapy Breakthrough Therapy status for Treatment Resistant Depression (COMPASS, 2018). Treatment resistant depression is a form of depression that has been unsuccessfully treated with traditional methods used to treat depression. Symptoms include a negative affective state, ranging from unhappiness and discontent to an extreme feeling of sadness, pessimism, and despondency that interferes with daily life.

In a preliminary trial of treatment-resistant depression, psilocybin-assisted therapy substantially reduced depressive symptoms in over 65% of patients, which remained significant 6 months post-treatment (Carhart-Harris et al., 2018). COMPASS Pathways is currently completing a 216 participant Phase 2b study researching the safety and efficacy of Psilocybin in participants with Treatment Resistant Depression (P-TRD).

Indication	Details	Dose	Sponsor	Comments
Treatment Resistant Depression	N = 216	1st dose 10mg 2nd dose 25mg	Compass Pathways	Phase 2 Clinical Trails - The Safety and Efficacy of Psilocybin in Participants with Treatment Resistant Depression (P-TRD)

ii. Major Depressive Disorder

The FDA has also granted psilocybin-assisted therapy Breakthrough Therapy status for Major Depressive Disorder (BusinessWire, 2018). Major Depressive Disorder is characterised by persistent sadness and other symptoms of a major depressive episode but without accompanying episodes of mania or hypomania or mixed episodes of depressive and manic or hypomanic symptoms.

Usona Institute is currently in phase 2 of an 80-participant study using Psilocybin for the treatment of Major Depressive Disorder (Usona, 2018). The study is randomized under double-blind conditions to receive a single 25mg oral dose of psilocybin or single 100mg oral dose of niacin (Vitamin B3). Niacin serves as an active placebo. The purpose of this study is to evaluate the potential efficacy of a single 25 mg oral dose of psilocybin for Major Depressive Disorder compared to the active placebo.

Indication	Details	Dose	Sponsor	Comments
Treatment Resistant Depression	N= 80 3 months	Single dose 25 mg	Usona Institute	Phase 2 Clinical Trail A study of Psilocybin for Major Depressive Disorder (MDD)

iii. End of life Anxiety and Depression

End-of-life anxiety and depression affect many Australian's in palliative care. The ageing population shows the highest use of anti-depressant medication with Australian's over 68 consuming 25% of all antidepressant prescriptions (OECD, 2015).

End of life or existential anxiety and depression is characterised by a general sense of anguish or despair associated with an individual's recognition of the inevitability of death and associated suffering. Psilocybin has been shown to be effective in treating end of life anxiety with long-lived results; 60-80% of patients still showed clinically significant improvements at a four -year follow up (Agin-Liebes, 2020).

Psilocybin for end-of-life anxiety and depression is currently being trialed in Australia: Psilocybin is currently being used in conjunction with psychotherapy to treat depression and anxiety in terminally ill patients in a trial at St Vincent's Hospital in Melbourne (SVHM, 2020). The trial began in January 2020 with 40 patients recruited from the hospital's palliative care unit who have not responded to anti-depressant or anti-anxiety therapies. This trial is double-blind and placebo-controlled. Patients will be given 25mg of synthetic psilocybin in conjunction with psychotherapy sessions.

iv. Other promising indications currently being trialled internationally:

It has been suggested that psilocybin-assisted therapy is most effective in conditions characterised by rigid thoughts and behaviours such as depression, anxiety, addiction, OCD and eating disorders. This is in part due to the neurological changes psilocybin facilitates (Part 2.1[F]E). Recent evidence suggests there may be application for pain relief, immune function and learning disorders (Nichols et al. 2017). Psilocybin is currently being studied for the treatment of the following conditions:

Treatment Indication	Institution
Addiction including Tobacco, Opioid, Alcohol and Cocaine	Johns Hopkins University & University of Zurich & New York University
Obsessive- Compulsive Disorder (OCD)	Yale University
Anorexia Nervosa	Imperial College London & Johns Hopkins University
Depression associated with AIDS recovery	University of California
Cluster Headache	Harvard University & Yale University
Early-stage cognitive decline	Johns Hopkins University
Lyme Disease recovery	Johns Hopkins University
Post-traumatic stress disorder	Lieber Institute for Brain Development

Table 9. Current indications being investigated by institution

For full details of trials please see Part 3.

B. INTERNATIONAL EXPANDED ACCESS SCHEMES

The FDA has approved an “Expanded Access” or “Compassionate Use” scheme using psilocybin to treat both treatment-resistant depression and major-depressive disorder in patients who have exhausted all other options. A treating physician must obtain approval from the internally created Institutional Review Board of Usona Institute (a not for profit organisation in the US) along with approval from the FDA under its Expanded Access Scheme to receive these medicines from Usona. Treatment will occur as directed by Usona’s set and setting guidelines (Usona 2020).

Recently the TGA approved the first application for psilocybin-assisted therapy for the treatment of a patient with depression and PTSD under Special Access Scheme B.

PART 2.1 [C] TOXICITY AND SAFETY OF THE SUBSTANCE

A. UN CONVENTION SCHEDULING

Psilocybin is included in the Schedule I of the United Nations Convention on Psychotropic Substances 1971; https://www.unodc.org/pdf/convention_1971_en.pdf.

B. DOES PSILOCYBIN PRODUCE DEPENDENCY AT ITS ESTABLISHED THERAPEUTIC DOSE?

Psilocybin does not produce dependency at its established therapeutic dose, nor at any dose (see subsection 2.1[A]A[1]).

C. DOES PSILOCYBIN HAVE AN ESTABLISHED THERAPEUTIC USE BUT CARRY SUBSTANTIAL RISK OF MISUSE, ABUSE OR ILLICIT USE?

Psilocybin does have established therapeutic use (Part 2.1[B]). Whilst relatively low psilocybin carries potential risk for misuse, abuse or illicit use (Part 2.1[E]) which is why we believe that Schedule 8 is appropriate for this substance.

D. TOXICITY

Psilocybin has very low risks of toxicity (see Part 1[C]4 (toxicity) and Part 2.1[A]A3 (therapeutic index)).

PART 2.1 [D] DOSAGE, FORMULATION, PACKAGING AND PRESENTATION OF PSILOCYBIN

Note: Psilocybin in synthetic form is not currently manufactured in Australia and so, for the time being, will need to be imported from overseas. When received it will be held securely at a compounding pharmacy with Schedule 8 holding facilities.

A. DOSAGE

- A single dose of 25 mg of psilocybin for a person weighing under 90 kg.
- A single dose of 30 mg of psilocybin for a person weighing between 90 kg and 115 kg.
- A single dose of 35 mg of psilocybin for a person weighing over 115 kg.

A standardised dose of 25 mg is employed until 90 kg, where 0.3 mg/kg = 30 mg

B. FORMULATION

25 mg per capsule of psilocybin per therapeutic session unless pharmacist compounds for a person weighing over 90 kg (see A. above)

C. LABELLING

i. Labelling Requirements

- The container, intermediate packaging (if any) and primary pack in which the medicine is packed must each bear a label or labels that comply with the requirements of this Part 2.1[D]
- The registration number, which must be in a text size of not less than 1.0 millimetre height as required by subparagraph 15(1)(c)(i) of the Regulations; and
    - Be in a colour or colours contrasting strongly with the background, except for:
    - The expiry date and expiry date prefix; and
    - The batch number and batch number prefix when that information is embossed or debossed and not printed; and
    - Be in metric units of measurement.

ii. Information required on label

- The name of the medicine; and
- The name of the dosage form; and
- The quantity of the medicine; and
- The batch number of the medicine preceded by the batch number prefix; and
- The expiry date of the medicine, preceded by the expiry date prefix; and
- The storage conditions applicable to the medicine; and
- The name and contact details of the sponsor or distributor of the medicine; and
- Relevant warning statements (see below)

iii. Statements of caution on packaging

- CONTROLLED DRUG
    - Written on the first line or lines of the main label; and
- POSSESSION WITHOUT AUTHORITY ILLEGAL
    - Written in a separate line or lines immediately below the signal words required by "CONTROLLED DRUG"
- KEEP OUT OF REACH OF CHILDREN
    - Written on a separate line or lines where the cautionary statement "POSSESSION WITHOUT AUTHORITY ILLEGAL", on the line immediately below that statement.

iv. Statements of quantity, proportion and strength

- In the manner prescribed by orders made under subsection 10(3) of the Commonwealth Therapeutic Goods Act 1989.
- A certificate of GMP can be supplied by the manufacturer

D. Packaging

The pack size per patient is one capsule of 25mg of psilocybin (or higher if the patient weighs more than 90 kg – see A and B above) with appropriate child resistant locks and the above warnings.

Psilocybin 25 mg [or specified higher level if the patient weighs over 90kg] Caps (1): Take one capsule only in the presence of your psychiatrist/ specialist physician/therapist. For in-clinic use only. Do not take this medicine at home. Do not drive a motor vehicle or consume alcohol within 24 hours of taking this capsule.

E. Presentation

To be given to a patient by a treating psychiatrist or specialist addiction physician in a clinical setting after they have read and signed a patient informed consent form specifically applicable to psilocybin-assisted therapy.

F. Pharmacy procedure

The intermediary importation pack will be held at a compounding pharmacy under schedule 8 regulations with a reporting register of mg use. Each primary pack will be compounded and provided to psychiatrists or physicians only under authorised Schedule 8 prescription.

PART 2.1 [E] POTENTIAL FOR MISUSE/ABUSE OF PSILOCYBIN

A. BACKGROUND

Psilocybin itself has not been abused, misused, accidentally ingested, or had any recorded overdose in a medical setting. All information in this section is of psilocybin-containing mushrooms in an uncontrolled setting. Section C below is the only peer-reviewed literature available on overdose. Sections D and F are reports of misuse and accidental ingestion taken from newspapers (reliability of journalist stories isn't peer-reviewed). Section E below is the theoretical potential of psilocybin abuse. The data is taken from a literature review of psilocybin-containing mushroom harm potential by Amsterdam et al. 2011.

The Australian Bureau of Statistics (ABS) has never reported a psilocybin-containing mushroom fatality, overdose, or toxicity (directly or indirectly).

Source;
https://search.abs.gov.au/s/search.html?clicked_fluster=causes+of+death+statistics&cluster0=Causes+of+death&form=simple&query=%60Causes+of+Death+Statistics%60&profile=_default&collection=abs

B. AUSTRALIAN TRENDS

The 2019 Australian Drug Trends by the National Drug & Alcohol Research Center (NDARC) from the University of New South Wales reports no overdose, misuse, abuse, or public use of psilocybin or psilocybin-containing mushrooms between the years 2000 and 2019 (Peacock et al. 2019).

C. OVERDOSE

There are only two fatal cases described in literature, in 1996 and 1961, due to overdosing with psilocybin-containing mushrooms (Amsterdam et al. 2011, p. 425). As the same paper estimates that the lethal dose of fresh psilocybin containing mushrooms is likely to be 17kg it is not clear how this over-dosing would have occurred. The authors go on to say that
" *…normally people do not die from a magic mushroom overdose, because they are not very toxic and the potential victim will spontaneously vomit keeping the final dose low.*"

D. MISUSE

[i]. Combination with other drugs: two people died from falling from heights after combined use of psilocybin-containing mushrooms and alcohol, in 2005 a 31 year old English man and in 2006, a 33 year -old Irish man (Amsterdam et al. 2011). A young French girl in 1999, died falling from a window with the combination of psilocybin-containing mushrooms and cannabis. A 20 year-old Dutch male died after he became sick following the use of psilocybin-containing mushrooms, ecstasy, and alcohol.

[ii]. Suicide: in 2004, a suicide was reported in the Czech Republic, in which the presence of psilocybin-containing mushrooms was confirmed by autopsy (Amsterdam et al. 2011, p. 426). Two young foreign male tourists died after they jumped out of the window of an Amsterdam hotel after the consumption of magic mushrooms. An 18 year-old Dutch male died after he jumped out of a window following ingestion of psilocybin-containing mushrooms.

[iii]. Circumstantial: in 2002, a 27 year-old man was found dead in a canal; he had ingested a large amount of Psilocybe cubensis (Amsterdam et al. 2011, p. 426).

E. ABUSE

[i]. Australia has never conducted an official governmental investigation into psilocybin abuse.

[ii]. In 2007, The Dutch National Criminal Intelligence Service (DNCIS) conducted an inquiry into the criminal involvement of psilocybin-containing mushrooms (Amsterdam et al. 2011, p. 427). The DNCIS found no evidence of public nuisance as a result of sale or use of psilocybin-containing mushrooms. The 2007 briefing of the DNCIS reported no criminal acts related to psilocybin-containing mushrooms in relation to:

- Psilocybin-containing mushroom growers and criminals
- No offenders of law in regard to users (except for one shop for selling dried magic mushrooms)
- The police intercepted postal mailings containing illegal dried psilocybin-containing mushrooms on occasion

The DNCIS also reported the following:

- The border police at the Belgium border regularly observed the export of dried mushrooms
- The customs at the Schiphol airport, Amsterdam, occasionally confiscated small amounts of psilocybin-containing mushrooms
- In 2007, the German customs confiscated one large mailing of 27 kg of psilocybin-containing mushrooms

F. ACCIDENTAL INGESTION

A six-year-old child in 1962, developed hyperthermia and status epilepticus following accidental ingestion of Psilocybe baeocystis (Amsterdam et al. 2011).

Please note that these cases all refer to the recreational use of mushroom containing psilocybin. We are proposing a rescheduling to Schedule 8 on the basis that the medicine will only be able to be authorised by psychiatrists and specialist physicians in medically controlled environments under strict supervision. The medicine will never be available to the patient to take home.

PART 2.1 [F] OTHER CONSIDERATIONS

A. WHY PSILOCYBIN SHOULD BE IN SCHEDULE 8

Poisons Standard February 2020

Schedule 8 - **Controlled Drug** – Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.

Schedule 9 - **Prohibited Substance** – Substances which may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities.

Schedule 9 contains substances that should be available only for teaching, training, medical or scientific research including clinical trials conducted with the approval of Commonwealth and/or State and Territory health authorities. Although appearing as a Schedule in this Standard, the method by which it is implemented in the States and Territories may vary.

This application has supplied evidence that psilocybin shows therapeutic benefit for individuals who have been previously unsuccessful with traditional forms of treatment. Given the therapeutic benefits and high remission rates in clinical trials, the FDA's designation of Breakthrough Therapy status and international "Expanded Access Schemes", psilocybin does not fit into the requirements of a Schedule 9 Substance and more closely reflects the requirements of Schedule 8.

Currently, the Schedule 9 classification of psilocybin places additional hurdles on research (cost, stigma and ease of access) and on its medical use in a medically controlled environment. Reclassifying Psilocybin as a Schedule 8 substance will reduce cost and improve ease of access for researchers and specialist medical practitioners for individuals seeking relief for their treatment resistant conditions via the Special Access Scheme.

This treatment is only to be used in clinical settings under the guidelines of a Schedule 8 controlled substance in the Poisons Standards and in accordance with strict safety protocols in supplying psilocybin assisted therapy through health care providers in a medically controlled environment.

Ibogaine, another psychedelic compound, is currently Schedule 4 in Australia. Ibogaine has a far narrower therapeutic index, greater range of risk factors, and is substantially less researched than psilocybin (Brown, 2013). Reclassifying psilocybin as a Schedule 8 substance will ameliorate some of this discrepancy and reflect an evidence-based approach to drug policy.

As the evidence outlined in this Application shows, in the above subsections of a. through to e., psilocybin-containing mushrooms have limited abuse, misuse, or overdose potential internationally. Further, there are no adverse reports within Australia. Current antidepressants and benzodiazepines hold far greater abuse, misuse, or overdose potential, as discussed in Part 2.1[F]B[ii]. With the breakthrough therapeutic potential discussed in Part 2.1[B], we believe that psilocybin should be rescheduled to schedule 8.

B. HAZZARDS OF PSILOCYBIN COMPARED TO CURRENT SCHEDULE 4 MEDICATIONS

i. The online survey referred to in Part 2.1[A]B4[i] provides some evidence that 0.15% of the psilocybin-containing mushroom users in the sample reporting on their most psychologically difficult or challenging experience in an uncontrolled setting attempted to commit suicide. There is one death of intentional reported suicide in the literature (Part 2.1[E]D[ii]). In 1999, 2007, and 2016, the ABS reported that in Australia there were 2,227, 2,392, and 2,862 suicide cases in total respectively (ABS, 2018). The ABS points out that benzodiazepines and antidepressants are more common in intentional self-harm drug deaths (ABS, 2018).

ii. Part 2.1[E] lists a total of twelve reported deaths associated with (but not always necessarily due to) psilocybin-containing mushrooms internationally from 1961-2011. When compared to current schedule 4 drugs; in 1999, 2007, and 2016 (Fergusson et al., 2005), the ABS reported that in Australia there were 503, 354, and 663 cases of benzodiazepine-caused direct deaths respectively (ABS, 2018). Benzodiazepines are a schedule 4 drug. In 1999, 2007, and 2016, the ABS reported 441, 127, and 361 cases of prescription antidepressant-induced deaths (ABS, 2018). The difference is even more striking when it is recognized that the psilocybin associated figure comes from a global search whereas the figures relating to benzodiazepines and anti-depressants relate only to Australia.

C. META – ANALYSIS OF ANTIDEPRESSANT MEDICATIONS

There is academic debate on the extent of efficacy of conventional antidepressant classes of SSRIs and SNRIs and the increased risk of suicide that these medications may cause, which is described by the ABS in Part 2.1[F]B[i]. Below are the findings from three meta-analyses, one population study and one review on the evidence against SSRIs having antidepressant efficacy. Although the analysis is of SSRIs, it is noted that there does not appear to be significant difference in effectiveness between SSRIs and SNRIs (Gartlehner et al. 2011).

- A meta-analysis in 2008 of 47 studies concluded that, SSRIs provide no clinically significant benefit in the treatment of depression (Kirsch et al., 2008). No effect on mild or moderate depression and relatively small efficacy for severe depression. A small percentage of severely depressed people get noticeable benefit from SSRIs.
    - The researchers attributed SSRI efficacy for severely depressed people, to a decrease in placebo effect rather than an increase in the efficacy of SSRIs (Kirsch et al., 2008).
- Another meta-analysis completed in 2010, confirmed the results of SSRIs having no effect on mild or moderate depression and relatively small to noticeable effect on severe depression (Fournier et al., 2010).
- In 2009, the UK National Institute of Health and Care Excellence (NICE), conducted a comprehensive review on antidepressants (NICE 2009). They concluded that antidepressants have no advantage over placebo in treating mild depression. There is available evidence supporting antidepressant treatment for persistent depressive disorder and other forms of mild chronic depression.
- A population study, the STAR*D trial, found that all anti-depressants led to remission from depression in only 3% of the over 4000 participants surveyed (Rush et al., 2009).
- The largest meta-analysis of 21 antidepressants was conducted in 2018 and reviewed 522 individual trials with 116, 477 patients. It was found that while antidepressants were more

effective than placebo in adults with major depressive disorder, the effect sizes was modest (g=0.30) (Cipriani, 2018).

We provide this analysis because the conventional medical treatments for depression, antidepressants, show low effect size. There is therefore a strong need to increase the treatment paradigm available in Australia through medical specialists for patients suffering from depression.

D. PSILOCYBIN-ASSISTED PSYCHOTHERAPY PROTOCOL

Psychedelic-assisted therapy involves 'talk-therapy' alongside the ingestion of a psychedelic compound such as psilocybin (Schenberg, 2018). Importantly, the non-psychedelic elements of this approach are essential for both effectiveness and safety. Medicinal psilocybin is not a complete therapy, but rather acts as a catalyst or accelerator for the therapeutic process. Psilocybin increases mental flexibility and sensitises the patient to the therapeutic environment. Researchers and clinicians often describe three distinct therapy phases that take place over several days: preparation, the psychedelic experience and integration.

- **Preparation** sessions before medicine-assisted therapy to support development of a therapeutic bond and patient education.
- **Acute medicinal experience** provides an opportunity for therapy while patients are in a receptive, flexible, open state.
- **Integration** is a process by which therapists support patients to process and implement insights from their experiences. Patients are encouraged to pursue other opportunities to further integrate the experience into their lives.

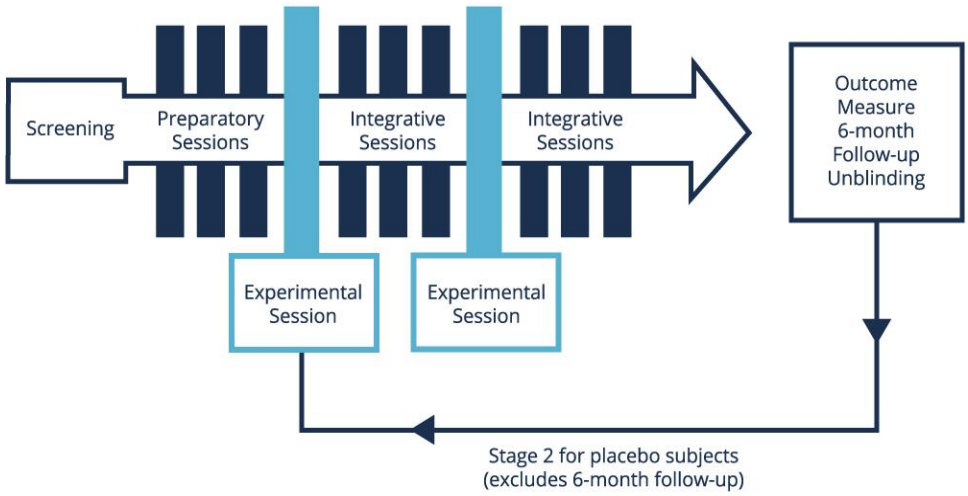

Image 2. Psilocybin-assisted therapy protocol

Psilocybin-assisted psychotherapy occurs within a clinical, aesthetic and private space. As the dosed sessions generally last 6-8 hours, two trained specialist therapists work together. For some of the experience, patients are invited to listen to music played through headphones and are encouraged to wear an eye-mask. The patient is made aware of all safety measures and equipment put in place to ensure their safety in the unlikely event of a medical complication.

While the therapy can be challenging and bring up difficult experiences, these may be crucial to the therapeutic process; most participants rate the experience as among the most significant of their lives (Agin-Liebes, 2020). While the psychological risks are increasingly better understood and mitigated, fine attention to psychological support and a controlled clinical context is vital. Anxiety during the

experience can be ameliorated with careful preparation by the individual and therapist as well as support during the active session.

E. POSSIBLE NEUROLOGICAL MECHANISMS OF PSILOCYBIN

A number of theories have been put forward to account for the therapeutic effects of psilocybin. The most prominent theories are based on recent brain imaging data (Carhart-Harris et al, 2017). In the past decade, brain imaging technologies have come to describe multiple "hubs" of functional connectivity in the brain called resting-state networks (RSN) (Nichols, 2017). The analysis of functional connectivity (FC) can illuminate how brain regions are coupled (RSFC). fMRI studies have opened a window into the mechanisms of psilocybin-assisted therapy and the study of consciousness itself. The way psilocybin changes brain network dynamics, or RSFC may help explain its observed efficacy in the treatment of mental illnesses. Psilocybin reduces the activity of a brain network, an area of FC, called the Default Mode Network (DMN).

The DMN is associated with rumination about the past, daydreaming and autobiography and is known to be tightly correlated, or overactive, in several mental illnesses. By temporarily decoupling the activity of the DMN, psilocybin appears to enable communication among more diverse brain regions (Carhart-Harris et al, 2017). In this way, psilocybin may facilitate a more plastic, receptive brain state. This hypothesis, along with the proposed effects of $5HT_{2a}$ receptors, accounts for the importance of the environment or therapeutic context (Carhart-Harris & Goodwin, 2017). It has been proposed that integration (Part 2.1[F]D) occurs in a window after treatment where the patient is more open to change.

E. CONTRAINDICATIONS

i. Antidepressants: Cause down regulation of the 5-HT2a receptor which may limit treatment benefit (Carhart-Harris and Goodwin, 2017). A washout period of at least two weeks is advised and is current practice in major clinical trials of psilocybin-assisted therapy. Careful consideration of patient safety and monitoring during the washout phase is advised.

ii. Particular caution should be taken with MAOi type antidepressants which may increase the effects of psilocybin.

iii. Anti-psychotics: Some anti-psychotic medications act as antagonists at the 5-HT2a receptor and others (atypical anti-psychotics) contribute to downregulation.

iv. Psilocybin has no other major drug-related contraindications.

PART 2.2 CRITERIA TO CHANGE THE POISONS STANDARD

The application has given medical and scientific justification, reasoning, and critical objective discussion addressing all the legislative requirements set out in Section 52E of the Therapeutic Goods Act 1989 which the Secretary must take into account in exercising powers. The following is a brief discussion of the evidence presented in this application:

1. **In exercising a power under subsection 52D(2), the Secretary must take the following matters into account (where relevant):**

    a. **the risks and benefits of the use of a substance;**

        - The therapeutic benefits of psilocybin, psilocybin's very low toxicity, and psilocybin's non-addictive properties outweigh the associated risks which can be fully mitigated with medical use in a medically controlled setting (See particularly Part 1, Part 2.1[A] and Part 2.1[B] of this Application)

    b. **the purposes for which a substance is to be used and the extent of use of a substance;**

        - Psilocybin-assisted psychotherapy for depression and anxiety and for substance abuse (and potentially other indications) in a controlled medical setting (Part 2.1[B]).

    c. **the toxicity of a substance;**

        - Psilocybin has extremely low toxicity (Part 1[C]4) and a therapeutic index of 1000 (Part 2.1[A]A3) and has no history of severe adverse effects in a clinical setting.

    d. **the dosage, formulation, labelling, packaging and presentation of a substance;**

        - See Part 2.1[D].

    e. **the potential for abuse of a substance;**

        - There is no record of synthetic psilocybin being abused in Australia or internationally (Part 2.1[E]A).

        - Australia has no official record of psilocybin abuse or psilocybin-containing mushroom abuse (Part 2.1[E]B).

        - There are very few recorded cases internationally of overdose, misuse and abuse (Part 2.1[E].C,D and E)

f. any other matters that the Secretary considers necessary to protect public health.

Current schedule 4 drugs for anxiety and depression (antidepressants and benzodiazepines) have more hazards, greater suicide risk, abuse potential, toxicity, and less efficacy; than psilocybin (Part 2.1[F]). Psilocybin -assisted therapy in a medically-controlled environment would therefore provide a safer and more effective alternative and one that requires only 2-3 sessions with the medicine.

Conclusion

The application meets all the criteria specified in the Therapeutic Goods Act 1989, subsection 52E. With the strong results and efficacy of psilocybin for anxiety and depression and for substance abuse and its very low toxicity and abuse potential in a medically controlled setting, it would be detrimental for suffering Australians not to have medically supervised access to this breakthrough medicine. There would not only be a large saving in the Australian economy through getting more people suffering from mental illness into remission but an improvement in the quality of life of Australians suffering from these illnesses. This would have profound and vastly positive societal implications.

We acknowledge and accept the premise that the use of psilocybin should only be authorised by psychiatrists or specialist addiction physicians and only used under medical supervision in a medically controlled environment. We therefore believe that it is reasonable to reschedule psilocybin from being a schedule 9 drug to being a schedule 8 drug under the above conditions.

Part 3 - SUPPORTING DATA

A. Supporting Data Summary

The tables on the following pages contain the following data;

1. Patterns of Australian use of psilocybin – incomplete clinical trials
2. Patterns of overseas use of psilocybin – completed clinical trials
3. Patterns of overseas use of psilocybin – incomplete clinical trials
4. Other patterns of use of psilocybin and psilocybin-containing mushrooms.
5. Pre-clinical completed trials

B. Supporting Data Details – Expert Letters of Support

Appendix A contains a letter of support for the proposed rescheduling of psilocybin in accordance with this application from 42 psychiatrist, psychologists, specialist physicians, pharmacologists, researchers and other relevant health experts from both Australia and overseas.

Appendix A also contains separate Expert Letters of Support from;

1. Dr Robin Carhart-Harris *, who heads the Centre for Psychedelic Research at Imperial College, London and is one of the leading researchers in the World into the medical application of psilocybin.
2. Professor Arthur Christopoulos, who is Dean of the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University and a Professor of Analytical Pharmacology.
3. Professor Roland Griffiths+, who is the Centre Director of the Johns Hopkins Centre for Psychedelic and Consciousness Research in the United States. His principal research focus in both clinical and preclinical laboratories has been on the behavioural and subjective effects of mood altering drugs including multiple studies on the impact and effects of psilocybin. Professor Griffiths is a World leader in this area..
4. Drug Science (www.drugscience.org.uk), the leading independent scientific body on drugs in the UK. The Chair of Drug Science, Professor David Nutt**+** is head of Neuropsychopharmacology and the Deputy Head of the Centre for Psychedelic Research at Imperial College, London. Professor Nutt is one of the World's foremost authorities on the medical use of psilocybin for treatment resistant depression and on the medical use of other psychedelic substances. The Drug Science Application is signed by its Chief Executive and supported by 25 members of its Scientific Advisory Committee including Professor David Nutt.

* Dr Robin Carhart-Harris is a member of the Advisory Panel of Mind Medicine Australia. This is an honorary position with no financial or other benefit attached.

\+ Professor Rolland Griffiths and Professor David Nutt are both Ambassadors of Mind Medicine Australia. This is an honorary position with no financial or other benefit attached

C. Copies of Papers Referenced

Copies of all papers referenced in this application can be found in **Appendix B (separate attachment)** at the following link:

https://www.dropbox.com/s/0u1gwtog6y4o0ba/Mind%20Medicine%20Australia%20Psilocybin%20Rescheduling%20S9%20to%20S8%2014%20July%202020_Appendix%20B.pdf?dl=0

We have also posted via Express Mail a USB stick to you containing all the papers in **Appendix B.**

SUPPORTING DATA SUMMARY

Table 10. Patterns of Australian use of psilocybin - incomplete clinical trials

Outcome	Institute	Comments	Reference
Depression & Anxiety	St Vincent's Hospital, Melbourne	The St Vincent's Melbourne trial will see 40 patients receive psilocybin (the psychoactive compound in magic mushrooms) alongside a short program of psychotherapy and clinical support. The trial is for terminally ill patients who are experiencing depression or anxiety. This treatment has been shown to dramatically reduce symptoms of anxiety and depression in cancer patients, and in many cases produces a substantial positive shift in patients' perspectives on life, and death.	SVHM 2020

Table 11. Patterns of overseas use of psilocybin - completed clinical trials

Outcome	Impact	Dose	Institute	Comments	Reference
Depression	**Significant** Reduction		University of California	**Phase 1 Clinical Trials** Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors	Anderson et al. 2018
	Significant Reduction	22mg/70kg 33mg/70kg	Johns Hopkins University	**Phase 2 Clinical Trials** Psychopharmacology of Psilocybin in Cancer Patients	Griffiths et al. 2016
	Significant Reduction	10mg 25mg	Imperial College London	**Clinical Study** Psilocybin with psychological support for treatment-resistant depression	Carhart-Harris et al. 2016
	Significant Reduction	Not applicable	Imperial College London	**Imaging Study** Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms	Carhart-Harris et al. 2017
	Significant Reduction	Not applicable	Imperial College London	**Self-Efficacy Study** Psilocybin with psychological support for treatment-resistant depression: six-month follow-up	Carhart-Harris et al. 2018

Table 11. Patterns of overseas use of psilocybin - completed clinical trials

Outcome	Impact	Dose	Institute	Comments	Reference
Anxiety	**Significant** Reduction	22mg/70kg 33mg/70kg	Johns Hopkins University	**Phase 2 Clinical Trials** Psychopharmacology of Psilocybin in Cancer Patients	Griffiths et al. 2016
	Significant Reduction	0.2mg/kg = 14mg/70kg	Harbor-UCLA Medical Center	**Phase 1 Clinical Trials** Effects of Psilocybin in Advanced-Stage Cancer Patients With Anxiety	Grob et al. 2011
	Significant Reduction	0.3mg/kg = 21mg/70kg	NYU Langone Health	**Early Phase 1 Clinical Trials** Psilocybin Cancer Anxiety Study	Ross et al. 2016
Alcohol Dependence	**Significant** Reduction	0.3mg/kg = 21mg/70kg 0.4mg/kg = 28mg/70kg	NYU Langone Health	**Phase 2 Clinical Trials** A Double-Blind Trial of Psilocybin-Assisted Treatment of Alcohol Dependence	Bogenschutz et al. 2015
Tobacco Addiction	**Significant** Reduction	20mg/70kg 30mg/70kg	Johns Hopkins University	**Clinical Study** Pilot Study of the 5-HT2AR Agonist Psilocybin in the Treatment of Tobacco Addiction	Griffiths et al. 2014
Cluster Headaches	**Significant** Reduction	Not applicable	Harvard Medical School	**Self-Efficacy Study** Response of cluster headache to psilocybin and LSD	Sewell et al. 2016

Table 11. Patterns of overseas use of psilocybin - completed clinical trials

Outcome	Impact	Dose	Institute	Comments	Reference
Grief	**Significant** Reduction		University of California	**Phase 1 Clinical Trials** Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors	Anderson et al. 2018
Distress	**Significant** Reduction		University of California	**Phase 1 Clinical Trials** Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors	Anderson et al. 2018
Safety	**Significant** Safe	0.3mg/kg = 21mg/70kg 0.45mg/kg 0.6mg/kg = 42mg/70kg	University of Wisconsin, Madison	**Phase 1 Clinical Trials** Psilocybin Pharmacokinetics Study	Brown et al. 2017

Table 12. Patterns of overseas use of psilocybin - incomplete clinical trials

Outcome	Institute	Comments	Reference
Depression	Great Lakes Clinical Trial Johns Hopkins University New York University Segal Trials University of California, San Fransisco University of Wisconsin, Madison Yale University	**Phase 2 Clinical Trial** A Study of Psilocybin for Major Depressive Disorder (MDD)	**2019**, ClinicalTrials.gov Identifier: NCT03866174
	Imperial College London	**Phase 2 Clinical Trial** Psilocybin vs Escitalopram for Major Depressive Disorder: Comparative Mechanisms (Psilodep-RCT)	**2018**, ClinicalTrials.gov Identifier: NCT03429075
	Johns Hopkins University	**Early Phase 1 Clinical Trial** Psilocybin for Depression in People With Mild Cognitive Impairment or Early Alzheimer's Disease	**2019**, ClinicalTrials.gov Identifier: NCT04123314

Table 12. Patterns of overseas use of psilocybin - incomplete clinical trials

Outcome	Institute	Comments	Reference
Depression	University of Helsinki	**Phase 2 Clinical Trial** Psilocybin and Depression (Psilo101)	**2017**, ClinicalTrials.gov Identifier: NCT03380442
	Johns Hopkins University	**Phase 2 Clinical Trial** Effects of Psilocybin in Major Depressive Disorder	**2017**, ClinicalTrials.gov Identifier: NCT03181529
	Yale University	**Phase 1 Clinical Trial** Psilocybin - Induced Neuroplasticity in the Treatment of Major Depressive Disorder	**2018**, ClinicalTrials.gov Identifier: NCT03554174
	University of Zürich	**Phase 2 Clinical Trial** Clinical, Neurocognitive, and Emotional Effects of Psilocybin in Depressed Patients - Proof of Concept	**2018**, ClinicalTrials.gov Identifier: NCT03715127
	COMPASS Pathways	**Phase 2 Clinical Trial** The Safety and Efficacy of Psilocybin in Participants With Treatment Resistant Depression (P-TRD)	**2018**, ClinicalTrials.gov Identifier: NCT03775200

Table 12. Patterns of overseas use of psilocybin - incomplete clinical trials

Outcome	Institute	Comments	Reference
Cocaine Addiction	University of Alabama at Birmingham	**Phase 2 Clinical Trial** Psilocybin-facilitated Treatment for Cocaine Use	**2014**, ClinicalTrials.gov Identifier: NCT02037126
Smoking Addiction	Johns Hopkins University	**Clinical Study** Psilocybin-facilitated Smoking Cessation Treatment: A Pilot Study	**2013**, ClinicalTrials.gov Identifier: NCT01943994
Alcohol Addiction	University of Zürich	**Phase 2 Clinical Trial** Clinical and Mechanistic Effects of Psilocybin in Alcohol Addicted Patients	**2019**, ClinicalTrials.gov Identifier: NCT04141501
	NYU Langone Health	**Phase 2 Clinical Trial** A Double-Blind Trial of Psilocybin-Assisted Treatment of Alcohol Dependence	**2014**, ClinicalTrials.gov Identifier: NCT02061293
Opioid Addiction	University of Wisconsin, Madison	**Phase 1 Clinical Trial** Adjunctive Effects of Psilocybin and Buprenorphine	**2019**, ClinicalTrials.gov Identifier: NCT04161066
Anorexia Nervosa	Johns Hopkins University	**Phase 1 Clinical Trial** Effects of Psilocybin in Anorexia Nervosa	**2019**, ClinicalTrials.gov Identifier: NCT04052568

Table 12. Patterns of overseas use of psilocybin - incomplete clinical trials

Outcome	Institute	Comments	Reference
Obsessive Compulsive Disorder	University of Arizona	**Phase 1 Clinical Trial** Psilocybin for Treatment of Obsessive Compulsive Disorder (PSILOCD)	**2017**, ClinicalTrials.gov Identifier: NCT03300947
	Yale University	**Phase 1 Clinical Trial** Efficacy of Psilocybin in OCD: a Double-Blind, Placebo-Controlled Study	**2017**, ClinicalTrials.gov Identifier: NCT03356483
Migraine Headaches	Yale University	**Phase 1 Clinical Trial** Repeat Dosing of Psilocybin in Migraine Headache	**2020**, ClinicalTrials.gov Identifier: NCT04218539
Cluster Headaches	Gitte Moos Knudsen	**Phase 1 & 2 Clinical Trials** Prophylactic Effects of Psilocybin on Chronic Cluster Headache (EPOCH)	**2020**, ClinicalTrials.gov Identifier: NCT04280055
	Yale University	**Phase 1 Clinical Trial** Psilocybin for the Treatment of Cluster Headache	**2016**, ClinicalTrials.gov Identifier: NCT02981173
Post-Traumatic Headaches	Yale University	**Phase 1 Clinical Trial** Effects of Psilocybin in Post-Traumatic Headache	**2019**, ClinicalTrials.gov Identifier: NCT03806985

Table 13. Other patterns of use for psilocybin and psilocybin-containing mushrooms

Pattern of Use	City/Institute	Reference
Breakthrough Therapy Designation for psilocybin-assisted therapy for treatment-resistant depression in 2018	Food and Drugs Administration (FDA), USA	COMPASS 2018
Breakthrough Therapy Designation for psilocybin therapy treating major depressive disorder in 2019	Food and Drugs Administration (FDA), USA	Businesswire 2019
Decriminalisation of psilocybin-containing mushrooms	Santa Cruz, California, USA Oakland, California, USA Denver, Colorado, USA	Kaur 2020
Psychedelic therapy centre opens up	New York, NY, USA	Hasse 2020

Table 14. Pre-clinical completed studies

Outcome	Impact	Institute	Comments	Reference
Post-Traumatic Stress Disorder	**Significant** Reduction	Lieber Institute for Brain Development, Baltimore, MD, US	**Pre-Clinical Study** Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning	Catlow et al. 2013
Neurogenesis	**Notable** Increase	Lieber Institute for Brain Development, Baltimore, MD, USA	**Pre-Clinical Study** Effects of psilocybin on hippocampal neurogenesis and extinction of trace fear conditioning	Catlow et al. 2013

PART 4 - BIBLIOGRAPHY

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Application to Reschedule Psilocybine[2] from Schedule 9 to Schedule 8 of the Poisons Standard

APPENDIX A - Experts' Letters of Support

For Rescheduling of Psilocybin from Schedule 9 of the Poisons Standard to Schedule 8

14 July 2020

Mind Medicine Australia Limited

Level 1/ 10 Dorcas St
South Melbourne VIC 3006

1 The SUSMP spells psilocybine with an 'e' on the end. All the literature spells psilocybin without an 'e' on the end. For the purposes of this document psilocybin will be spelt without an 'e' on the end from this point.

MIND MEDICINE AUSTRALIA

14 July 2020

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration
Canberra
Australia

Application to Amend the Poisons Standard in Relation to Psilocybin

Mind Medicine Australia Limited is applying to the Therapeutic Goods Administration to amend the Poisons Standard by rescheduling Psilocybin (spelt in the Poisons Standard as "Psilocybine") from Schedule 9 (Prohibited Substance) to Schedule 8 (Controlled Drug).

The experts listed below have read the application prepared by Mind Medicine Australia and have authorised Mind Medicine Australia to advise the Therapeutic Goods Administration that they support the proposed rescheduling.

Title	First Name	Surname	Position
Dr	Tanveer	Ahmed +	Australian Psychiatrist and Author based in NSW.
Dr	Christopher	Bench	Australian Psychiatrist in private practice in Newcastle, NSW.
Dr	Jillian	Broadbear	Adjunct Clinical Associate Professor, Monash University; Senior Research Fellow, Spectrum - Statewide Service for Personality Disorder, Eastern Health.
Prof	Ashley	Bush +	NHMRC Senior Principal Research Fellow, Director of the Melbourne Dementia Research Centre.
Dr	Robin	Carhart-Harris (UK)* +	Head of the Centre for Psychedelic Research - Imperial College London. Leading published researcher in psychedelic assisted therapies. Holds a PhD in Psychopharmacology.
Dr	Ted	Cassidy +	Australian psychiatrist. Chief Medical Officer and Co-Founder of TMS Australia, Australia's largest provider of outpatient Depression and PTSD treatment using transcranial magnetic stimulation technology.
Dr	Juthica	Chaudhary	Australian Psychiatrist in private practice in South Australia.
Dr	Lukas	Cheney	Australian consultant psychiatrist in Victoria.
Prof	Arthur	Christopoulos*	Dean, Faculty of Pharmacy and Pharmaceutical Sciences and Head of the Analytical and Structural Neuropharmacology Laboratory, Monash Institute of Pharmaceutical Sciences at Monash University. World leading molecular Pharmacologist.

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Dr	Mark	Cross +	Psychiatrist, Senior Conjoint Lecturer at the Universities of NSW and Western Sydney, and SANE Board Director.
A/Prof	Mark	Daglish	BSc MBChB MD FRANZCP Associate Professor in Addiction Psychiatry, University of Queensland.
Dr	James	Fadiman (USA) +	American Psychologist, Author and Researcher. Co-founder, Institute of Transpersonal Psychology, which later became Sofia University.
	Amanda	Fielding (UK) +	Founder and Executive Director of The Beckley Foundation in the UK, which has been a major funder of research into psychedelic assisted therapies.
Prof	Paul	Fitzgerald +	Professor of Psychiatry at Monash University and Director of the Epworth Centre for Innovation in Mental Health.
Prof	David	Forbes +	Director of Phoenix Australia - Centre for Posttraumatic Mental Health and Professor in the Dept of Psychiatry, Melbourne University.
Dr	Nick	Ford	Australian Psychiatrist in private practice in South Australia, specializing in PTSD.
Dr	Robert	Gordon	Australian Psychiatrist in private practice in Sydney, NSW.
Prof	Roland	Griffiths (USA) * #	Departments of Psychiatry and Neuroscience at the Johns Hopkins University School of Medicine. Principal research area has been on the behavioral and subjective effects of mood-altering drugs. Pioneering and World-leading researcher into the effects of psychedelics and particularly psilocybin.
Dr	Al	Griskaitis	Australian Psychiatrist in private practice in Wollongong, NSW.
Dr	Walter	Hipgrave	Psychiatry Registrar at Alfred Hospital, VIC
Dr	Karen	Hitchcock +	Specialist Physician (acute and general medicine) based in Melbourne and Author.
Prof	Malcolm	Hopwood +	Ramsay Health Care Professor of Psychiatry, University of Melbourne, specialising in clinical aspects of mood and anxiety disorders, psychopharmacology and psychiatric aspects of acquired brain injury and epilepsy. Past President of RANZCP.
Dr	Pieter	Hurter	Psychiatrist at Eastern Health, Melbourne.
Dr	Linda	Kader +	Psychiatrist and Senior Lecturer at the Department of Psychiatry, University of Melbourne.

	Michael	Kornhauser +	Australian Pharmaceutical and Clinical Trial Research Specialist.
Dr	Eli	Kotler +	Psychiatrist and Director of Medicine at Malvern Private Hospital, Melbourne, specialising in addictions.
Dr	Anish	Modak	Psychiatry Registrar, Adult Mental Health Unit Canberra Hospital, ACT Health.
Prof	Rob	Moodie AM +	Professor of Public Health – University of Melbourne and Advisor to World Health Organisation (WHO).
A/Prof	David	Nichols (USA) +	Adjunct Professor of Chemical Biology and Medicinal Chemistry - University of North Carolina, Chapel Hill. Published over 300 scientific articles. Major focus on psychedelic chemistry.
Professor	David	Nutt (UK) #	BA, MB BChir, MRCP, MA, DM, MRC Psych, FRCPsych, FMedSci, FRCP, FSB Head of Neuropsychopharmacology at Imperial College London, one of the world's foremost psychedelic research laboratories, publishing landmark research on psychedelic therapies and neuroimaging studies of the psychedelic state.
Dr	Nikola	Ognyenovits +	Australian Addiction Medicine Specialist Physician, QLD.
Dr	Prash	Puspanathan +	Previously a Medical Doctor at the Alfred Hospital where he most recently held the position of Neuropsychiatry Fellow.
A/Prof	Sathya	Rao	Executive Clinical Director of Spectrum, Personality Disorder Service for Victoria, Australia. He is also the Deputy President of Australian Borderline Personality Disorder Foundation, Adjunct Associate Clinical Professor at Monash University and a Consultant Psychiatrist at Delmont Private Hospital.
Dr	James	Rucker (UK) +	Consultant Psychiatrist & Senior Clinical Lecturer at Kings College London where he leads the Clinical Trials Group which is currently undertaking clinical trials using psilocybin in healthy volunteers and patients with resistant depression.
Dr	Anne	Schlag (UK) *	Head of Research at Drug Science, UK and Honorary Fellow at Imperial College London.
Dr	Ben	Sessa (UK) #	MBBS, B.SC, MRC PSYCH Psychiatrist and researcher at Bristol and Imperial College London University, He is currently conducting the world's first clinical study using MDMA to treat alcohol addiction.
Dr	Steven	Stankevicius	Australian Consultant Psychiatrist and Accredited TMS Clinician at Toowong Private Hospital, QLD.

Dr	Jorg	Strobel	Senior Consultant Psychiatrist / Clinical Lead Mental Health Informatics Research Unit, SA Health and Flinders University.
Prof	John	Tiller **+**	MD, MBCHB, BSC, DPM, FRACP, FRANZCP, GAICD Professor Emeritus Psychiatry, University of Melbourne and Albert Road Clinic. Past President of RANZCP. His primary research interests have been in the assessment and treatment of depressive and bipolar disorders, anxiety disorders including PTSD and psychoses.
Dr	Emile	Touma	Senior Addiction Psychiatrist and Addiction Medicine Specialist, Senior Lecturer, School of Clinical Medicine University of Queensland.
Dr	John	Webber +	Australian Psychiatrist in private practice in Melbourne.
Dr	Alex	Wodak AM +	Physician with expertise in addiction. Previously Director of the Alcohol and Drug Service at St Vincent's Hospital in Sydney.

*** Signatory to separate letter addressed to the Medicines Scheduling Secretariat at the Therapeutic Goods Administration endorsing the rescheduling application.**

 # Ambassador of Mind Medicine Australia. Note that this is an honorary position with no financial or other benefit attached.

+ Member of the Mind Medicine Australia Advisory Panel. Note that this is an honorary position with no financial or other benefit attached.

Yours sincerely

Peter Hunt AM
Chairman
Mind Medicine Australia Limited

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Southbank Vic 3006
Australia

Centre for Psychedelic Research
Burlington Danes Building, Du Cane Rd
London
W12 0NN
Dr. Robin Carhart-Harris
r.carhart-harris@imperial.ac.uk

June 13th, 2020

Dear Sir/ Madam,

I head the Centre for Psychedelic Research at Imperial College London. The world's first Centre dedicated to scientific and medical research with psychedelic compounds, founded in April 2019. Here in the UK, the Conservative Drug Policy Reform group is presently making a case to the UK Govt. to reschedule psilocybin from its present position as a Schedule 1, Class A drug. This campaign is backed by signatures from the leading scientists in this field.

There is no scientific basis for the present scheduling. Psilocybin has consistently been ranked in the lowest bracket harm among drugs of potential abuse according to a number of independent scientific assessments (1) and increasing evidence has shown its considerable potential as a therapeutic adjunct to treat a broad range of serious mental health conditions (2).

Regarding my expertise on this topic, I have the highest annual citation rate in the field (see below), was ranked in the Times top 31 medical scientists (REF) and have over 85 original publications in the field, having pioneered neuroimaging studies with both psilocybin and MDMA and impactful clinical trials of psilocybin for depression that were the main inspiration for the FDA's decisions to designate psilocybin a 'breakthrough therapy'.

Peter Hunt has forwarded to me the applications by Mind Medicine Australia (MMA) to reschedule psilocybin and MDMA in Australia and I have reviewed the rescheduling applications. The argument to reschedule psilocybin is compelling. As this is the compound with which I have the most scientific expertise, I am happiest to lend my support to its rescheduling. Psilocybin has a remarkably good therapeutic index, negligible toxicity and addiction potential and an extremely promising medical potential. Given my expertise on this topic, I strongly support the campaign to reschedule psilocybin from Schedule 9 to 8 in Australia. I support the same rescheduling for MDMA therapy, as the evidence for its efficacy as a tool to facilitate trauma-focused psychotherapy, is compelling.

Declaration
I am on the Advisory Panel of MMA. This is purely an honorary position and I receive no payments (either directly or indirectly) for undertaking this role.

In stating my views in this letter I have made an objective and impartial assessment of MMA's Rescheduling Applications in the light of current scientific knowledge.

Sincerely,

Dr Robin Carhart-Harris, BSc, MA, PhD
Head of Centre for Psychedelic Research
https://www.imperial.ac.uk/psychedelic-research-centre
Dept. Brain Sciences
Faculty of Medicine
Imperial College London
r.carhart-harris@imperial.ac.uk

References

1. Carhart-Harris RL, Nutt DJ. Experienced drug users assess the relative harms and benefits of drugs: a web-based survey. Journal of psychoactive drugs. 2013;45(4):322-8.
2. Nutt D, Erritzoe D, Carhart-Harris R. Psychedelic Psychiatry's Brave New World. Cell. 2020;181(1):24-8.

Rank	First Author	Title	Year	Journal	Annual Citation Rate	Total Number of Citations	Country	Classic psychedelic(s) Studied	Study Type	Outcome of Interest (where applicable)
1	RL Carhart-Harris	Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study	2016	The Lancet Psychiatry	111.3	334	UK	Psilocybin	Experimental case-series	Treatment-resistant depression
2	RL Carhart-Harris	Neural correlates of the LSD experience revealed by multimodal neuroimaging	2016	PNAS	98.7	296	UK	LSD	Experimental case-series	Neuroimaging (PET) and neurophysiology
3	RR Griffiths	Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial	2016	Journal of Psychopharmacology	96.3	289	USA	Psilocybin	Randomized, double-blind, placebo-like crossover trial	Cancer-related depression and anxiety
4	S Ross	Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial	2016	Journal of Psychopharmacology	87.7	263	USA	Psilocybin	Randomized, double-blind, placebo-controlled, crossover trial	Cancer-related depression and anxiety
5	RL Carhart-Harris	Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin	2012	PNAS	74.7	523	UK	Psilocybin	Placebo-controlled, open crossover study	Neuroimaging (fMRI)
6	Nicols DE	Hallucinogens	2004	Pharmacology & Therapeutics	72.6	1089	USA	LSD, psilocybin, DMT, mescaline	Review	Historical perspective, toxicity, pharmacology, and therapeutic applications
7	RL Carhart-Harris	The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs	2014	Frontiers in Human Neuroscience	71.4	357	UK	Psilocybin, LSD, and DMT	Review	Neuroimaging and neurophysiology
8	RL Carhart-Harris	Psilocybin with psychological support for treatment-resistant depression: six-month follow-up	2018	Psychopharmacology	71.0	71	UK	Psilocybin	Experimental case-series	Treatment-resistant depression

MONASH University
Pharmacy and Pharmaceutical Sciences

June 28th, 2020

Dear Sir/Madam

I have been asked by Mr Peter Hunt, the Chairman of Mind Medicine Australia, to comment on their application for psilocybin and MDMA to be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard.

My Background

I am the Professor of Analytical Pharmacology and the Dean of the Faculty of Pharmacy & Pharmaceutical Sciences, Monash University, which is currently ranked as No. 2 in the world (after Oxford) in Pharmacy and Pharmacology (QS World Rankings 2020). Prior to my appointment as Dean, I was a Senior Principal Research Fellow of the National Health and Medical Research Council of Australia. I am a world leader in novel modes of drug discovery, with a particular focus on neuropharmacology, neuropsychiatric diseases and protein targets for psychoactive medicines, including those modulated by mood-altering compounds such as psilocybin and MDMA. I have published over 320 peer reviewed articles, delivered over 180 invited presentations, served on the Editorial Board of 8 international journals and consult for numerous pharmaceutical companies. I have been the recipient of the highest Pharmacology awards from the Australian, American, British and International Pharmacological Societies, as well as having received the GSK Award for Research Excellence and a Doctor of Laws from the University of Athens. In 2018, I was elected a Fellow of the Australian Academy of Health and Medical Sciences. Since 2014-present, Clarivate Analytics have named me a Highly Cited Researcher in Pharmacology and Toxicology, which places me in the top 1% of all cited scientists worldwide in my field.

Safety and Efficacy of Psilocybin and MDMA in a Medically Controlled Environment

There is now a substantive body of highly compelling scientific evidence to support the fact that both psilocybin and MDMA offer superior efficacy to existing psychotherapies in treating major mental health conditions, including depression, PTSD, substance abuse disorders and anxiety, to name a few. In addition, and given the short dosing regimens associated with clinical application of the substances, there is minimal likelihood of any safety concerns or addiction liabilities. It is also worth highlighting that the US Food and Drug Administration have granted MDMA-assisted therapies for PTSD “breakthrough therapy” status, paving the way for availability of this form of therapy as a prescribed medicine pending further clinical trial results. Given that virtually all currently marketed medicines to treat psychiatric illnesses are based on science that is over 50 years old, it is imperative that we explore newer, more efficacious and safer alternatives for treating mental illness; medicinal psilocybin and medicinal MDMA represent such alternatives.

Proposed Change of Scheduling

Based on my professional experience and a review of the international data I believe that psilocybin and MDMA should be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard. There is simply no reasonable scientific rationale for the current scheduling of either substance as Schedule 9; in a clinical environment, they

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ABN 12 377 614 012 CRICOS provider number 00008C

present minimal risks of harm, adverse events or addictive liability compared to the majority of other psychoactive medicines currently listed as either Schedule 8 or even Schedule 4. I therefore support the applications for rescheduling being made by Mind Medicine Australia Limited.

Declaration

In stating my views in this letter, I have made an objective and impartial assessment of Mind Medicine Australia's Rescheduling Application in the light of current scientific knowledge.

Sincerely,

Arthur Christopoulos, B.Pharm., Ph.D.
Professor of Analytical Pharmacology
Dean
Faculty of Pharmacy and Pharmaceutical Sciences
Monash University

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Roland R. Griffiths, Ph.D.
The Oliver Lee McCabe, III Professor in the Neuropsychopharmacology of Consciousness
Director, Center for Psychedelic and Consciousness Research
Departments of Psychiatry and Neuroscience

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June 8, 2020

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration
Canberra
Australia

Dear Sir/Madam

I have been asked by Mr. Peter Hunt, the Chairman of Mind Medicine Australia, to comment on their application for psilocybin to be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard.

My Background

I am Professor in the Departments of Psychiatry and Neuroscience, and Director of the Center for Psychedelic and Consciousness Research at Johns Hopkins University School of Medicine. My principal research focus in both clinical and preclinical laboratories has been on the behavioral and subjective effects of mood-altering drugs of abuse. My research has been largely supported by grants from the National Institute on Health and from private foundations and I am author of over 400 journal articles and book chapters. I have been a consultant to the National Institutes of Health and to numerous pharmaceutical companies in the development of new psychotropic drugs, and a member of the Expert Advisory Panel on Drug Dependence for the World Health Organization. I have conducted extensive research with sedative-hypnotics, caffeine, and novel mood-altering drugs. In 1999 I initiated a research program investigating the effects of the classic psychedelic psilocybin that includes studies in healthy volunteers, in beginning and long-term meditators, and in religious leaders. Therapeutic studies with psilocybin include treatment of psychological distress in cancer patients, treatment of cigarette smoking cessation, and psilocybin treatment of major depression. Other studies have examined the effects of salvinorin A, dextromethorphan, and ketamine which produce altered states of consciousness having some similarities to psilocybin. As Director of the Johns Hopkins Center for Psychedelic and Consciousness Research [https://hopkinspsychedelic.org], I oversee a clinical and basic science research program of 8 physicians and research scientists investigating therapeutic and other effects of psilocybin and other psychedelic compounds.

Safety and Efficacy of Psilocybin in a Medically Controlled Environment

As documented in published research we and others have demonstrated the safety of psilocybin treatment when administered to carefully screening participants who are prepared and psychologically supported during and after psilocybin sessions. To date we have administered psilocybin to more than 375 participants in more than 700 sessions. We have no evidence that participants in our studies have subsequently become recreational abusers of psilocybin. We

have recently published an extensive review on the abuse potential of psilocybin [Johnson et al., The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act, Neuropharmacology, 142, 2018] in which we concluded:

(1) Psilocybin has an abuse potential appropriate for scheduling under the United States Controlled Substances Act if it is approved as medicine
(2) Psilocybin can provide therapeutic benefits that may support the development of an approvable New Drug Application (NDA) but further studies are required which this review describes
(3) Adverse effects of medical psilocybin are manageable when administered according to risk management approaches
(4) Although further study is required, this review suggests that placement in Schedule IV may be appropriate if a psilocybin-containing medicine is approved.

It is noteworthy that the Controlled Substances Act has five schedules running from Schedule 1 (highest potential for abuse and no current medical use in treatment in the United States) to Schedule V (lowest potential for abuse and accepted medical use in treatment in the United States). Schedule IV contains drugs with the second lowest potential for abuse in this rating scale and which have an accepted medical use in treatment in the United States.

Our published and ongoing research has provided compelling preliminary evidence that psilocybin may have efficacy in treatment of depression and anxiety in patients with life-threatening cancer diagnoses, in patients with Major Depressive Disorder, and in addicting cigarette smokers.

Proposed Change of Scheduling

Based on my professional experience and a review of the international data I support the application for rescheduling being made by Mind Medicine Australia Limited which acknowledges and accepts the premise that the use of psilocybin should only be authorised by psychiatrists and specialist physicians and only used under strict medical supervision in a medically controlled environment.

Declaration

I am an Ambassador of Mind Medicine Australia Limited. This is purely an honorary position and I receive no payments (either directly or indirectly) for undertaking this role.

In stating my views in this letter I have assessed Mind Medicine Australia's Rescheduling Application in the light of current scientific knowledge.

I would be pleased to respond to any questions that you may have.

Sincerely,

Roland R. Griffiths, Ph.D.
The Oliver Lee McCabe, III Professor in the Neuropsychopharmacology of Consciousness
Director, Center for Psychedelic and Consciousness Research
Department of Psychiatry and Behavioral Sciences
Department of Neuroscience

London, June 18th 2020

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration
Canberra
Australia

Dear Sir/Madam,

we have been asked by Mr Peter Hunt, the Chairman of Mind Medicine Australia, to comment on their application for psilocybin to be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard.

Drug Science

Drug Science is the leading independent scientific body on drugs in the UK. We work to provide clear, evidence-based information without political or commercial interference.
Drug Science was formed by a committee of scientists with a passionate belief that the pursuit of knowledge should remain free of all political and commercial interest. Our expert scientists comprise a wide range of disciplines: https://drugscience.org.uk

Prof David Nutt, Chair of Drug Science, is deputy Head of the Centre for Psychedelic Research at Imperial College London (https://www.imperial.ac.uk/psychedelic-research-centre/). He has extensive experience and scientific understanding of psilocybin being used in a clinical setting, having been leading- amongst other areas- psilocybin trials for treatment resistant depression.

Safety and Efficacy of Psilocybin in a Medically Controlled Environment

No drug related serious adverse events have been reported from any previous research investigating psilocybin's effects in healthy participants, and any adverse effects can be appropriately managed with safeguards in a clinical setting. Psilocybin has been shown to be tolerated well even in more at-risk patient groups, such as those facing a cancer diagnosis

Psilocybin-assisted therapy has yielded remarkable clinical results for depression and anxiety in numerous trials at leading Universities internationally. The proportion of participants who show positive clinical improvements, and the degree to which they improve, are substantially higher than clinical outcomes associated with currently available treatments.

Proposed Change of Scheduling

Based on our professional experience and a review of the international data we believe that psilocybin should be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard. We therefore support the application for rescheduling being made by Mind Medicine Australia Limited.

Declaration

Prof David Nutt is an Ambassador of Mind Medicine Australia Limited. This is purely an honorary position and David Nutt receives no payments (either directly or indirectly) for undertaking this role.

In stating our views in this letter, we have made an objective and impartial assessment of Mind Medicine Australia's Rescheduling Application in the light of current scientific knowledge.

We would be happy to respond to any questions that you may have.

Yours Faithfully,

David Badcock (CEO Drug Science)

Drug Science signatories

Prof David Nutt- Founder and Chair of Drug Science, Imperial College London
Dr Dima Abdulrahim
Dr Steve Bazire
Dr Simon Brandt
Prof Brigitta Brander
Prof Val Curran
Prof Colin Drummond
Niamh Eastwood
Prof Barry Everitt
Dr Roz Gittins
Prof Patrick Hargreaves
Prof Graeme Henderson
Prof Michael Lynsky
Dr John Marsden
Prof Fiona Measham
Ian Miller
Prof Jo Neill
Prof Larry Phillips
Dr John Ramsey
Steve Rolles
Prof Ilina Singh
Prof Alex Stevens
Dr Polly Taylor
Dr Steven Willot
Prof Adam Winstock