



Interim decisions & reasons for decisions by delegates of the Secretary to the Department of Health

15 September 2017

(ACMS, Joint ACCS-ACMS, and ACCS meetings – March and July 2017)

Notice under subsection 42ZCZN/42ZCZP of the Therapeutic Goods Regulations 1990 (the Regulations)

In accordance with subsection 42ZCZN of the Regulations, the delegate of the Secretary to the Department of Health has made an interim decision in relation to a proposed amendment; and under subsection 42ZCZP of the Regulations hereby gives notice of the delegates' interim decisions for amending the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons - SUSMP). This notice also provides the reasons and the date of effect (the implementation date) for each decision.

The delegate's interim decisions and reasons related to:

- scheduling proposals initially referred to the July 2017 meeting of the Advisory Committee on Medicines Scheduling (ACMS #21);
- scheduling proposals initially referred to the March 2017 and July 2017 Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS #15 and #16 respectively); and
- scheduling proposals initially referred to the July 2017 meeting of the Advisory Committee on Chemicals Scheduling (ACCS #20).

Pre-meeting public notices

On [22 December 2016](#), [3 February 2017](#), [17 May 2017](#) and [7 June 2017](#), under subsection 42ZCZK of the *Therapeutic Goods Regulations 1990* (the Regulations), the delegate published a [pre-meeting public notice](#) on the TGA website which specified the proposed amendments to the current Poisons Standard. The notice also invited public comment on the scheduling proposals referred to the expert advisory committees.

The pre-meeting consultation period was open for public comment for 20 business days and closed on 10 February 2017, 3 March 2017, 15 June 2017 and 7 July 2017.

In accordance with subsection 42ZCZL of the Regulations, redacted versions of public submissions received in response to this invitation for public comment will be published on or after the date of this notice on the TGA website at [Public submissions on scheduling matters](#).

Interim decisions

In accordance with subsections 42ZCZN and 42ZCZP of the Regulations, this notice provides the interim decisions of the delegates and the reasons for those decisions and invites further submissions from the applicant and parties who made valid submissions in response to the original invitations for submissions (see Pre-meeting public notices above).

Further submissions must be relevant to the proposed amendment, must address a matter mentioned in section 52E of the *Therapeutic Goods Act 1989* and be received by the closing date, 3 October 2017.

Further submissions from parties other than those who made a valid submission in response to the original invitation or the applicant, or those received after the closing date, need not be considered by the delegate.

Please note that all valid submissions received on or before the closing date will be published following removal of confidential information. It is up to the person making the submissions to highlight any information that they wish to be considered as confidential. Material claimed to be commercial-in-confidence will be considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the *Scheduling Policy Framework for Medicines and Chemicals* (SPF, 2015), issued by the Australian Health Ministers' Advisory Council (AHMAC). The SPF is accessible at: [AHMAC - Scheduling policy framework for medicines and chemicals](#).

Persons making submissions are strongly encouraged to lodge submissions in electronic format (word or unsecured PDF preferred) via the email address provided below. Submissions, preferably in electronic format, should be made to:

Chemicals.Scheduling@health.gov.au for items referred to the Advisory Committee on Chemicals Scheduling; and

Medicines.Scheduling@health.gov.au for items referred to the Advisory Committee on Medicines Scheduling.

The closing date for further submissions is 3 October 2017.

Privacy and your personal information

Your personal information is protected by law, including the *Privacy Act 1988*. It is collected by the Australian Government Department of Health for the purposes of identifying the person making a submission as part of the public invitation process, and contacting that person about their submission, for example to seek clarification of issues raised in the submissions.

The consequences of not providing your personal information may result in the Department being unable to communicate with you about your submission.

The Department is unlikely to disclose your personal information it has collected as part of the public comment process to any other Department, body or person or to overseas recipients.

More information about the Department's management of personal information is contained in the Department's privacy policy. The Department's privacy policy contains information such as how you may access the personal information the Department holds about you, how you can seek correction of it, and how you may complain about a breach of the Australian Privacy Principles.

The [Department's privacy policy](#) is available on the Department of Health website.

Alternatively, you may contact the Department by telephone on 02 6289 1555 or free call 1800 020 103, or by using the [online enquiries form](#).

Glossary

Abbreviation	Name
AAN	Australian Approved Name
AC	Active constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable daily intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSOM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service (now Biosecurity)
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
CAS	Chemical Abstract Service

Abbreviation	Name
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
EU	European Union
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (United States)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network
IMAP	Inventory Multi-tiered Assessment Prioritisation

Abbreviation	Name
INN	International Non-proprietary Name
IUPAC	International Union of Pure and Applied Chemistry
ISO	International Standards Organization
LC ₅₀	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD ₅₀	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])

Abbreviation	Name
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (formerly Office of Prescription and Non-prescription Medicines)
OOS	Out of session
OTC	Over-the-counter
PACIA	Plastics and Chemicals Industries Association
PAR	Prescription animal remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority existing chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted flow insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
SPF	Scheduling Policy Framework
STANZHA	States and Territories and New Zealand Health Authorities

Abbreviation	Name
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working party
WS	Warning statement

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Part A - Interim decisions on matters referred to an expert advisory committee (March and July 2017)

1. Advisory Committee on Medicines Scheduling (ACMS #21)

Summary of delegate's interim decisions

Substance	Interim decision
Sildenafil	The delegate's interim decision is that the current scheduling of sildenafil remains appropriate.
Vardenafil	The delegate's interim decision is that the current scheduling of vardenafil remains appropriate.
Ibuprofen combined with paracetamol	The delegate's interim decision is that the current scheduling of ibuprofen combined with paracetamol remains appropriate.
Esomeprazole	Schedule 4 – Amend Entry ESOMEPRAZOLE except when included in Schedule 2. Schedule 3 – Delete Entry Schedule 2 – Amend Entry ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply. The proposed implementation date is 1 February 2018 .
Stiripentol	Appendix K – New Entry STIRIPENTOL The proposed implementation date is 1 February 2018 .

1.1. Sildenafil

Referred scheduling proposal

An application was submitted to create a new entry for sildenafil in Schedule 3 in oral preparations containing 50 mg of sildenafil per dosage unit in packs of not more than 8 dosage units, to include sildenafil in Appendix H and to include additional warning statements in Appendix F for Schedule 3 sildenafil.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 3 – New Entry

SILDENAFIL in divided preparations for oral use containing 50 mg of sildenafil per dosage unit in packs of not more than 8 dosage units when compliant with the requirements of Appendix F warning statements.

Schedule 4 – Amend Entry

SILDENAFIL **except** when included in Schedule 3.

Appendix H – New Entry

SILDENAFIL.

Appendix F, Part 3 – New Entry

SILDENAFIL

Warning Statements: 109, 110

Appendix F, Part 1 – New Warning Statements

- 109:** Do not take [*this product/name of the product*] if you:
- do not have an erection problem
 - take any nitrate medicine for chest pain or heart failure
 - take riociguat for high blood pressure in the lungs
 - take ritonavir for the treatment of HIV
 - have been advised by your doctor to avoid sexual activity because of a problem with your heart or blood vessels
 - have a severe heart or liver problem
 - have low blood pressure
 - have ever had severe vision loss or a rare inherited eye disease
 - have a deformed penis
 - have an allergy to sildenafil or similar medicines, or to any other ingredient in this product
- 110:** Unless your doctor has told you to, do not take [*this product/name of the product*] if you:
- get very breathless or feel chest pain with light or moderate physical activities
 - have a heart problem
 - have high blood pressure that is not controlled
 - take any other medicines listed in the package leaflet
 - take any other treatment for erectile dysfunction
 - ever had a persistent or prolonged erection that lasted for more than 4 hours
 - have a stomach ulcer or bleeding disorder
 - have diagnosed mild to moderate liver problems
 - have diagnosed severe kidney problems

The applicant's reasons for the proposal are:

- The risks associated with use of non-prescription sildenafil by men with erectile dysfunction (ED) who have underlying aetiology are low, and can be managed within the pharmacy setting. Non-prescription status will not delay diagnosis of underlying aetiology but is expected to encourage treatment-seeking behaviour and access to appropriate advice.
- The use of sildenafil has been shown to be safe in those with concomitant ED and cardiovascular disease (CVD), including congestive heart failure (CHF) and coronary artery disease (CAD).
- Men with undiagnosed diabetes would be less likely to obtain satisfactory results with the proposed non-prescription sildenafil dosing regimen, and would be directed by the product labelling or pharmacist to consult a physician.
- For men who consult a physician about their ED, co-existing conditions are not commonly detected in the initial consultation. The availability of non-prescription sildenafil provides the potential to directly educate men around the causes of ED and bring more men into the healthcare system.
- Most low-risk patients can initiate or resume sexual activity and begin ED treatment without further testing or evaluation. Data demonstrates that in the majority of cases, men are immediately prescribed a PDE-5 inhibitor (for example, sildenafil) without a physical examination or diagnostic testing.
- The availability of non-prescription sildenafil 50 mg, and increased awareness of ED and its association with other medical conditions, will facilitate dialogue between those men not currently seeking medical assistance or a pharmacist around sexual function. This could lead to earlier assessment of medical conditions associated with ED.
- A maximum of 8 tablets is proposed for Schedule 3 sildenafil, with only one pack provided per consultation. Accessing each pack would require a man to actively engage with the pharmacist and for the pharmacist to undertake appropriate assessment and counselling. Men who have not been given the product will be advised to see the doctor, and those that are provided the product will be advised to see a doctor within 6 months of receiving sildenafil. The frequent interaction with a pharmacist provides repeated opportunities for the pharmacist to recommend seeing a doctor for further assessment.

Current scheduling status and relevant scheduling history

Sildenafil is currently listed in Schedule 4 of the [Poisons Standard](#) as follows:

Schedule 4

SILDENAFIL.

The chemically and pharmacologically similar vardenafil and tadalafil are also in Schedule 4 of the Poisons Standard.

Sildenafil

In August 1998, the National Drugs and Poisons Schedule Committee (NDPSC) considered a proposal to schedule sildenafil as a new medicine. The committee decided to list sildenafil in Schedule 4 on the grounds that the committee considered that the contraindications, precautions and drug interactions were such that medical advice was required.

Vardenafil

In June 2003, the NDPSC considered a proposal to schedule vardenafil as a new medicine. The committee decided to list vardenafil in Schedule 4 on the grounds that the condition being treated

necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

In November 2016 the ACMS considered a proposal to reschedule vardenafil in oral preparations containing up to 10 mg in Schedule 3. The committee recommended that the current scheduling of vardenafil remains appropriate on the basis that erectile dysfunction can be a marker of an underlying cardiovascular disease, diabetes or endocrine disorder and men should be assessed by a medical practitioner prior to (or at the very least concurrent with) initiation of PDE5 inhibitor treatment. The delegate agreed with the committee's advice that there are currently no risk management plans for Schedule 3 medicines considering it to be premature to down schedule vardenafil when there are no mandated requirements to minimise the risk relating to underlying medical conditions. The delegate also noted that no other PDE5 inhibitors have been down-scheduled. The delegate agreed with the committee's advice and decided that the scheduling for vardenafil remained appropriate.

Australian regulatory information

According to the [TGA Ingredient Database](#), sildenafil is available for use as an:

- Active ingredient in biologicals, export only and prescription medicines;
- Excipient ingredient in biologicals, devices and prescription medicines; and
- Equivalent ingredient in prescription medicines.

Sildenafil is listed in 102 registered products on the Australian Register of Therapeutic Goods (ARTG). These include 25 mg, 50 mg and 100 mg tablets.

In the last 20 years there have been 1075 adverse event reports in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 967 cases with a single suspected medicine and 39 cases of death as a reported outcome. Of the cases where sildenafil was suspected, reactions include dyspepsia, dizziness, headache, insomnia, urinary tract infection, diarrhoea, flushing and nausea.

International regulations

Canada

Health Canada regulates sildenafil as a prescription only medicine. Tablet strengths available include 25 mg, 50 mg and 100 mg, and there is also a 0.8 mg/mL solution of sildenafil registered (as a 10 mg/12.5 mL product) for intravenous use.

New Zealand

Medsafe New Zealand regulate sildenafil as a prescription medicine with the exception of sildenafil for oral use containing 100 mg or less per dose unit sold in the manufacturer's original pack containing not more than 12 dosage units. This is indicated for the treatment of erectile dysfunction in males aged 35-70 years and is provided by a registered pharmacist who has successfully completed a training programme endorsed by the Pharmaceutical Society of New Zealand.

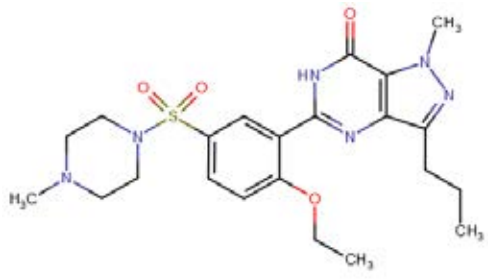
USA

The US FDA regulates sildenafil as a prescription medicine. It was first registered in March 1998.

Substance summary

Sildenafil citrate, a sildenafil salt, is an orally active selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). cGMP PDE5 is the predominant isoenzyme in the human corpora cavernosa responsible for the degradation of cGMP. With sildenafil acting as a potent inhibitor, there is an increased level of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and allowing an inflow of blood to the area.

Table 1.1.1: Chemical properties of sildenafil

Property	Sildenafil
CAS number	171599-83-0 (as citrate)
Chemical structure	 (free sildenafil)
Molecular formula	C ₂₈ H ₃₈ N ₆ O ₁₁ S (sildenafil)
Molecular weight	666.7 g/mol (as citrate)
IUPAC and/or common and/or other names	5-[2-ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one dihydrogen 2-hydroxypropane-1,2,3- tricarboxylic acid.

PDE-5 inhibitors are a class of medicines for the treatment of erectile dysfunction (ED). They work by helping to relax the blood vessels in the penis, allowing blood flow to the penis when sexually excited. To be effective, sexual stimulation is required.

Sildenafil facilitates penile erection by enhancing the relaxant effect of nitric oxide (NO) released in response to sexual stimulation. By inhibiting PDE-5, the enzyme responsible for cGMP catabolism, sildenafil causes NO-induced cGMP concentrations to remain elevated in the corpus cavernosum smooth muscle. Elevated cGMP levels signal smooth muscle relaxation, resulting in an inflow of more blood in the corpus cavernosum and subsequent penile erection.^{1, 2}

Pre-meeting public submissions

Eight (8) submissions were received, six (6) in support and two (2) opposed.

Main points in support:

- The key issue facing men with erectile dysfunction (ED) is related to their reluctance to engage with their doctor. It is well known that the vast majority of men with ED have this condition due to vascular issues and have the same risk factors (such as hypertension, dyslipidemia, smoking and diabetes) that are associated with the development of atherosclerotic cardiovascular disease.
- Enabling access to an over-the-counter (OTC) PDE-5 inhibitor (supported with learning and educational materials) would encourage awareness of cardiovascular risk factors and will open discussions between the patient and their pharmacist about necessary tests, leading to an early diagnosis.

¹ Boolell M, *et al.*, **1996** Sildenafil: An orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int, J, Impot, Res.*, 8(2), 47-52.

² Burnett A.L., **1995** Role of nitric oxide in the physiology of erection. *Biol, Reprod*, 52(3), 485-9.

- ED medicines are currently the most counterfeited medicines seized by European Union customs. Having a TGA-approved product available through an easy accessible healthcare professional could reduce the number of counterfeit medicines purchased online.
- PDE-5 inhibitors are generally regarded as safe, well-tolerated medicines with a good toxicological profile that exert a beneficial cardio-protective effect in men with cardiovascular disease.
- Pharmacists are able to offer point of care testing in the pharmacy in relation to blood pressure, cholesterol and blood glucose tests to accompany the sale of OTC PDE-5 inhibitors, and provide appropriate lifestyle advice.
- The pack size proposed for inclusion in Schedule 3 is consistent with the starting dose of this substance. With a recommended maximum dose of 1 tablet in 24 hours, the pack represents 8 days' supply. This reflects the proposal currently being considered in the UK. In New Zealand, pharmacists are able to supply an original manufacturer's pack containing not more than 12 dosage units.
- While there may be a level of non-therapeutic use of PDE-5 inhibitors, there is no data to support the notion that this class of medicines is 'commonly misused'.

Main points opposed:

- Sildenafil can prolong the QT interval and increase the risk of arrhythmia. Its use is also cautioned in hepatic impairment.
- Pharmacies in the community setting do not have adequate resources to screen for these risks.
- Erectile dysfunction (ED) is a marker of the state of the blood vessels in other parts of the cardiovascular system and should be thoroughly investigated before phosphodiesterase inhibitors are prescribed. This is best investigated by the patient's usual medical practitioner in a consultation where this issue can be teased out and if appropriate, alternatives discussed.
- Pharmacists may know about a patient's usual medicines. However, a patient's regular general practitioner will know the full range of medicines currently prescribed, why those particular medicines were prescribed, and be able to discuss safe alternative approaches knowing the full medical history of the patient. A pharmacist identifying a potential adverse drug interaction will, in any event, have to refer the patient to their general practitioner.
- A medical practitioner consultation to obtain a prescription of sildenafil also provides an opportunity to screen for diabetes mellitus and sexually transmissible infections, as well as undertake unrelated but important health prevention activities.

The public submissions will be made available on the [TGA website](#).

Summary of ACMS advice to the delegate

The committee recommended that the current scheduling of sildenafil remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- Potential for incorrect assessment of ED and lack of screening of underlying and asymptomatic chronic conditions leading to a worsened health outcome due to self-management.
- There is evidence to suggest that the combination of type 2 diabetes and ED with significantly increased risk of cardiovascular disease.³
- Adverse events and drug interactions of sildenafil can be potentially severe. The adverse event profile requires medical monitoring. Drug interactions may potentiate sildenafil toxicity.
- Possible misuse and/or abuse by men who do not have ED, or by men who take other drugs.
- Risk of worsened health outcomes is heightened by the possibility of men never going to their doctor for assessments and obtaining repeat supplies from pharmacists.
- The proposed Schedule 3 entry is intended for use in men aged 18 years old and older, with no upper age limit.
- Proposed pack size of eight (8) units does not appropriately address the risk of harms brought on by a lack of medical oversight in supply of sildenafil.
- Internet purchasing is recognised, as is counterfeiting. However, increased access through down-scheduling is not considered an appropriate mechanism to address this issue.
- Consumer education and information is a better avenue to help overcome the stigma of ED and improve treatment rates.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is that the current scheduling of sildenafil remains appropriate.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

³ Kouidrat, Y *et al*, **2017** 'Systematic Review of Meta-analysis: High prevalence of erectile dysfunction in diabetes: a systematic review and meta-analysis of 145 studies' *Diabetic Medicine*, 1464-5491.

The reasons for the interim decision are:

(a) the risks and benefits of the use of a substance:

- Adverse events and drug interactions of sildenafil can be potentially severe. The adverse event profile requires medical monitoring. Drug interactions may potentiate sildenafil toxicity.
- There is increasing evidence of a direct link between erectile dysfunction and cardiovascular disease. Erectile dysfunction is a marker of early atherosclerosis and as an independent predictor of cardiovascular events and all-cause mortality.
- There is evidence to suggest that the combination of type 2 diabetes and ED with significantly increased risk of cardiovascular disease.³
- Risk of worsened health outcomes is heightened by the possibility of men never going to their doctor for assessments and obtaining repeat supplies from pharmacists.
- Potential for incorrect assessment of ED and lack of screening of underlying and asymptomatic chronic conditions leading to a worsened health outcome due to self-management.
- The proposed warning statements by the applicant actually reinforce the requirement for medical assessment before prescribing.
- Risk it would be used by men who are unfit and/or by those who have contraindications and are not prepared to tell pharmacist.
- Risk is heightened by the possibility of some consumers never going to their doctor for assessment, and obtaining repeat supplies through a pharmacist.
- Any benefits of improved access for consumers are greatly outweighed by the risk of improper diagnosis or treatment of ED or associated risk factors by a pharmacist.

(b) the purposes for which a substance is to be used and the extent of use of a substance:

- The proposed Schedule 3 entry is intended for use in men aged 18 years old and older, with no upper age limit.
- Approximately 20% of Australian men greater than 40 years suffer from ED with a significantly increased risk with aging and cardiovascular disease.

(c) the toxicity of a substance:

- Safety data indicates that NAION and priapism are potential serious AEs, as are interactions with nitrates & some other drugs metabolised via CYP450.
- Sildenafil has a significant AE profile that requires medical monitoring.
- Drug-drug interactions may potentiate sildenafil toxicity.

(d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Proposed pack size of eight (8) units does not appropriately address the risk of harms brought on by a lack of medical oversight in supply of sildenafil.
- Sildenafil has a wide therapeutic index and the proposed 50 mg dose is the recommended starting dose, 1 hour before sexual activity. The PI states that 100 mg is the maximum dose.

(e) the potential for abuse of a substance:

- Possible misuse and/or abuse by men who do not have ED, or by men who take other drugs.

(f) any other matters that the Secretary considers necessary to protect public health:

- Good clinical practice mandates a cardiovascular assessment and history in all patients presenting with erectile dysfunction. This is best done by a patient's general practitioner.
- Internet purchasing is recognised, as is counterfeiting, however increased access through down-scheduling is not considered an appropriate mechanism to address this issue.
- Consumer education and information is a better avenue to help overcome the stigma of ED and improve treatment rates.
- Although reticence to speak to GP about ED it not likely to be easier to speak to unknown pharmacists with whom there is no on-going relationship.
- Low public health benefit as access is still outweighed by risks.
- Men do not see GP often anyway, so any opportunity to review for holistic review is good.

In view of the reasons above the current scheduling of sildenafil is appropriate.

1.2. Vardenafil

Referred scheduling proposal

An application was submitted to create a new Schedule 3 entry for vardenafil in oral preparations containing up to 10 mg per dosage unit in pack containing not more than 8 dosage units.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 3 – New Entry

VARDENAFIL in oral preparations, containing up to 10 mg per dosage unit in packs containing not more than 8 dosage units.

Schedule 4 – Amend Entry

VARDENAFIL **except when included in Schedule 3.**

The applicant's reasons for the proposal are:

- Following consideration by the ACMS and Scheduling Delegate in 2016, this proposal aims to address the concerns raised by the ACMS and Scheduling Delegate at that time. The primary concerns were:
 - The underlying aetiology of the presented erectile dysfunction (ED) requires initial assessment by a medical practitioner;
 - PDE5 inhibitors (for example vardenafil) are commonly misused and no data were provided to support a reduction in internet purchasing; and
 - The ACMS/Scheduling Delegate has no remit to mandate pharmacist training or a supply protocol and there is currently no TGA requirement for Risk Management Plans for down-scheduled OTC medicines.
- With regards to the need for patient assessment by a medical practitioner, the ongoing professional responsibilities for pharmacists to identify situations where patient symptoms are possibly caused by underlying diseases especially in relation to supply of Schedule 3 medicines, will ensure that appropriate investigation into any potentially underlying disease is investigated where clinically indicated.

- The ACMS/Scheduling Delegate concerns regarding the extent of misuse of PDE5 inhibitors may have been based on the assumption that internet-sourced products are intended for misuse, but available data on the use of illicit substances in Australia does not indicate this. Local social science health research evidence presented in this submission indicates that the level of misuse of PDE5 inhibitors in the general and homosexual/bisexual male population is very low, and concomitant use with 'recreational drugs' lower still. While there is no published evidence to support the contention that the availability of Schedule 3 vardenafil will reduce internet sourcing, statements included herein from pharmacists involved in the non-prescription supply of another PDE5 inhibitor in New Zealand demonstrates that a proportion of internet-sourcing has been converted to pharmacy-sourcing. Furthermore, it is clear that Schedule 3 availability will ensure increased healthcare professional interaction compared to unrestricted internet procurement, and there is most certainly no evidence suggesting that expanded availability will lead to increase internet sourcing. Consequently, the concerns expressed are not supported by the evidence and there remains the real possibility that Schedule 3 vardenafil will result in reduced sourcing of unapproved and unsafe PDE5 inhibitors via the internet.
- The capacity to mandate provision of pharmacist training materials and treatment protocols is considered to already reside with the TGA in their consideration of any Schedule 3 vardenafil 'medicine registration application', under the powers currently vested in the TGA via s3, s25(1)(e), s25(1)(k), s28(b) and/or s28(e) the Therapeutic Goods Act 1989 and associated Regulations. While the current TGA guidelines for over-the-counter (OTC) medicine registration do not specifically cover mandating conditions of registration such as pharmacist training or treatment protocol use, this does not preclude the TGA from invoking such conditions, with regulatory guideline updates following as required in due course. The logistical and administrative particulars of the pharmacist training program and use of the treatment protocol are most pertinent to peak pharmacy bodies and for TGA Schedule 3 product registration applications.
- The current international precedents of non-prescription supply of PDE5 inhibitors in New Zealand and the United Kingdom, and significantly the MHRA's 28 March 2017 view that sildenafil is safe enough to be recommended for reclassification to Pharmacy medicine status. Vardenafil has been acknowledged to be well-tolerated with a good toxicological profile, and provides a safe and effective treatment option for ED.

Current scheduling status and relevant scheduling history

Vardenafil is currently listed in Schedule 4 of the [Poisons Standard](#) as follows:

Schedule 4

VARDENAFIL.

The chemically and pharmacologically similar sildenafil and tadalafil are also in Schedule 4 of the Poisons Standard.

Vardenafil

In June 2003, the National Drugs and Poisons Committee (NDPSC) considered a proposal to schedule vardenafil as a new medicine. The committee decided to list vardenafil in Schedule 4 on the grounds that the condition being treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

In November 2016 the ACMS considered a proposal to reschedule vardenafil in oral preparations containing up to 10 mg in Schedule 3. The committee recommended that the current scheduling of vardenafil remains appropriate on the basis that erectile dysfunction can be a marker of an underlying cardiovascular disease, diabetes or endocrine disorder and men should be assessed by a medical practitioner prior to (or at the very least concurrent with) initiation of PDE5 inhibitor treatment. The delegate agreed with the committee's advice that there are currently no risk management plans for Schedule 3 medicines considering it to be premature to down schedule vardenafil when there are no

mandated requirements to minimise the risk relating to underlying medical conditions. The delegate also noted that no other PDE5 inhibitors have been down-scheduled. The delegate agreed with the committee's advice and decided that the scheduling for vardenafil remained appropriate.

Sildenafil

In August 1998, the National Drugs and Poisons Schedule Committee (NDPSC) considered a proposal to schedule sildenafil as a new medicine. The committee decided to list sildenafil in Schedule 4 on the grounds that the committee considered that the contraindications, precautions and drug interactions were such that medical advice was required.

A rescheduling proposal for sildenafil is also being considered at this meeting.

Australian regulatory information

According to the [TGA Ingredient Database](#), vardenafil is available for use as an:

- Active ingredient in biologicals and prescription medicines;
- Excipient in biologicals, devices and prescription medicines; and
- Equivalent ingredient in prescription medicines.

Vardenafil is listed in 4 entries on the Australian Register of Therapeutic Goods (ARTG). The products marketed include a 5 mg, 10 mg and 20 mg film-coated tablet blister pack and a 10 mg orodispersible tablet blister pack registered.

In the last 20 years there have been 34 adverse event reports in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 29 cases with a single suspected medicine and 1 case of death as a reported outcome. Of the cases where vardenafil was the suspected causative medicine, reactions included ataxia, headache, blurred vision, cyanopsia, erythema, muscle rigidity, deafness, dysphagia, dysphonia, urogenital haemorrhage, thrombocytopenia, atrial fibrillation, prostatic specific antigen increased, and prostate cancer.

International regulations

Canada

Health Canada regulates vardenafil as a prescription medicine, in strengths of 5 mg, 10 mg and 20 mg.

New Zealand

Medsafe New Zealand classifies vardenafil and its structural analogues as prescription only medicines.

USA

The US FDA regulates vardenafil as a prescription only medicine, in strengths of 2.5 mg, 5 mg, 10 mg and 20 mg.

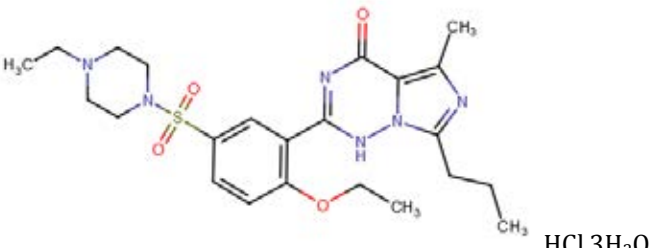
UK

In the UK vardenafil is a prescription only medicine.

Substance summary

Vardenafil hydrochloride is a benzenesulfonamide derivative and an inhibitor of phosphodiesterase type 5 (PDE5), the most prominent PDE in the corpus cavernosum of the penis responsible for the hydrolysis of cGMP. By preventing the breakdown of cGMP, vardenafil allows the male to reach and maintain an erection when sexually stimulated. Vardenafil is used to treat erectile dysfunction (ED) in adult males. The maximum recommended dose is one orodispersible tablet daily (10 mg vardenafil).

Table 1.2.1: Chemical properties of vardenafil

Property	Vardenafil
CAS number	224785-90-4 (vardeafil)
Chemical structure	 <p>HCl.3H₂O</p> <p>(as hydrochloride trihydrate)</p>
Molecular formula	C ₂₃ H ₃₂ N ₆ O ₄ S.HCl.3H ₂ O (as hydrochloride trihydrate)
Molecular weight	488.6 g/mol (vardeafil)
IUPAC and/or common and/or other names	<p>2-[2-ethoxy-5-(4-ethylpiperazin-1-yl)sulfonylphenyl]-5-methyl-7-propyl-1H-imidazo[5,1-f][1,2,4]triazin-4-one hydrochloride (IUPAC);</p> <p>1-(((3-(3,4-dihydro-5-methyl)-4-oxo-7-propylimidazo(5,1-f)-as-triazin-2-yl)-4-ethoxyphenyl)sulfonyl)-4-ethylpiperazine.</p>

Pre-meeting public submissions

Six (6) submissions were received, four (4) in support and two (2) opposed.

Main points in support:

- Implementation of the proposed scheduling amendment will encourage men suffering from ED into the healthcare system and provide the opportunity for men to engage in more health-related discussions with their pharmacist.
- Pharmacists are well-placed to ensure the appropriate, judicious, and safe supply of PDE inhibitors.
- The increased accessibility of ED treatment will assist men who see themselves as otherwise healthy interacting with a health professional where they may not have ordinarily. This, in turn, provides the opportunity for cardiovascular risk screening and referral to a GP of those patients who may not currently have a relationship with their GP.
- Sildenafil and vardenafil have been available in Australia for a significant period of time as Schedule 4 medicines. To facilitate Schedule 3 supply, additional information and advice will be provided, based on current available evidence, to offer pharmacists contemporary, realistic and useful guidance to support good decision-making in practice.
- Allowing controlled access to this medicine without a prescription has led to an increase in discussions between men and healthcare providers in New Zealand, where erectile dysfunction medicines are already available for supply by pharmacists under certain conditions.
- British Medicines and Healthcare Products Regulatory Agency is considering an application to re-schedule sildenafil, to make it available over-the-counter in pharmacies.

Main points opposed:

- Vardenafil can prolong the QT interval and increase the risk of arrhythmia. Its use is also cautioned in hepatic impairment.
- Pharmacies in the community setting do not have adequate resources to screen for these risks.
- Erectile dysfunction (ED) is a marker of the state of the blood vessels in other parts of the cardiovascular system and should be thoroughly investigated before phosphodiesterase inhibitors are prescribed. This is best investigated by the patient's usual medical practitioner in a consultation where this issue can be teased out and if appropriate, alternatives discussed.
- Pharmacists may know about a patient's usual medicines. However, a patient's regular general practitioner will know the full range of medicines currently prescribed, why those particular medicines were prescribed, and be able to discuss safe alternative approaches knowing the full medical history of the patient. A pharmacist identifying a potential adverse drug interaction will, in any event, have to refer the patient to their general practitioner.
- A medical practitioner consultation to obtain a prescription for vardenafil also provides an opportunity to screen for diabetes mellitus and sexually transmissible infections, as well as undertake unrelated but important health prevention activities.

The public submissions will be made available on the [TGA website](#).

Summary of ACMS advice to the delegate

The committee recommended that the current scheduling of vardenafil remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- Approximately 20% of Australian men greater than 40 years suffer from ED with a significantly increased risk of having CVD. There is evidence to suggest that men who have Type 2 Diabetes and ED have a significantly increased risk of having CVD.³ As a consequence, there is a major risk of the underlying CVD potentially not being identified and subsequently managed.
- Toxicity of vardenafil is low and it is well tolerated. However, the benefits of down-scheduling vardenafil from Schedule 4 to Schedule 3 do not outweigh the risks.
- The proposed vardenafil preparations containing up to 10 mg in a pack size of eight (8) units does not appropriately address the risk of harms brought on by a lack of medical oversight in supply.
- Possible misuse/abuse by men who do not have ED, or by men who take other drugs. The extent in Australia is currently unknown.
- Good clinical practice mandates a cardiovascular assessment and history in all patients presenting with ED, and this is best done by a general practitioner.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACMS advice

- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is that the current scheduling of vardenafil remains appropriate.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

(a) the risks and benefits of the use of a substance:

- Adverse events and drug interactions of vardenafil can be potentially severe. The adverse event profile requires medical monitoring. Drug interactions may potentiate vardenafil toxicity.
- There is a risk of QT prolongation.
- There is increasing evidence of a direct link between erectile dysfunction and cardiovascular disease. Erectile dysfunction is a marker of early atherosclerosis and as an independent predictor of cardiovascular events and all-cause mortality.³
- There is evidence to suggest that the combination of type 2 diabetes and ED with significantly increased risk of cardiovascular disease.³
- Risk of worsened health outcomes is heightened by the possibility of men never going to their doctor for assessments and obtaining repeat supplies from pharmacists.
- Potential for incorrect assessment of ED and lack of screening of underlying and asymptomatic chronic conditions leading to a worsened health outcome due to self-management.
- The proposed warning statements by the applicant actually reinforce the requirement for medical assessment before prescribing.
- Risk it would be used by men who are unfit and/or by those who have contraindications and are not prepared to tell pharmacist.
- Risk is heightened by the possibility of some consumers never going to their doctor for assessment, and obtaining repeat supplies through a pharmacist.
- Any benefits of improved access for consumers are greatly outweighed by the risk of improper diagnosis or treatment of ED or associated risk factors by a pharmacist.

(b) the purposes for which a substance is to be used and the extent of use of a substance:

- The proposed Schedule 3 entry is intended for use in men aged 18 years old and older, with no upper age limit.
- Approximately 20% of Australian men greater than 40 years suffer from ED with a significantly increased risk with aging and cardiovascular disease.

(c) the toxicity of a substance:

- Safety data indicates that NAION and priapism are potential serious AEs, as are interactions with nitrates & some other drugs metabolised via CYP450.
- Vardenafil has a significant AE profile that requires medical monitoring.
- Drug-drug interactions may potentiate vardenafil toxicity.

(d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Proposed pack size of eight (8) units does not appropriately address the risk of harms brought on by a lack of medical oversight in supply of vardenafil.

(e) the potential for abuse of a substance:

- Possible misuse and/or abuse by men who do not have ED, or by men who take other drugs.

(f) any other matters that the Secretary considers necessary to protect public health:

- Good clinical practice mandates a cardiovascular assessment and history in all patients presenting with erectile dysfunction. This is best done by a patient's general practitioner.
- Internet purchasing is recognised, as is counterfeiting, however increased access through down-scheduling is not considered an appropriate mechanism to address this issue.
- Consumer education and information is a better avenue to help overcome the stigma of ED and improve treatment rates.
- Although reticence to speak to GP about ED it not likely to be easier to speak to unknown pharmacists with whom there is no on-going relationship.
- Low public health benefit as access is still outweighed by risks.
- Men do not see GP often anyway, so any opportunity to review for holistic review is good.

In view of the reasons above the current scheduling of vardenafil is appropriate.

1.3. Ibuprofen combined with paracetamol

Referred scheduling proposal

An application was submitted to amend the Schedule 2 of ibuprofen combined with paracetamol to increase the pack size from 12 to 24 dosage units or less.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 2 – Amend Entry

PARACETAMOL for therapeutic use:

- a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than ~~12~~**24** dosage units per pack

The applicant's reasons for the proposal are:

- Paracetamol and ibuprofen packed separately have been classified for many years as 'unscheduled' in packs of up to 24 dose units and as Schedule 2 in packs of up to 100 dose units. Two paracetamol/ibuprofen combination products have been approved by TGA and are currently marketed in Australia:

- Combination tablet 1 (paracetamol 500 mg with ibuprofen 150 mg) approved on 23 December 2013; and
- Combination tablet 2 (paracetamol 500 mg with ibuprofen 200 mg) approved on 4 July 2014.
- Fixed dose combinations of paracetamol and ibuprofen offer greater analgaesic efficacy at a lower dose while maintaining the acceptable safety profile of each active alone. These combination products are a logical replacement for codeine/paracetamol and codeine/ibuprofen combinations as noted in the Scheduling Delegate's interim decision in relation to codeine on 1 Oct 2015:

“The combination of two non-opioid analgaesics (ibuprofen plus paracetamol) appears to be more effective than the codeine-containing analgaesics (CCAs), with a number needed to treat (NNT) of 1.5. This combination would fill any gap left by the unavailability of CCAs over the counter, giving consumers access to a more effective analgaesic without requiring a prescription and without the risks of the marked variability in pharmacokinetics or abuse potential that are associated with codeine”.
- However, the current 12 dose units pack size limit provides a significant incentive in terms of convenience and price for consumers to purchase separate packs of paracetamol and ibuprofen (20 tablets of paracetamol or 25 tablets of ibuprofen in the supermarket or 100 tablets of each in the pharmacy) then take them together.
- The problem with this approach is that the recommended daily doses of the separate analgaesics are higher (paracetamol 4000 mg and ibuprofen 1200 mg separately vs paracetamol 1500 mg and ibuprofen 600 mg together). While some people may be aware of these differences and compensate accordingly, others may be exposed to unnecessarily high doses of analgaesic. The proposed increase in pack size will lessen the impact of this imbalance in availability of the substances when presented for sale separately and together.
- Estimated total cumulative exposure to the combination product from launch to 29 February 2016 worldwide is 10,160,928 patients. The 29 February 2016 PSUR concludes that post-marketing data for company products containing ibuprofen and paracetamol supports the good safety profile of the product with a low incidence of adverse events in relation to the estimated cumulative exposure, and that the risk-benefit balance for the company products containing ibuprofen and paracetamol remains positive.
- The benefit/risk equation for the proposed 24 dose unit pack in Schedule 2 is positive, based on closer consistency with the maximum pack sizes in separate products, a reduction in the incentive for people to use separate products concurrently and the very low incidence of post-market adverse event reports in New Zealand and worldwide.

Current scheduling status

Paracetamol

Paracetamol is currently listed in Schedules 2, 3 and 4 in the [Poisons Standard](#) as follows:

Schedule 4

PARACETAMOL:

- a) when combined with aspirin or salicylamide or any derivative of these substances except when separately specified in these Schedules;
- b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;
- c) in slow release tablets or capsules containing more than 665 mg paracetamol;
- d) in non-slow release tablets or capsules containing more than 500 mg paracetamol;

- e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
- f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in schedule 2;
- g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;
- h) for injection.

Schedule 3

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2.

Schedule 2

PARACETAMOL for therapeutic use:

- a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or
- b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or
- d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or
- e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or
- f) in other preparations **except**:
 - i) when included in Schedule 3 or 4; or
 - ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaifenesin or when combined with effervescent agents) when:
 - (A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules,
 - (B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,
 - (C) not labelled for the treatment of children 6 years of age or less, and
 - (D) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaifenesin; or

iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

- (A) packed in blister or strip packaging or in a container with a child-resistant closure,
- (B) in a primary pack containing not more than 20 tablets or capsules,
- (C) compliant with the requirements of the Required Advisory Statements for Medicine Labels,
- (D) not labelled for the treatment of children 6 years of age or less, and
- (E) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaifenesin.

It is also included under the entry PARACETAMOL in Appendix F with the following statements:

Appendix F, Part 3

PARACETAMOL

Warning Statements: 97 (Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor) AND/OR 98 (Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor), 99 (If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage), 100 (Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist).

Ibuprofen

Ibuprofen is currently listed in Schedules 2, 3 and 4 of the [Poisons Standard](#) as follows:

Schedule 4

IBUPROFEN except:

- a) when included in or expressly excluded from Schedule 2 or 3; or
- b) in preparations for dermal use.

Schedule 3

IBUPROFEN in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units when labelled:

- a) with a recommended daily dose of 1200 mg or less of ibuprofen; and
- b) not for the treatment of children under 12 years of age;

except when included in or expressly excluded from Schedule 2.

Schedule 2

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:

- a) in liquid preparations when sold in the manufacturer's original pack containing 8 g or less of ibuprofen; or

- b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:
- i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent);
 - ii) packed in blister or strip packaging or in a container with a child-resistant closure;
 - iii) in a primary pack containing not more than 25 dosage units;
 - iv) compliant with the requirements of the Required Advisory Statements for Medicine Labels;
 - v) not labelled for the treatment of children 6 years of age or less; and
 - vi) not labelled for the treatment of children under 12 years of age when combined with phenylephrine.

It is also included under the entry IBUPROFEN in Appendix F with the following statements:

Appendix F, Part 3

IBUPROFEN

Warning Statement:

101: Don't use [this product/name of the product]:

If you have a stomach ulcer.

In the last 3 months of pregnancy. [This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.]

If you are allergic to (name of substance) or anti-inflammatory medicines

104: Unless a doctor has told you to, don't use [*this product/name of the product*]:

For more than a few days at a time.

With other medicines containing (name of substance) or other anti-inflammatory medicines.

If you have asthma.

If you are pregnant. [*This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.*]

Relevant scheduling history

Paracetamol and ibuprofen individually have a long scheduling history. Only the relevant scheduling history for paracetamol/ibuprofen combinations is presented below.

Paracetamol/ibuprofen combinations

In June 2010 the National Drugs and Poisons Scheduling Committee (NDPSC) considered the scheduling of a combination of ibuprofen and paracetamol and agreed that the current scheduling remained appropriate - Schedule 2 for combinations of up to 200 mg ibuprofen and 500 mg paracetamol in packs of up to 100 dosage units.

In February 2011, the Advisory Committee on Medicines Scheduling (ACMS) considered a proposal from the Advisory Committee on Non-prescription Medicines (ACNM) that the delegate/ACMS consider up-scheduling paracetamol/ibuprofen combinations (containing up to 500 mg paracetamol/200 mg ibuprofen) from Schedule 2 to Schedule 3. The ACNM had also recommended

consideration of a maximum pack size for Schedule 3 paracetamol/ibuprofen combinations. The ACNM, in an assessment of an application to register a combination paracetamol/ibuprofen product, had raised concerns that the sponsor had not satisfactorily established the safety of the product, and considered that pharmacist intervention was needed to assist consumers with safe use of the combination. The ACMS recommended that the combination paracetamol/ibuprofen products that were in Schedule 2 should be rescheduled to Schedule 3, when in packs containing 30 dosage units or less, with larger packs to be included in Schedule 4. The delegate agreed with the ACMS advice and in September 2011 the Poison Standard was amended to move 'paracetamol combined with ibuprofen' to Schedule 3 in pack sizes of 30 units or less and Schedule 4 (all other products).

In October 2012, the ACMS considered proposals to reschedule paracetamol 500 mg when combined with ibuprofen 200 mg from Schedule 3 to Schedule 2 in packs containing 12 dosage units or less, and to also include Schedule 3 paracetamol when combined with ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol in combination with ibuprofen remained appropriate, and that paracetamol in combination with ibuprofen should not be included in Appendix H. The reasons for opposing rescheduling to Schedule 2 included insufficient data to disprove the safety concerns with the combination, lack of evidence to support rescheduling, lack of long-term evidence of safety of the combination, potential for additive gastrointestinal side effects, potential for inadvertent misuse and no experience with use of paracetamol/ibuprofen combination products in Australia. The ACMS also considered that there were no public health benefits with inclusion of the combination in Appendix H, and that advertising could lead to inappropriate use. The delegate agreed with the ACMS advice.

In March 2015 the ACMS considered a proposal to create a new entry for paracetamol/ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol when combined with ibuprofen remains appropriate. The ACMS considered that the public health risk from advertising is that it would be seen as first line therapy and that there was little evidence to support the applicant claim that an Appendix H entry would transfer demand from codeine combination analgaesics to non-codeine combination analgaesics. The delegate agreed with the committee's advice.

In November 2015 the ACMS considered a proposal to amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less. The ACMS supported the proposal on the basis of the well-established safety profile, low risk diversion/abuse/addiction and that the medicine provides an effective option for short term use for moderate pain. Following an interim decision in alignment with committee advice and subsequent consideration of the submissions on the interim decision, the delegate decided to vary the interim decision. In view of the dosage levels of paracetamol and ibuprofen the delegate considered it is more appropriate to limit the Schedule 2 entry to 12 dosage units per pack rather than 3 days' supply packs as this would ensure the total paracetamol available in the pack would not be excessive. The implementation date was 1 June 2016.

Australian regulatory information

According to the [TGA Ingredient Database](#), paracetamol is available for use as an:

- Active ingredient in biologicals, export only, over-the-counter and prescription medicines; and
- Excipient ingredient in biologicals, devices and prescription medicines.

According to the [TGA Ingredient Database](#), ibuprofen is available for use as an:

- Active ingredient in biologicals, export only, over-the-counter and prescription medicines; and
- Excipient ingredient in biologicals, devices and prescription medicines.

The Australian Register of Therapeutic Goods (ARTG) has 836 entries for products containing paracetamol, and 250 entries for products containing ibuprofen listed. The products marketed vary in dose form, strength and quantity.

In the last 20 years there have been 3188 reported cases of adverse events related to paracetamol, and 1244 related to ibuprofen in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 1190 cases with the single suspected medicine being paracetamol with 120 cases reported death as the outcome, and 831 cases with the single suspected medicine being ibuprofen with 36 cases reported death as the outcome.

International regulations

One combination tablet (paracetamol 500 mg with ibuprofen 200 mg) was approved in the United Kingdom (Pharmacy medicine, 2010) and Poland (Pharmacy medicine, 2010). In New Zealand it was approved as a 'general sale' medicine in 2011 and in Australia it was listed on the ARTG in July 2014. It has also been approved as an over-the-counter medicine in Ukraine, Russia, Saudi Arabia, United Arab Emirates, Kuwait, Bahrain, Oman, Qatar and Yemen.

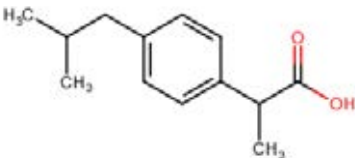
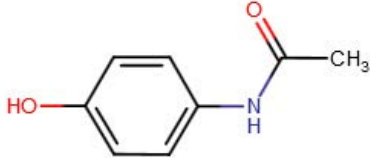
Another combination tablet (paracetamol 500 mg with ibuprofen 150 mg) was approved in New Zealand on 5 March 2009 and also listed on the ARTG in Australia on 23 December 2013.

Substance summary

Paracetamol is a *p*-aminophenol derivative that has analgaesic and antipyretic effects and has weak anti-inflammatory activity. It has been available in Australia since the 1970s and is marketed in many OTC medicine brands. Like ibuprofen it is indicated for the management of mild to moderate pain in conditions such as period pain, headache, muscular pain, dental pain, cold and flu symptoms, back pain, rheumatic pain and sinus pain and to reduce fever.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used as an OTC medicine in the management of mild to moderate pain and inflammation in conditions such as period pain, headache, muscular pain, dental pain, cold and flu symptoms, back pain, arthritic pain and sinus pain. It is also used to reduce fever.

Table 1.3.1: Chemical properties of ibuprofen and paracetamol

Property	Ibuprofen	Paracetamol
CAS number	15687-27-1	103-90-2
Chemical structure		
Molecular formula	C ₁₃ H ₁₈ O ₂	C ₈ H ₉ NO ₂
Molecular weight	206.3 g/mol	151.2 g/mol
IUPAC, common and/or other names	(<i>RS</i>)-2-(4-(2-Methylpropyl)phenyl)propanoic acid (IUPAC); α-Methyl-4-(isobutyl)phenylacetic acid, (±)-2-(4-isobutylphenyl)propanoic acid; isobutylphenylpropionic acid.	<i>N</i> -(4-hydroxyphenyl)acetamide (IUPAC); 4'-Hydroxyacetanilide; 4-Acetamidophenol, <i>N</i> -Acetyl-4-aminophenol; <i>N</i> -acetyl- <i>p</i> -aminophenol (APAP); acetaminophen.

Pre-meeting public submissions

Three (3) submissions were received, one (1) in support and two (2) opposed.

Main points in support:

- Paracetamol and ibuprofen have a long history of use, and a well-documented, favourable safety profile.
- To avoid any unintentional overdose, the products should include specific labelling outlining the dose and any warnings, to facilitate its appropriate use.
- One submission noted that in New Zealand, combination paracetamol and ibuprofen products are suitable for general sale in packs of up to 20 dosage units.

Main points opposed:

- Combination ibuprofen/paracetamol products are a relatively new product and there is still a large degree of patient confusion regarding appropriate dosing.
- Typically, consumers will choose a combined ibuprofen/paracetamol product to treat pain when a single ingredient analgesic is insufficient. These consumers should consult a pharmacist when requesting these combined products in a larger pack to investigate the potential for a more serious underlying cause.
- The availability of a larger pack size available as Schedule 2 will increase the probability of consumers self-managing more severe forms of pain.
- The risk of overdosing is high, and there is a need for ongoing patient education regarding the safe and appropriate use of these medicines.

The public submissions will be made available on the [TGA website](#).

Summary of ACMS advice to the delegate

The committee recommended that the current scheduling of ibuprofen combined with paracetamol remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- A risk of overdosing on ibuprofen and paracetamol and an increased risk of potential adverse effects if the pack size of ibuprofen combined with paracetamol is increased in Schedule 2 from 12 dosage units to 24. The risk is mitigated by maintaining a pack size of 12 dosage units in Schedule 2.
- Pharmacist advice is likely to be significantly reduced if the pack size is increased from 12 to 24 dosage units in Schedule 2. Pharmacist intervention is required to manage acute pain, including inflammation and/or aches and pains associated with colds and flu. The current pack size of 12 dosage units is sufficient for initial use of combination analgesia, given that the combination is only to be used for a few days.
- An increased risk of potential delay in consumers seeking health practitioner advice, confusion in the market and potential increase in duration of inappropriate use if the pack size is increased to 24 dosage units in Schedule 2.

- Adverse events of ibuprofen combined with paracetamol can be potentially severe. The adverse effects are liver damage, gastric ulcers, gastrointestinal bleeding, anaemia and melaena.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is that the current scheduling of ibuprofen combined with paracetamol remains appropriate.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

(a) the risks and benefits of the use of a substance:

- A risk of overdosing on ibuprofen and paracetamol and an increased risk of potential adverse effects if the pack size of ibuprofen combined with paracetamol is increased in Schedule 2 from 12 dosage units to 24. This risk is mitigated by maintaining the small pack size in Schedule 2.
- NPSMedicineWISE report that the NSW Poisons Information Centre has recorded a marked increase in calls about possible dosing errors with new combination paracetamol ibuprofen pain relievers since mid-2016.
- Pharmacist advice is likely to be significantly reduced if the pack size is increased from 12 to 24 dosage units in Schedule 2. Pharmacist intervention is required to manage acute pain, including inflammation and/or aches and pains associated with colds and flu. The current pack size of 12 dosage units is sufficient for initial use of combination analgesia, given that the combination is only to be used for a few days.
- An increased risk of potential delay in consumers seeking health practitioner advice, confusion in the market and potential increase in duration of inappropriate use if the pack size is increased to 24 dosage units in Schedule 2.
- Potential increase in duration of inappropriate use.
- The small pack sizes might mitigate the risk and encourages consumers to have conversation with pharmacist.

(b) the purposes for which a substance is to be used and the extent of use of a substance:

- Same as for current 12 unit pack size.

(c) the toxicity of a substance:

- A 24 pack size increases the risk of harm from overdose (12 g paracetamol and 3600 to 4800 mg ibuprofen).
- Adverse events of ibuprofen combined with paracetamol can be potentially severe. The potential adverse effects are liver damage, gastric ulcers, gastrointestinal bleeding, anaemia and melaena.

(d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Current pack of 12 dosage units is sufficient for initial use of combination analgesia.
- Need to maintain the maximum duration of 3 days statement.

(f) any other matters that the Secretary considers necessary to protect public health:

- Risk of consumer confusion in the market.
- Pharmacist intervention is required to deal with different types of pain.

1.4. Esomeprazole

Referred scheduling proposal

An application was submitted to down-schedule esomeprazole from Schedule 3 to Schedule 2 of the Poisons Standard in oral preparations containing 20 mg or less per dosage unit in packs containing not more than 14 days' supply and to delete the current Schedule 3 entry for esomeprazole.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 4 – Amend Entry

ESOMEPRAZOLE **except** when included in Schedule 2 ~~or 3~~.

Schedule 3 – Delete Entry

~~ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days supply.~~

Schedule 2 – Amend Entry

ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than ~~7~~**14** days supply.

The applicant's reasons for the proposal are:

- Increasing the pack size limit of Schedule 2 esomeprazole from 7 to 14 days' supply will result in improved access to a safe and effective 14-day proton pump inhibitor (PPI) treatment course which is recommended as the initial therapy for frequent heartburn sufferers.
- For over 2 years, consumers in other comparable overseas countries such as the UK and US have been able to self-select 14 days' supply of PPIs. It would be appropriate for consumers in Australia to be afforded similar access to an effective treatment course within the pharmacy setting where support and advice from a pharmacist can be still be accessed as needed.
- Ranitidine, a histamine 2 receptor antagonist (H2RA) is currently available from the pharmacy for self-selection in packs containing 14 days' supply. Tolerance can develop with H2RAs resulting in a

diminished therapeutic effect with continued administration, and resistance to increased doses of this class of medications.

- H2RAs are inferior in the inhibition of food stimulated acid secretion. In fact, only 15% of gastro-oesophageal reflux disease (GORD) patients treated with H2RAs achieve complete symptom relief. Of note, an Australian-based population study shows that a significant number of frequent heartburn sufferers are not satisfied with their treatment outcomes on H2RAs.
- The limitations of H2RAs underscore the need to improve access to a more effective PPI treatment course aligned with that already available for ranitidine.
- A clinical study evaluating the efficacy and quality of life (QOL) impact of a daily dose esomeprazole 20 mg clearly demonstrated that at this strength and dosing frequency, there are significant benefits regarding relief/reduction of both the frequency and severity of heartburn and acid regurgitation.
- Importantly, an improved QOL outcome (improved sleep quality, work productivity and functionality) resulting from the effective relief of the symptoms of heartburn and acid reflux was also clearly demonstrated.
- An Australian survey recently undertaken revealed that a significant proportion of consumers (61%) who purchased a 7-day pack of esomeprazole needed to be treated for longer than 7 days and had to go back to the pharmacy to obtain another pack. As a result, consumers are not currently afforded appropriate access to the recommended 14-day treatment regimen as initial therapy. The inconvenience of having to return to the pharmacy to purchase another pack may potentially result in less than optimal therapy for those who require 14-day treatment as initial therapy.
- Access to the 14-tablet pack of esomeprazole will be more cost-effective and convenient than access to two of the 7-tablet pack on separate occasions, for consumers requiring 14-day treatment as initial therapy.

Current scheduling status and relevant scheduling history

Esomeprazole is currently listed in Schedules 2, 3 and 4 of the [Poisons Standard](#) as follows:

Schedule 4

ESOMEPRAZOLE **except** when included in Schedule 2 or 3.

Schedule 3

ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply **except** when in Schedule 2.

Schedule 2

ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

Appendix H

ESOMEPRAZOLE.

In November 2000, the National Drugs and Poisons Committee (NDPSC) considered a proposal to schedule esomeprazole in Schedule 4 of the Poison Standard. The committee supported this proposal based on esomeprazole being a new substance, and the indicated condition being one that requires medical management. The decision was further based on the grounds of harmonisation with New Zealand.

In November 2013, the Advisory Committee on Medicines Scheduling (ACMS) considered an application to down-schedule esomeprazole from Schedule 4 to Schedule 3 in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply. The ACMS recommended the delegate to down-schedule esomeprazole to Schedule 3, as requested.

In March 2015, the ACMS delegate accepted a proposal to include esomeprazole in Appendix H.

In August 2015, the ACMS considered a proposal to down-schedule esomeprazole in oral preparations containing 20 mg or less per dosage unit in packs containing not more than 7 days' supply from Schedule 3 to Schedule 2. The delegate supported the proposal, and down-scheduled as requested.

Australian regulatory information

According to the [TGA Ingredient Database](#), esomeprazole is available for use as an:

- Active ingredient in biologicals and prescription medicines;
- Excipient ingredient in biologicals, devices and prescription medicines; and
- Equivalent ingredient in prescription medicines.

Esomeprazole (and its salts) is listed in 142 products on the Australian Register of Therapeutic Goods (ARTG). The dose forms approved include tablets, enteric coated tablets, enteric capsules, sachets of enteric coated granules for oral suspension and powder for injection. The ARTG also includes a listing for a composite pack, containing clarithromycin tablets, amoxicillin capsules and esomeprazole tablets.

In the last 20 years there have been 731 adverse event reports listed on the [Database of Adverse Event Notifications - Medicines](#): 523 cases with a single suspected medicine and 13 cases of death as a reported outcome. In the cases where the single medicine suspected was esomeprazole, reactions included: affect lability, arthralgia, dyspnoea, malaise, paraesthesia, abdominal pain, diarrhoea, nausea, hypoglycaemia, insomnia, aggression, agitation, confusion, depression, suicide attempt.

International regulations

USA

The USA down-scheduled esomeprazole from a prescription medicine to an over-the-counter medicine in 20 mg delayed release capsules/tablets in 2014.

Canada

Health Canada regulated esomeprazole as a prescription medicine until August 2016 when the first over-the-counter product was registered, and indicated for the treatment of frequent heartburn (heartburn occurring on 2 or more days of the week). The 20 mg capsules are provided in bottles of 14, contained in a carton with 1, 2 (total 28 capsules) or 3 bottles (total of 42 capsules).

New Zealand

In New Zealand, Medsafe lists esomeprazole as a prescription and pharmacy only medicine. The conditions for pharmacy only use are *"in divided solid dosage forms for oral use containing 20 milligrams or less with a maximum daily dose of 20 milligrams for the short-term symptomatic relief of gastro-oesophageal reflux-like symptoms in sufferers aged 18 years and over when sold in the manufacturers original pack containing not more than seven dosage units"*.

United Kingdom

In 2014, the UK's government body The Medicines and Healthcare products Regulatory Agency (MHRA) reclassified esomeprazole from a pharmacy (P) medicine to a general sales list medicine

(GSL) in the UK for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

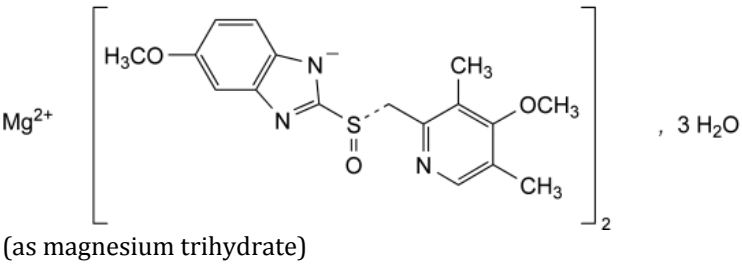
Substance summary

Esomeprazole is a proton pump inhibitor (PPI) and is the *S*-isomer of the PPI omeprazole. It is optically stable *in vivo*, with negligible conversion to the *R*-isomer. Esomeprazole reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H⁺, K⁺-ATPase proton pump in the parietal cell.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits both basal and stimulated acid secretion.

Esomeprazole is acid labile and is therefore formulated as gastro-resistant enteric-coated pellets of esomeprazole magnesium trihydrate in tablets, capsules or granules for oral suspension. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence, esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Table 1.4.1: Chemical properties of esomeprazole

Property	Esomeprazole
CAS number	217087-09-7 (as magnesium trihydrate)
Chemical structure	 <p>(as magnesium trihydrate)</p>
Molecular formula	C ₃₄ H ₃₆ N ₆ O ₆ S ₂ Mg.3H ₂ O (as magnesium trihydrate)
Molecular weight	767.2 g/mol (as magnesium trihydrate)
IUPAC and/or common and/or other names	di-(<i>S</i>)-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1 <i>H</i> -benzimidazole magnesium salt trihydrate

Pre-meeting public submissions

Five (5) submissions were received, two (2) in support and three (3) opposed.

Main points in support:

- The down-scheduling of a larger pack size will allow for better availability for non-prescription use via pharmacist advice.
- The side-effect profile of the medicine is well-known, and potential risk factors could be identified by the consumer through appropriate packaging and labelling. The quality use of the medicine can be facilitated through this same manner.
- The use of the medicine at established therapeutic dose levels is not likely to mask the symptoms of a serious condition or delay diagnosis.

- The inclusion of 14 days' supply of esomeprazole in Schedule 2 is consistent with current scheduling factors and comparable overseas regulations.

Main points opposed:

- The current arrangement as a Pharmacist Only Medicine allows the pharmacist to consider the therapeutic appropriateness of a 14 day treatment in the context of individual patient factors, and can recommend immediate referral if atypical or alarm symptoms are reported.
- It was flagged that the long term use of proton pump inhibitors (PPIs) is one of the top 5 tests, treatments or procedures which should be questioned by GPs and their patients. That statement is based on the evidence that a high proportion of patients are kept on maximal doses long term, and adverse effects of long term use include increased risk of gastrointestinal infection (incl. *Clostridium difficile*), community acquired pneumonia, osteoporotic fractures, interstitial nephritis, and nutritional deficiencies, particularly in the elderly or immunocompromised.
- Pharmacists are best-placed to identify risk factors and consider any lifestyle modifications that may enhance the outcomes of esomeprazole use.

The public submissions will be made available on the [TGA website](#).

Summary of ACMS advice to the delegate

The committee recommended that the Schedule 3 entry for esomeprazole in the Poisons Standard be deleted, and the Schedule 2 and Schedule 4 entries for esomeprazole be amended as follows:

Schedule 4 – Amend Entry

ESOMEPRAZOLE **except** when included in Schedule 2 ~~or 3~~.

Schedule 3 – Delete Entry

~~ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days supply.~~

Schedule 2 – Amend Entry

ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than ~~7~~**14** days' supply.

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- Esomeprazole is a safe and effective first line treatment for the common symptoms of GORD and heartburn.
- A 14 day supply of esomeprazole in Schedule 2 better reflects the appropriate initial treatment duration for GORD.
- The majority of adverse effects of esomeprazole are mild and transient in nature and the safety and tolerability is well-established. The toxicity is low when used for 14 days at 20 mg. The risks are primarily associated with longer term use.

- A decrease in pharmacist advice may result in underlying conditions being undiagnosed or an overuse of the medicine. However, there is still access to a pharmacist as the proposed product is in Schedule 2 and therefore available in a pharmacy.
- The proposed pack size, labelling (including RASML warning statements) and provision of CMI will help ensure appropriate use of the 14 day pack size as a Schedule 2 medicine. Available information does not suggest that over-the-counter proton pump inhibitors use that is consistent with label instructions is associated with substantial health risks.
- Esomeprazole is a more effective treatment of GORD than ranitidine, which is currently available as an unscheduled medicine (seven days' supply) and as a Schedule 2 medicine (fourteen days' supply).

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to down-schedule esomeprazole from Schedule 3 to Schedule 2 in oral preparations containing 20 mg or less per dosage unit in packs containing not more than 14 days' supply and to delete the current Schedule 3 entry. The proposed Schedule entry is:

Schedule 4 – Amend Entry

ESOMEPRAZOLE **except** when included in Schedule 2.

Schedule 3 – Delete Entry

Schedule 2 – Amend Entry

ESOMEPRAZOLE in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

(a) the risks and benefits of the use of a substance:

- Esomeprazole is a safe and effective first line treatment for the common symptoms of GORD and heartburn.

- Risks are primarily with longer term use.
- Risk with lack of pharmacist discussion and advice may result in underlying conditions being undiagnosed and overuse.
- Available information does not suggest that over-the-counter proton pump inhibitors use that is consistent with label instructions is associated with substantial health risks.
- Benefit is that a 14 day supply of esomeprazole in Schedule 2 better reflects the appropriate initial treatment duration for GORD.

(b) the purposes for which a substance is to be used and the extent of use of a substance:

- Heartburn and other symptoms of GORD are common.

(c) the toxicity of a substance:

- The safety and tolerability of esomeprazole are well-established. The majority of adverse events are mild and transient in nature. Esomeprazole has low toxicity when used for 14 days' treatment at a dose of 20 mg per day. The risks are primarily associated with longer term use.

(d) the dosage, formulation, labelling, packaging and presentation of a substance:

- The proposed pack size, labelling (including RASML warning statements) and provision of CMI will help ensure appropriate use of the 14 day pack size as a Schedule 2 medicine.

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

- Esomeprazole is more effective in the treatment of GORD than ranitidine which is currently available as an unscheduled medicine (seven days' supply) and as a Schedule 2 medicine (in a pack containing 14 days' supply).
- The available information does not suggest that over-the-counter proton pump inhibitor use that is consistent with label instructions is associated with substantial health risks.
- Although a decrease in pharmacist advice may result in underlying conditions being undiagnosed or an overuse of the medicine. There is still access to advice from a pharmacist if the product is purchased from a pharmacy.

1.5. Stiripentol

Referred scheduling proposal

A New Chemical Entity (NCE) delegate from the Therapeutic Goods Administration has referred the proposal to create a new Appendix K entry for stiripentol.

Scheduling application

The delegate's proposed amendments to the [Poisons Standard](#) are:

Appendix K – New Entry

STIRIPENTOL

The reason for the request is that stiripentol is an antiepileptic medicine capable of causing sedation.

Scheduling status and relevant scheduling history

The NCE delegate has determined that a new entry in Schedule 4 will be created for STIRIPENTOL, with an implementation date of **1 February 2018**.

There is no scheduling history available for stiripentol. This is the first committee presentation for this medicine.

Australian regulatory information

Stiripentol not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#).

According to the [TGA Ingredient Database](#), stiripentol is available for use as an:

- Active ingredient in export only and prescription medicines.

A search on the Australian Register of Therapeutic Goods (ARTG) confirmed no results for products containing stiripentol as this is an NCE.

In the last 20 years there have been no adverse event reports listed on the [Database of Adverse Event Notifications - Medicines](#) for stiripentol.

International regulations

Health Canada regulates stiripentol as a prescription medicine. Registered products include a 250 mg and 500 mg capsule, and 250 mg and 500 mg powders for oral suspension.

Medsafe New Zealand classifies stiripentol as a prescription medicine.

The European Commission granted a conditional marketing authorisation for stiripentol valid throughout the European Union in January 2007. This was updated to a full marketing authorisation in January 2014.

Substance summary

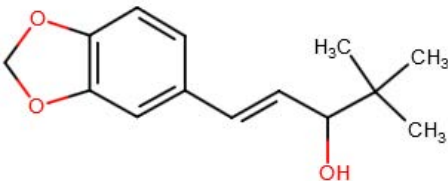
Stiripentol was designated as an orphan drug by the TGA in June 2016 for the treatment of severe myoclonic epilepsy in infancy.

Stiripentol is an antiepileptic intended for the treatment of severe myoclonic epilepsy in infancy (SMEI), also known as Dravet syndrome.

Stiripentol is a pentenol derivative with anticonvulsant activity in animals and antiepileptic efficacy in patients with Dravet syndrome. As with most anticonvulsants, the precise mechanism of action is unknown. However, it has been demonstrated that Stiripentol may increase γ -aminobutyric acid (GABA) levels in brain tissue by interfering with its reuptake and metabolism. Stiripentol has also been shown to improve the effectiveness of many other anticonvulsants (such as clobazam and valproate), possibly due to its inhibition of certain enzymes, slowing the drug's metabolism and increasing blood plasma concentrations. Stiripentol is an antiepileptic medicine capable of causing sedation.

It is chemically unrelated to other anticonvulsants and belongs to the group of aromatic allylic alcohols.

Table 1.5.1: Chemical properties of stiripentol

Property	Stiripentol
CAS number	49763-96-4
Chemical structure	
Molecular formula	C ₁₄ H ₁₈ O ₃
Molecular weight	234.3 g/mol
IUPAC and/or common and/or other names	(<i>RS</i>)-(<i>E</i>)-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol (IUPAC); Stiripentol (ANN and INN).

Pre-meeting public submissions

Two (2) submissions were received and both supported the proposal.

Main points in support:

- One submission outlined stiripentol's use in the management of epilepsy, with its main effect being exerted on the central nervous system, resulting in sedation.
- Stiripentol also enhances the central depressant effects of other substances, e.g. antipsychotics.

The public submissions will be made available on the [TGA website](#).

Summary of ACMS advice to the delegate

The committee recommended that an Appendix K entry is not required for stiripentol.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice were:

- Stiripentol is an anticonvulsant medicine used as an adjunct therapy in severe myoclonic epilepsy in infancy.
- There is not enough clinical evidence to suggest that stiripentol causes drowsiness when administered, even when added to clobazam.
- Stiripentol is not currently available in Australia as an active ingredient in a registered product.
- Stiripentol is a prescription medicine in overseas countries (NZ, UK, Europe, Canada, and Japan).

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is that an Appendix K entry is required for stiripentol. The proposed Schedule entry is:

Appendix K – New Entry

STIRIPENTOL

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are:

(a) the risks and benefits of the use of a substance:

- Stiripentol is an anticonvulsant medicine used as an adjunct therapy in severe myoclonic epilepsy in infancy.
- The Canadian Product Monograph in its Warning and Precautions section states:

In 2 double-blind, placebo-controlled studies, drowsiness/sleepiness was reported in up to 71% of patients receiving stiripentol. Patients and their caregivers should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating. Patients and their caregivers should be advised that patients treated with DIACOMIT should not operate machinery or drive until they have gained sufficient experience on DIACOMIT to assess whether it affects their mental and/or motor performance.

(b) the purposes for which a substance is to be used and the extent of use of a substance:

- As above (indicated only for treatment of severe myoclonic epilepsy in infancy). No use in Australia at all.
- No current registered products containing stiripentol in Australia.
- Stiripentol is a prescription medicine in overseas countries (NZ, UK, Europe, Canada, and Japan).

(c) the toxicity of a substance:

- The risk of drowsiness/sleepiness as identified in clinical trials.

(d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Currently not available in Australia as an active ingredient of any registered products.
- The scheduling delegate notes the NCE delegate's decision to create a new entry in Schedule 4 for stiripentol.

2. Joint meeting of the Advisory Committee on Chemicals and Medicines Scheduling (ACCS-ACMS #16 and ACCS-ACMS #15)

Summary of delegate's interim decisions

Substance	Interim Decision
Plasmid DNA Vaccine	<p>Schedule 4 – New Entry</p> <p>VACCINES - PLASMID DNA for animal use except when separately specified in these Schedules.</p> <p>Index – New Entry</p> <p>VACCINES - PLASMID DNA cross reference: PLASMID DNA (rE. coli DH5α pINGhT)</p> <p>Schedule 4</p> <p>The proposed implementation date is 1 February 2018.</p>
Quinine and its salts	<p>Schedule 6 – New Entry</p> <p>QUININE in cosmetic preparations except:</p> <ol style="list-style-type: none"> in rinse-off hair preparations containing 0.5 per cent or less of quinine; or in leave-on hair preparations containing 0.2 per cent or less of quinine. <p>Appendix F, Part 3 – New Entry</p> <p>QUININE</p> <p>Warning Statement: 28 (Repeated exposure may cause sensitisation).</p> <p>Index – Amend Entry</p> <p>QUININE cross reference: QUININE (CAS No. 130-95-0), QUININE SULFATE (1:1) (CAS No. 549-56-4), QUININE SULFATE (2:1) (CAS No. 804-63-7), QUININE SULFATE (2:1) DIHYDRATE (CAS No. 6119-70-6), QUININE SULFATE (1:1) HEPTAHYDRATE (CAS No. 6183-68-2), QUININE DIHYDROCHLORIDE (CAS No. 60-93-5), QUININE MONOHYDROCHLORIDE (CAS No. 130-89-2), QUININE HYDROCHLORIDE DIHYDRATE (CAS No. 6119-47-7), QUININE HYDROCHLORIDE (UNSPECIFIED) (CAS No. 7549-43-1)</p> <p>Schedule 7 Schedule 6 Schedule 5 Schedule 4 Appendix F, Part 3</p>

Substance	Interim Decision
	The proposed implementation date is 1 February 2018 .
Phenibut	<p>Schedule 9 – New Entry</p> <p>PHENIBUT.</p> <p>Index – New Entry</p> <p>PHENIBUT cross reference: BETA-PHENYL-GAMMA-AMINO BUTYRIC ACID</p> <p>Schedule 9</p> <p>The proposed implementation date is 1 February 2018.</p>
Docusate sodium	The delegate's interim decision is that the current Appendix B (7.1, any use) entry for docusate sodium in the Poisons Standard remains appropriate.
Vinyl acetate	<p>Schedule 6 – New Entry</p> <p>VINYL ACETATE MONOMER (excluding its derivatives) except:</p> <ul style="list-style-type: none"> a) in preparations for therapeutic use; or b) in preparations for domestic use containing 1 per cent or less of vinyl acetate; or c) in preparations containing 0.01 per cent or less of vinyl acetate as residual monomer in a polymer. <p>Appendix E, Part 2 – New Entry</p> <p>VINYL ACETATE</p> <p>Standard Statements: A (For advice, contact a Poisons Information Centre or a doctor); R1 (If inhaled, removed from contaminated area. Apply artificial respiration if not breathing).</p> <p>Appendix F, Part 3 – New Entry</p> <p>VINYL ACETATE</p> <p>Warning Statement: 11 (Vapour may be harmful).</p> <p>Safety Directions: 8 (Avoid breathing vapour); 9 (Use only in well ventilated area).</p> <p>The proposed implementation date is 1 June 2018.</p>
Methylisothiazolinone	<p>Schedule 6 – Amend Entry</p> <p>METHYLISOTHIAZOLINONE except:</p> <ul style="list-style-type: none"> a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.0015 per cent or less of methylisothiazolinone; or b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone.

Substance	Interim Decision
	The proposed implementation date is 1 June 2018 .
Epidermal growth factor	<p>Appendix G – New Entry</p> <p>Column 1 – Poison: EPIDERMAL GROWTH FACTOR Column 2 – Concentration (quantity per litre or kilogram): 10 micrograms</p> <p>Index – Amend Entry</p> <p>EPIDERMAL GROWTH FACTOR cross reference: SH-OLIGOPEPTIDE-1, RH-OLIGOPEPTIDE-1</p> <p>Schedule 7 Appendix G Appendix J, Part 2</p> <p>The proposed implementation date is 1 February 2018.</p>
Chloroacetamide	<p>Schedule 6 – New Entry</p> <p>CHLOROACETAMIDE</p> <ul style="list-style-type: none"> a) in preparations for cosmetic use; or b) in preparations for topical therapeutic use; or c) in other preparations containing more than 0.3 per cent of chloroacetamide. <p>Appendix E, Part 1 – New Entry</p> <p>CHLOROACETAMIDE</p> <p>Standard Statement: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)).</p> <p>Appendix F, Part 1 – New Entry</p> <p>CHLOROACETAMIDE</p> <p>Warning Statement: 28 (Repeated exposure may cause sensitisation).</p> <p>Safety Direction: 4 (Avoid contact with the skin).</p> <p>The proposed implementation date is 1 June 2018.</p>
Benzyl salicylate	<p>Schedule 6 – New Entry</p> <p>BENZYL SALICYLATE except:</p> <ul style="list-style-type: none"> a) in preparations intended for therapeutic use; or b) in domestic preparations: <ul style="list-style-type: none"> i) intended for skin contact containing 15 per cent or less of benzyl salicylate when included in the list of ingredients; or ii) not intended for direct skin contact when included in the list of ingredients; or

Substance	Interim Decision
	<p>c) in leave-on cosmetic and personal care preparations:</p> <p>i) containing 0.001 per cent or less of benzyl salicylate; or</p> <p>ii) when included in the list of ingredients; or</p> <p>d) in rinse-off cosmetic and personal care preparations:</p> <p>i) containing 0.01 per cent or less of benzyl salicylate; or</p> <p>ii) when included in the list of ingredients.</p> <p>The proposed implementation date is 1 June 2018.</p>
Cinnamaldehyde	<p>Schedule 6 – New Entry</p> <p>CINNAMALDEHYDE except:</p> <p>a) in preparations intended for therapeutic use; or</p> <p>b) in domestic preparations not intended for direct skin contact containing 0.4 per cent or less of cinnamaldehyde when included in the list of ingredients; or</p> <p>c) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of cinnamaldehyde; or</p> <p>d) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of cinnamaldehyde.</p> <p>The proposed implementation date is 1 June 2018.</p>
Anise alcohol	<p>Schedule 6 – New Entry</p> <p>ANISE ALCOHOL except:</p> <p>a) in preparations intended for therapeutic use; or</p> <p>b) in domestic preparations not intended for direct skin contact containing 5 per cent or less of anise alcohol when declared on the label; or</p> <p>c) in leave-on cosmetic and personal care preparations containing more than 0.001 and up to 2.5 per cent of anise alcohol when declared on the label and labelled with the following statement:</p> <p style="padding-left: 40px;">WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.</p> <p style="padding-left: 40px;">written in letters not less than 1.5 mm in height; or</p> <p>d) in rinse-off cosmetic and personal care preparations containing more than 0.01 and up to 5 per cent or less of anise alcohol when declared on the label and labelled with the following statement:</p> <p style="padding-left: 40px;">WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.</p> <p style="padding-left: 40px;">written in letters not less than 1.5 mm in height; or</p> <p>e) in leave-on cosmetic and personal care preparations containing</p>

Substance	Interim Decision
	<p>0.001 per cent or less of anise alcohol; or</p> <p>f) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of anise alcohol.</p> <p>Appendix E, Part 2 – New Entry</p> <p>ANISE ALCOHOL</p> <p>Standard Statement: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)).</p> <p>Appendix F, Part 3 – New Entry</p> <p>ANISE ALCOHOL</p> <p>Warning Statement: 28 ((Over) (Repeated) exposure may cause sensitisation).</p> <p>Safety Direction: 4 (Avoid contact with skin).</p> <p>The proposed implementation date is 1 February 2019.</p>
Resorcinol	<p>Schedule 6 – New Entry</p> <p>RESORCINOL except:</p> <p>a) in preparations for human therapeutic use; or</p> <p>b) in oxidative hair dye preparations containing 1.25 per cent or less of resorcinol after mixing for use when the immediate container and primary pack are labelled with the following statements:</p> <p style="padding-left: 40px;">KEEP OUT OF REACH OF CHILDREN, and</p> <p style="padding-left: 40px;">WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.</p> <p style="padding-left: 40px;">written in letters not less than 1.5 mm in height; or</p> <p>c) in oxidative eyelash and eyebrow dye preparations containing 1.25 per cent or less of resorcinol after mixing for use when the immediate container and primary pack are labelled with the following statements:</p> <p style="padding-left: 40px;">KEEP OUT OF REACH OF CHILDREN, and</p> <p style="padding-left: 40px;">WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.</p> <p style="padding-left: 40px;">written in letters not less than 1.5 mm in height; or</p> <p>d) in hair lotions/shampoo products containing 0.5 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statement:</p> <p style="padding-left: 40px;">WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.</p>

Substance	Interim Decision
	<p>written in letters not less than 1.5 mm in height.</p> <p>Appendix E, Part 2 – New Entry</p> <p>RESORCINOL</p> <p>Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.)</p> <p>Appendix F, Part 3 – New Entry</p> <p>RESORCINOL</p> <p>Warning Statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes)</p> <p>Safety Directions: 1 (Avoid contact with eyes), 3 (Wear eye protections when mixing or using), 4 (Avoid contact with skin)</p> <p>Index – New Entry</p> <p>RESORCINOL cross reference: 1,3-benzenediol</p> <p>Schedule 6 Appendix E, Part 2 Appendix F, Part 3</p> <p>The proposed implementation date is 1 February 2019.</p>
Trans-anethole	The delegate's interim decision is to defer the decision and refer the application back to the applicant.

2.1. Plasmid DNA Vaccine

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new entry for plasmid DNA (*rE. coli* DH5α pINGhT) in Schedule 4 of the Poisons Standard, with no exemption cut-off.

Scheduling application

This was a general application. The APVMA's proposed amendments to the [Poisons Standard](#) are:

Schedule 4 – New Entry

PLASMID DNA (*rE. coli* DH5α pINGhT).

The applicant's reasons for the request are:

- The proposed new product contains a new active constituent, plasmid DNA (*rE. coli* DH5α pINGhT) that expresses the gene coding for the full-length sequence of human

tyrosinase. It is designed to stimulate an immune response targeted at canine melanoma cells expressing tyrosinase. It is proposed for the vaccination of dogs with Stage II or III oral melanoma, for which local disease control has been achieved, to aid the extension of survival time.

- No specific toxicity studies or associated data on either the active constituent or the formulated product were submitted with the application. However, some relevant studies from published literature were submitted in response to questions from the APVMA. These studies involved the administration to both humans and other animal species, of vaccines that were the same as or similar to the proposed product. Additionally, there were studies on other relevant DNA vaccines. Data from these studies suggested that the proposed product vaccine is unlikely to be associated with any significant toxic effects in humans.
- The product is a therapeutic vaccine that is applied by a spring powered device that does not require the use of needles. This technology has the potential to make the administration of medicine safer as well as efficient and convenient. Post-application exposure is likely to be negligible. Any residual vaccine on the skin surface is likely to be very small. The needle free device means that there are no needles that require disposal. However, the use of this canine transdermal device requires trained personnel.
- As the amounts of DNA injected are small (about 110 µg), treatment is systemic (IM administration), the DNA will not replicate in the body of the injected animal or be excreted intact, no exposure is anticipated to occur during re-handling. As DNA is a normal component of the body, its breakdown products are not toxic, so urine/faeces of the injected animal will not contain hazardous substances arising from vaccination.
- The applicant has requested scheduling as Schedule 4 Prescription animal remedy because of precedence of other vaccines in the Poisons Standard.

Current scheduling status and relevant scheduling history

Plasmid DNA (*rE. coli* DH5α pINGhT) is not specifically captured in the current [Poisons Standard](#). The proposed use for Plasmid DNA (*rE. coli* DH5α pINGhT) is as an active in a veterinary vaccine for canine melanoma. The Poisons Standard has a Schedule 4 entry for veterinary live virus vaccines as follows:

Schedule 4

VACCINES, veterinary live virus **except**:

- a) poultry vaccines;
- b) pigeon pox vaccine; or
- c) scabby mouth vaccine.

Plasmid DNA (*rE. coli* DH5α pINGhT) is not captured by any group entry (including the entry for vaccines, veterinary live viruses above) as it is not a live virus and does not meet the exemptions for the Schedule 4 entry for veterinary live viruses.

Australian regulatory information

Plasmid DNA vaccine has not been previously considered for scheduling. Therefore, a scheduling history is not available.

International regulations

USA

The USDA Animal and Plant Health Inspection Service approved the canine melanoma vaccine in the USA in March 2007.

In November 2007, FDA issued a guidance document, "[Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications](#)" to assist the developers of DNA vaccines. This document supersedes the 1996 "*Points to Consider on Plasmid DNA Vaccines for Preventive Infectious Disease Indications*" document, which delineated the manufacturing, preclinical, and clinical issues relevant to the development of DNA vaccines, and described potential safety concerns that the Centre for Biologics Evaluation and Research (CBER) recommended vaccine developers address prior to the initiation of phase 1 clinical studies. The recommendations involving DNA vaccine manufacture and testing provided in that document were based on experience with other types of vaccines and DNA-based products, including gene therapy agents.

In this time, the FDA has permitted the initiation of phase 1 clinical studies of DNA vaccines for a number of infectious diseases indications including malaria, hepatitis B, and human immunodeficiency virus (HIV). The initiation of phase 1 clinical studies is predicated on the manufacturers and/or sponsors of vaccine clinical studies documenting the quality and consistency of plasmid manufacture, combined with extensive preclinical safety studies. Considerable preclinical and clinical experience on plasmid DNA vaccines has been accumulated since the issuance of the 1996 Points to Consider document. This experience was taken into consideration in revising recommendations concerning preclinical testing of DNA vaccines.

Canada

In 2011, the Canadian Centre for Veterinary Biologicals (CCVB), based on assessment of available information, concluded that the importation and use of Canine Melanoma Vaccine in Canada would not be expected to have any significant adverse environmental effect when manufactured and tested, and used according to label directions.

The Permit to Import Veterinary Biologics was amended to allow the importation and distribution of a product containing plasmid DNA in Canada.

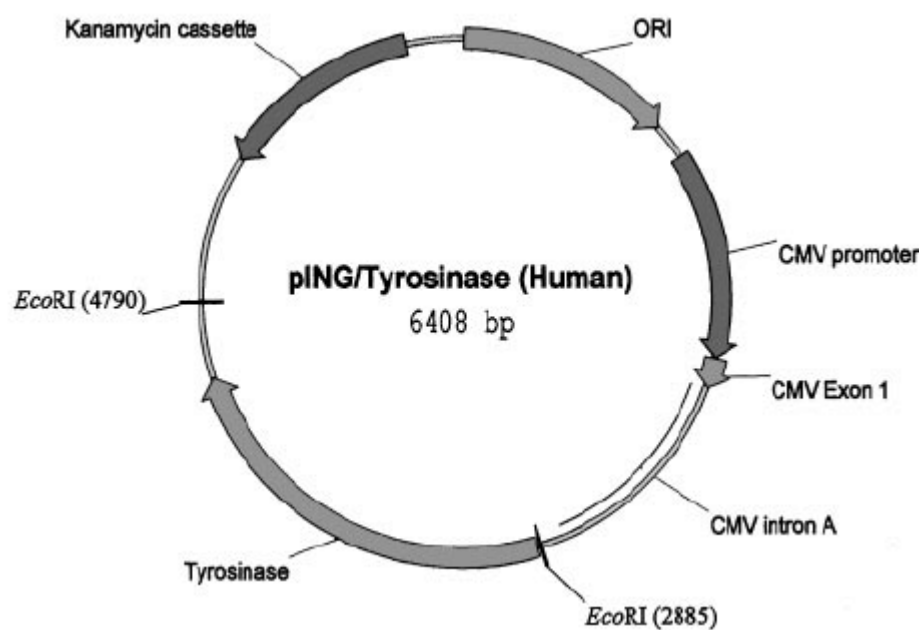
The [Canine Melanoma Vaccine, DNA - Environmental Assessment](#) is available on the Canadian Food Inspection Agency website.

Substance summary

DNA vaccines are defined by the Canadian Food Inspection Agency as highly purified plasmid preparations containing one or more DNA sequences capable of inducing and/or promoting an immune response against a pathogen. Typically, these plasmids possess DNA sequences necessary for selection and replication in bacteria. Additionally, these contain eukaryotic promoters and enhancers as well as transcription termination/-polyadenylation sequences to promote gene expression in vaccine recipients, and may contain immunomodulatory elements.⁴

⁴ [Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications](#) (Centre for Biologics Evaluation and Research, Food and Drug Administration).

Table 2.1.1: Chemical information for Plasmid DNA Vaccine

Property	Plasmid DNA Vaccine
Plasmid map of pING/hT plasmid used in ONCEPT	 <p>The diagram is a circular plasmid map for pING/Tyrosinase (Human), which is 6408 bp in size. Starting from the top and moving clockwise, the components are: a Kanamycin cassette, an ORI (origin of replication), a CMV promoter, CMV Exon 1, CMV intron A, the Tyrosinase gene, and two EcoRI restriction sites at 4790 and 2885 bp. The Tyrosinase gene is represented by a thick grey arc.</p>
IUPAC and/or common and/or other names	Plasmid DNA (rE. coli DH5α pINGhT)

Acute toxicity

No specific toxicity studies or associated data on either the active constituent were submitted with the application.

The applicant contends that both the non-living and highly purified nature of the plasmid constituent make it unlikely to be of toxicological concern.

The vaccine does not contain a living organism/infectious agent and therefore does not suffer the issues that might be associated with a live attenuated vaccine.

Furthermore, given the highly purified nature of the plasmid constituent means there will not be toxicological issues associated with residual endotoxin, RNA, genomic DNA, protein, antibiotics or residual solvent.

Other potential safety issues associated with a DNA vaccine, including toxicity of the plasmid DNA, toxicity associated with expression of the encoded protein (including autoimmune disease), and the potential for a transformation event resulting from the integration of the plasmid DNA into chromosomal DNA, have been studied for various DNA vaccines.

Repeat-dose toxicity

Parker *et al.*, (1999)⁵ conducted a GLP repeat dose study on a plasmid DNA vaccine for malaria, VCL-2510, by the IM route (right thigh) in 7-week old CD-1 mice (10/sex/dose). VCL-2510 was administered at dose levels of 1, 10 and 100 µg DNA (50 µL dose volume) twice weekly for 4 weeks. Control mice (10/sex) received injections of phosphate buffered saline (PBS) (50 µL). Two additional (satellite) groups of 10 mice/sex received doses of 0 or 100 µg DNA and were used only for the

⁵ Parker, S.E., *et al.* (1999) Plasmid DNA malaria vaccine: tissue distribution and safety studies in mice and rats. *Human Gene Ther.* 10: 741-758.

analysis of anti-nuclear antibodies (ANA) and antibodies to double-stranded (ds) DNA. Half the main study animals and half the satellite animals were killed at 48 hours after the last dose, while the remaining half ('recovery animals') were killed at 30 days after the last dose. Animals were examined twice daily for morbidity and mortality, once daily for clinical signs of toxicity, while a more thorough (hands-on) examination was conducted once weekly throughout the study. Food intake and body weight were also monitored (presumably weekly). Ophthalmological examinations were conducted pre-dosing, and in the main study high dose and control groups on the day before sacrifice (i.e. 24 hours and 29 days post the last dose). Injection sites (main study animals) were examined pre-dosing and daily throughout the study and scored for erythema and eschar formation using a modified Draize scoring system of 1-3, and for oedema using a similar modified Draize scoring system of 0-3 (the site was shaved weekly to facilitate scoring). At each of the 2 sacrifice times, clinical chemistry, haematology, ANA, antibodies to dsDNA, gross necropsy (including organ weights) and histological examination (full range of tissues, but histological examination only on control and high dose animals) were conducted. The analysis for ANA used 2 pools of nuclear antigens:

- i) single-stranded DNA, SSA, SSB and Jo-1; and
- ii) dsDNA, ribonucleoprotein, histones, Sm, and Scl-70.

There were no treatment-related deaths and no clinical signs were observed. Food consumption and body weight gains were not affected by treatment. Ophthalmological examination and clinical chemistry and haematology analyses did not reveal an effect of treatment. There were no treatment-related necropsies or histopathological findings or changes in organ weights. In particular, there was no indication of an inflammatory response that was suggestive of induction of autoimmune disease. Also suggesting a lack of immune pathology was the lack of an effect of treatment on ANA and dsDNA antibodies, although large standard deviations were observed for the results of these parameters (including for control animals). No irritation (erythema or oedema) was observed by Draize scoring at the injection sites (Draize scores of 0 at all time points in all animals). Inflammation was observed histologically at the injection site in 3 treated (high dose) animals.

The same authors also conducted a GLP repeat dose study by the IM route (right thigh) in 15-19-week old New Zealand White rabbits (8/sex/dose) in which VCL-2510 was administered at dose levels of 0.15 and 0.45 mg DNA (0.5 mL dose volume) once weekly for 6 weeks. Control rabbits (8/sex) received injections of PBS (0.5 mL). Half the animals were killed at 48 hours after the last dose, while the remaining half ('recovery animals') were killed at 30 days after the last dose. Monitoring was as described for the mouse study, except that ophthalmological examination was not conducted on the recovery animals, clinical chemistry and haematology analyses were conducted on days 15, 30, 43 and 57, in addition to the days of sacrifice (38 and 66), and analyses for ANA and antibodies to dsDNA were conducted on the main study animals.

There were no treatment-related deaths, and no clinical signs were observed. Food consumption was not affected by treatment. Body weight gains were significantly increased in high-dose males over the study but this was not considered to be biologically significant. Clinical chemistry and haematology analyses did not reveal an effect of treatment, although there were increases (significant at some time points) in white blood cell count and lymphocytes in high-dose females that may have been indicative of an immune response to the malaria sporozoite protein. There were no adverse treatment-related ophthalmological effects, and no treatment-related necropsy or histopathological findings or changes in organ weights. In particular, there were no findings suggestive of induction of autoimmune disease. There was no effect of treatment on ANA or dsDNA antibodies, although (as with mice) large standard deviations were observed for the results of these parameters (including for control animals). No treatment-related irritation was observed by Draize scoring at the injection sites, although slight erythema and slight oedema (Draize scores of 1) were observed at similar incidences in the control and treated animals. Inflammation was observed histologically at the injection site at the 48 hour sacrifice in 3/10 treated animals and 1/10 control animals. Observation in humans Wolchok *et al.*, (2007) conducted a clinical trial of human and mouse tyrosinase DNA vaccines in a total of 18 human patients with stage III/IV melanoma. The human tyrosinase DNA vaccine was either the same or comparable to the proposed product. Half the patients received 3 mouse tyrosinase DNA injections

followed by 3 human tyrosinase DNA injections, while the remaining half received the same vaccines in the opposite sequence. The vaccines were given by IM injection in either the deltoid or gluteus muscles (using a needle-free delivery system) every 3 weeks, with injection sites rotated for each immunisation. Three dose levels (100, 500 and 1500 µg DNA/injection) were used, with patients in 3 dose cohorts (no intra-patient dose escalation). The use of both syngeneic and xenogeneic gene vaccines was chosen based on nonclinical observations in which the injection of a xenogeneic gene vaccine for priming, followed by the syngeneic gene vaccine as a booster, yielded better immune responses compared with a xenogeneic gene vaccine for all injections (Weber *et al.*, 1998). The mouse and human cDNAs were cloned and inserted in the pING vector. Injection site examinations, haematology and clinical chemistry analysis, and assessment of adverse events were conducted, but no further details were provided. However, no significant toxicities were observed, i.e. no patient developed a dose-limiting toxicity, defined as any event specified in the National Cancer Institute Toxicity Criteria (CTC v2) at grade 3 or 2 allergic/immunologic toxicity. Most toxicities were grade 1 injection site reactions. Fourteen patients (78%) had injection site reactions.

Positive CD8+ T-cell responses, measured using 2 methods, were observed in 7 of 18 patients at one or more post- vaccination time points by either method. Positive responses were observed at all 3 dose levels, generally in the period at least 3-weeks after the last vaccination, and did not appear to be affected by the sequence of xenogeneic/syngeneic vaccination.

IgG antibodies against tyrosinase were not detected (2 methods used), nor was any persistent elevation of anti-DNA antibodies observed.

Public exposure

The chance of accidental exposure in humans is low.

The main persons likely to be exposed to the proposed product would be qualified veterinarians who are experienced/trained in the administration of veterinary drugs, including the use of needle-free devices. The vaccine is packaged in single dose vials and will be administered under controlled conditions.

The proposed product is not for use in food producing animals, so there will be no exposure of the public to residues in food. From a risk assessment based on the provided data, in conjunction with an exposure assessment which indicated low potential exposure of humans to the vaccine, the APVMA concluded that the proposed use of the product would not be an undue health hazard to humans.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS-ACMS advice to the delegate

The committee recommended that a new Schedule 4 entry be created in the Poisons Standard for VACCINES – PLASMID DNA and a cross-reference in the Index to Plasmid DNA (*rE. coli* DH5α pINGhT) as follows:

Schedule 4 – New Entry

VACCINES – PLASMID DNA for animal use **except** when separately specified in these Schedules.

Index – New Entry

VACCINES – PLASMID DNA

cross reference: PLASMID DNA (*rE. coli* DH5α pINGhT)

Schedule 4

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- The vaccine is used in dogs with stage II or III oral melanoma. Melanomas account for 4% of the tumours seen in dogs. The prognosis for dogs with stage II or III oral melanoma is poor. Administration of the vaccine increase life expectancy for dogs with oral melanoma.
- The dosage of plasmid DNA (*rE. coli* DH5α pINGhT) in the vaccine is low, 110 µg per 0.4 mL dose and the number of doses administered is small.
- The vaccine is well tolerated by dogs.
- There is no evidence of dog-to-dog transmission of plasmid DNA (*rE. coli* DH5α pINGhT).
- Use of the vaccine is not expected to significantly contribute to the dissemination of genetic material encoding antibiotic resistance.
- The vaccine is not intended for use in food producing species.
- The vaccine plasmid is unable to replicate autonomously in a eukaryotic host cell.
- Published studies of bio-distribution of DNA vaccines indicate that intramuscular delivery does not result in long-term persistence of plasmid at ectopic sites.
- Adverse events seen in dogs treated with the vaccine include injection site reactions and transient hyperthermia.
- Toxicity to humans is not expected as it is likely there would be minimal exposure to the plasmid DNA during administration of the vaccine. There is even less chance of exposure when re-handling a dog that received the vaccine. There does not appear to be a significant risk of immune-system related adverse events.
- The vaccine does not contain an adjuvant.
- The vaccine would be administered using a needle-free device by veterinary practitioners who are familiar with this method of administration. The risk of adverse events related to unintentional exposure in humans (inadvertent self-injection or through handling a dog that has received the vaccine) is low.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 4 entry in the Poisons Standard for vaccines – plasmid DNA with a cross-reference in the index to plasmid DNA (*rE. coli* DH5α pINGhT). The proposed Schedule entry is:

Schedule 4 – New Entry

VACCINES – PLASMID DNA for animal use **except** when separately specified in these Schedules.

Index – New Entry

VACCINES – PLASMID DNA

cross reference: PLASMID DNA (*rE. coli* DH5α pINGhT)

Schedule 4

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

- The vaccine is used in dogs with stage II or III oral melanoma. Melanomas account for 4% of the tumours seen in dogs. The prognosis for dogs with stage II or III oral melanoma is poor. Administration of the vaccine may result in an increase in life expectancy for dogs with oral melanoma.
- The dosage of plasmid DNA (*rE. coli* DH5α pINGhT) in the vaccine is low, 110 µg per 0.4 mL dose and the number of doses administered is small.
- The vaccine is well tolerated by dogs.
- There is no evidence of dog-to-dog transmission of plasmid DNA (*rE. coli* DH5α pINGhT).
- Use of the vaccine is not expected to significantly contribute to the dissemination of genetic material encoding antibiotic resistance.
- The vaccine is not intended for use in food producing species.
- The vaccine plasmid is unable to replicate autonomously in a eukaryotic host cell.
- Published studies of bio-distribution of DNA vaccines indicate that intramuscular delivery does not result in long-term persistence of plasmid at ectopic sites.
- Adverse events seen in dogs treated with the vaccine include injection site reactions and transient hyperthermia.
- Toxicity to humans is not expected as it is likely there would be minimal exposure to the plasmid DNA during administration of the vaccine. There is even less chance of exposure when re-handling a dog that received the vaccine. There does not appear to be a significant risk of immune-system related adverse events.
- The vaccine does not contain an adjuvant.

- The vaccine would be administered using a needle-free device by veterinary practitioners who are familiar with this method of administration. The risk of adverse events related to unintentional exposure in humans (inadvertent self-injection or through handling a dog that has received the vaccine) is low.

2.2. Quinine and its salts

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new entry for quinine in Schedule 6 of the Poisons Standard, with exemption concentration cut-offs and skin sensitisation warning labels.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – New Entry

QUININE in hair preparations **except** when the maximum concentration in ready-for-use hair preparations is 0.5 per cent or less of quinine base in rinse-off products or 0.2 per cent or less of quinine base in leave-in products.

Appendix F, Part 3 – New Entry

QUININE

Warning Statement: **28 (Repeated exposure may cause sensitisation).**

The applicant's reasons for the request are:

- Quinine and its salts are skin sensitisers;
- Quinine and its salts have moderate acute oral toxicity;
- Quinine and its salts are reported to be used in cosmetic products overseas and are therefore likely to be used in similar products in Australia; and
- Quinine and its salts have international restrictions on their use - the maximum concentration allowed in ready-for-use hair preparations is 0.5% (as quinine base) in rinse-off products and 0.2% (as quinine base) in leave-on products.

Current scheduling status and relevant scheduling history

Quinine is currently listed in Schedules 4, 5 and 7 in the [Poisons Standard](#) as follows:

Schedule 7

QUININE for veterinary use **except** when included in Schedule 5.

Schedule 5

QUININE in preparations for veterinary use containing 1 per cent or less of quinine.

Schedule 4

QUININE for human therapeutic use **except** when the maximum recommended daily dose is 50 mg or less of quinine.

In March 1980, the Poisons Schedule Committee (PSC) considered a new entry in Schedule 3 for quinine after several cases of children's deaths due to accidental overdose. The committee decided to agree to this proposal.

In November 1985, the PSC discussed the need for additional warnings as accidental children's deaths were still occurring. The committee agreed and quinine was included in Appendix F, Part 1 - Warning Statements (21 – WARNING – May be fatal to children) and Part 2 - Poisons Required to be Labelled with Warning Statements (Quinine ... 21). This was amended to Appendix F, Part 1 (8 – WARNING – May be fatal to children) and Part 3 (Quinine ... 8) in the SUSDP No. 5 as part of amendments to that Appendix.

In November 1986 the DPSC agreed to an exemption of liquids containing 40 mg/L or less of quinine from Schedule 3. The committee did not support a proposal to remove the “warning – may be fatal to children” statement from paediatric products.

In May 1990, the DPSC discussed placing quinine and its salts in Schedule 4 following reports of fatal cases of thrombocytopenia. The committee agreed that there was insufficient specific data to warrant the up-schedule and decided the scheduling remains appropriate. It was noted that the committee recommended that the PSA educate pharmacists on the risks.

In August 1992, the DPSC discussed down-scheduling low-dose quinine to Schedule 2. However, due to the risks previously discussed, the committee agreed that the scheduling remains appropriate. The committee agreed to change the current Schedule 3 entry with the exemption of 40 mg/L or 40 mg/kg or less of quinine that exempts soft drinks and low dose liquid and solid homoeopathic preparations.

In May 1993, the DPSC again discussed down-scheduling quinine from Schedule 3 to Schedule 2 and agreed that due to the risks, the current scheduling remained appropriate.

In February 1996, the NDPSC recommended the rescheduling of quinine from Schedule 3 to Schedule 4 due to quinine's potential to cause thrombocytopenia and reports of haemolytic uraemic syndrome. This was agreed in the May 1996 NDPSC meeting, and the appropriate amendments to the Poisons Standard were made.

In May 1998, the NDPSC discussed down-scheduling individual dosage units containing 15 mg or less of quinine up to a maximum daily dose of 50 mg of quinine from Schedule 4 to Schedule 2. The committee discussed prior meetings decisions and agreed that the current scheduling remains appropriate.

In June 2005, the NDPSC approved quinine for veterinary use and placed it in Schedule 7 and Schedule 5.

In June 2006, the NDPSC agreed to amend the Schedule 4 entry on international harmonisation grounds. The committee agreed to amend the entry to reflect therapeutic use instead of internal use.

Australian regulatory information

Quinine is listed in the *Australia New Zealand Food Standards Code* in Schedules 15 and 19. Quinine has a maximum permitted level as a food additive (Schedule 15) and a maximum level as a natural toxicant (Schedule 19) of:

- 100 mg/kg in water based flavoured drinks (only in tonic, bitter and quinine drinks);
- 300 mg/kg in wine based drinks and reduced alcohol wines; and
- 300 mg/kg in other mixed alcoholic beverages not classified elsewhere.
- Quinine is listed in the Therapeutic Goods (Permissible Ingredients) Determination No. 3 of 2017 as follows:

Table 2.2.1: Permissible ingredients and requirements applying to quinine when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
4187	QUININE ARSENITE	H	Only for use as an active homoeopathic ingredient. Quinine is a mandatory component of Quinine arsenite. The maximum recommended daily dose must be no more than 50 mg of quinine.
4188	QUININE SULFATE DIHYDRATE	H	Only for use as an active homoeopathic ingredient. Quinine is a mandatory component of quinine sulfate dihydrate. The maximum recommended daily dose must be no more than 50 mg of quinine.

Quinine is listed in 4 products on the [Australian Register of Therapeutic Goods \(ARTG\)](#) as an active ingredient.

Quinine is in two veterinary medicines (fish tank anti-protozoal medication products) that contain 1% quinine and are captured by Schedule 5.

In the last 20 years, there have been 575 adverse events reports in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#); 334 cases with a single suspected medicine and 14 cases of death as a reported outcome.

According to the [TGA Ingredient Database](#), quinine is available for use as follows:

- Quinine is available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines;
- Quinine is available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines;
- Quinine is available for use as an Equivalent Ingredient in: Listed Medicines; and
- Quinine salts are available for use as an Active Ingredient or Excipient Ingredient in a range of areas, but not available as an Equivalent Ingredient.

International regulations

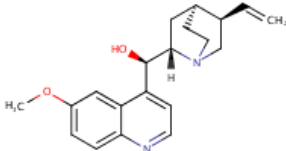
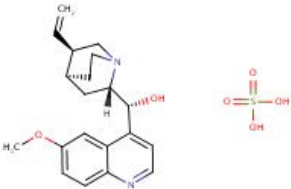
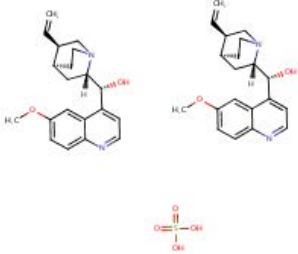
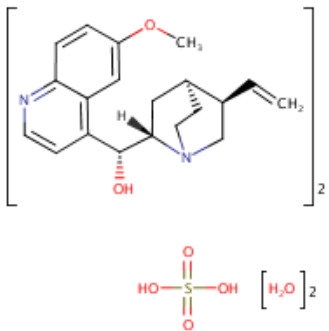
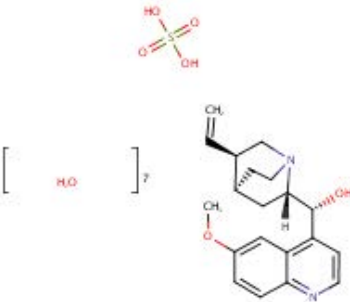
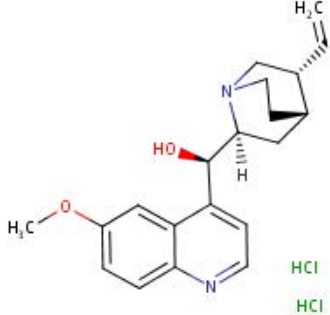
Quinine is currently listed in:

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down

For all of the above, the maximum concentration allowed in ready-for-use hair preparations is 0.5% (as quinine base) in rinse-off products and 0.2% (as quinine base) in leave-on products.

Substance summary

Quinine and its salts have key/expected uses in cosmetics, food flavourings, therapeutic and veterinary medicines.

 <p>130-95-0 quinine (INCI); cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)- (CAS); quinine anhydrous</p>	 <p>549-56-4 cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (1:1) (salt) (CAS); quinine sulfate (1:1)</p>	 <p>804-63-7 cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (2:1) (salt) (CAS); quinine sulfate (2:1)</p>
 <p>6119-70-6 methoxy-, (8.alpha.,9R)-, sulfate(2:1) (salt), dihydrate (CAS); quinine sulfate (2:1) dihydrate</p>	 <p>6183-68-2 cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (1:1) (salt), heptahydrate (CAS); quinine sulfate (1:1) heptahydrate</p>	 <p>60-93-5 cinchonan-9-ol, 6'-methoxy-, dihydrochloride, (8.alpha.,9R)- (CAS); quinine dihydrochloride</p>

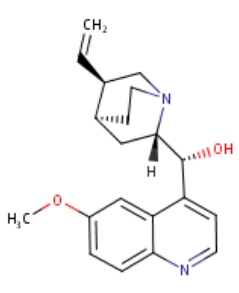

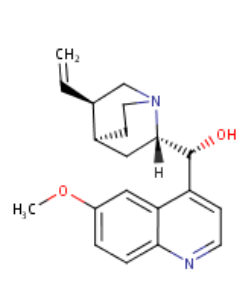
 <p>130-89-2</p> <p>cinchonan-9-ol, 6'-methoxy-, monohydrochloride, (8.alpha.,9R)- (CAS); quinine monohydrochloride</p>	 <p>6119-47-7</p> <p>cinchonan-9-ol, 6'-methoxy-, monohydrochloride, dihydrate, (8.alpha.,9R)- (CAS); quinine hydrochloride dihydrate</p>	 <p>7549-43-1</p> <p>cinchonan-9-ol, 6'-methoxy-, hydrochloride, (8.alpha.,9R)- (CAS); quinine hydrochloride (unspecified)</p>
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Figure 2.2.1: Chemical structures, alternative names and CAS numbers for quinine and its salts

The following information was extracted from the [Human Health Tier II Assessment report for Quinine and its salts](#), publicly available from the NICNAS website.

Table 2.2.2: Acute toxicity end-points for Quinine

Toxicity	Species	Quinine	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Human Rat Rabbit Mouse Rat Guinea pig	29–114 mg/kg bw (quinine, CAS No. 130-95-0) 456 mg/kg bw, equivalent to 351 mg/kg bw quinine base (quinine sulfate (1:1), CAS No. 549-56-4) 641 mg/kg bw (quinine dihydrochloride, CAS No. 60-93-5) 660 mg/kg bw (quinine dihydrochloride, CAS No. 60-93-5) 1392 mg/kg bw (quinine dihydrochloride, CAS No. 60-93-5) 1800 mg/kg bw (quinine, CAS No. 130-95-0)	Schedule 6
Acute dermal toxicity LD ₅₀ (mg/kg bw)	N/A	No data available	N/A
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	N/A	No data available	N/A
Skin irritation	Guinea pig	Not irritating up to 25% concentration (quinine monohydrochloride, CAS No. 130-89-2)	N/A

Toxicity	Species	Quinine	SPF (2015) Classification
Eye irritation	<i>In vitro</i> bovine corneal opacity and permeability (BCOP) test method (OECD TG 437)	Not irritating up to 20% concentration (quinine, CAS No. 130-95-0), but further testing is required based on the outcome of this test	N/A
Skin sensitisation (Guinea pig maximisation test and human case reports)	Guinea pig Human	Sensitisation reactions observed in 80–95% of exposed animals, reported as a 'grade V allergen or potent contact allergen' (quinine monohydrochloride, CAS No. 130-89-2) Skin sensitisation in humans assessed by patch testing and oral challenge test	Schedule 6

Acute toxicity

Quinine and its salts are considered to have moderate acute oral toxicity in animals. No data are available for acute dermal and acute inhalation toxicity.

The reported oral median lethal dose (LD₅₀) values were:

- 1800 mg/kg bw in guinea pigs exposed to quinine;
- 641, 660 and 1392 mg/kg bw in rabbits, mice and rats, respectively, exposed to quinine dihydrochloride; and
- 456 mg/kg bw in rats exposed to quinine sulfate (1:1), which is reported to equate to 351 mg/kg bw quinine base.

In humans, ingestion of 2–8 g of quinine has been reported to be fatal in adults. This equates to a dose of approximately 29–114 mg/kg bw in a 70 kg person.

Irritation

Quinine and its salts are not considered to cause skin irritation at concentrations up to 25%.

For eye irritation, only *in vitro* data are available and the outcome is that no prediction of eye irritancy can be made without additional testing.

Sensitisation

Quinine and its salts are considered to cause skin sensitisation.

In a guinea pig maximisation test conducted similar to OECD TG 406, animals (n = 20/group) were exposed to quinine hydrochloride at 0.25% in distilled water for intradermal induction; pre-treated with sodium lauryl sulfate before being exposed to quinine hydrochloride at 20% in petrolatum for epicutaneous induction; and challenged 21 days later with 1, 5 or 10% quinine hydrochloride in petrolatum by topical application for 24 and 48 hours. Quinine was reported to be a grade V allergen or potent contact allergen, since sensitisation was observed in 80–95% of animals exposed to quinine at 5 or 10% at both 24 and 48 hour time-points.

Observation in humans

Human case reports support the potential for skin sensitisation.

In five case studies in males (aged 25 – 40 years), exposure to quinine (indirectly from a contraceptive pessary used by their wives, which contained quinine, or directly through use of a hair lotion that contained quinine or via consumption of bitter flavoured beverages) caused present or past contact dermatitis (skin rash and inflammation). Patch testing using 1% quinine sulfate (n = 1) or 2% quinine sulfate (n = 4) resulted in positive reactions in all patients, confirming that quinine is a contact allergen.

Recurrent contact dermatitis was reported in a 15-month old child exposed on the upper chest for three months to a topical respiratory decongestion balm. Patch testing confirmed an allergy to quinine, one of the components of the topical balm.

In a 26-year old man, examination of asymptomatic swelling and redness led to a fixed eruption diagnosis (adverse skin reaction), secondary to quinine consumption of tonic beverages. An oral challenge test using tonic water, and a patch test using 1% quinine hydrochloride were both positive. Severe redness and swelling of the lips was observed four days after the man drank tonic water; a large blister with redness was observed at the patch test site two days after exposure to quinine hydrochloride. Eleven other cases (n = 6 males, n = 5 females, 23–57 years old) of fixed eruption attributed to quinine in tonic beverages have also been reported and confirmed by oral challenges or patch testing.

Other hypersensitivity reactions have also been reported in humans, including anaphylactic shock, anaphylactoid reactions, urticaria (hives, upper dermis swelling), angio-oedema (swelling below the dermis layer), serious skin rashes, facial swelling, bronchospasm and pruritus (severe skin itching).

Irritant dermatitis was reported in process workers in a factory manufacturing quinine sulfate (1:1), but with potential exposure to up to 13 different quinine or quinidine (the stereoisomer of quinine) products. Employees with a current or past history of skin disorders were examined (n = 23, from a total of 73 employees), and skin disorders from 15 of the 23 employees were deemed to be work-related. Exposure to quinine was deemed the cause of skin disorders in 13 of the 15 work-related cases, with development of symptoms typically occurring 4 to 8 weeks post-exposure (range 2 weeks to 8 months). However, negative results were observed during patch testing and medical opinion based on clinical examination suggested that the effects were caused by irritation, rather than allergy. For the majority of workers, the effects were reversed following cessation of exposure, or spontaneously cleared even with continued exposure.

Repeat-dose toxicity

Quinine and its salts are not considered to cause serious systemic health effects from repeated oral exposure. No data are available for repeated dermal and repeated inhalation exposure.

Genotoxicity

Quinine and its salts are not considered to be genotoxic.

Carcinogenicity

The available data are insufficient to derive a conclusion on carcinogenicity of quinine and its salts.

Reproduction and developmental toxicity

Quinine and its salts are not expected to cause developmental toxicity. The limited available data in female rats and pregnant women indicate quinine and its salts have no reproductive toxicity in females, but no test data are available on males.

Public exposure

Although specific use in cosmetic products in Australia is not known, quinine and its salts are reported to be used in cosmetic products overseas as denaturants, hair conditioning agents, masking agents and fragrance ingredients.

Pre-meeting submissions

Three (3) public submissions were received, all in support of the proposal to align concentration limits for quinine and its salts with international (EU) standards.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that a new Schedule 6 entry for QUININE be created in the Poisons Standard as follows:

Schedule 6 – New Entry

QUININE in cosmetic preparations **except:**

- a) in rinse-off hair preparations containing 0.5 per cent or less of quinine; or
- b) in leave-on hair preparations containing 0.2 per cent or less of quinine.

Appendix F, Part 3 – New Entry

QUININE

Warning Statement: 28 (Repeated exposure may cause sensitisation).

Index – Amend Entry

QUININE

cross reference: QUININE (CAS No. 130-95-0), QUININE SULFATE (1:1) (CAS No. 549-56-4), QUININE SULFATE (2:1) (CAS No. 804-63-7), QUININE SULFATE (2:1) DIHYDRATE (CAS No. 6119-70-6), QUININE SULFATE (1:1) HEPTAHYDRATE (CAS No. 6183-68-2), QUININE DIHYDROCHLORIDE (CAS No. 60-93-5), QUININE MONOHYDROCHLORIDE (CAS No. 130-89-2), QUININE HYDROCHLORIDE DIHYDRATE (CAS No. 6119-47-7), QUININE HYDROCHLORIDE (UNSPECIFIED) (CAS No. 7549-43-1)

Schedule 7

Schedule 6

Schedule 5

Schedule 4

Appendix F, Part 3

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- The potential risks of quinine are skin sensitisation and moderate acute oral toxicity.
- Other than therapeutics and its use as a food additive, the only reported use of quinine is in hair cosmetics (both leave-on and rinse-off).

- No cosmetic products are reported to exceed the proposed cut-off concentrations of quinine or its salts. Schedule 6 would allow for appropriate labelling and packaging of the product to provide appropriate protections for users and consumers.
- The proposed exemption concentration cut-offs will align with the maximum permitted concentrations in comparable countries, many of which are among our major trading partners – EU, ASEAN and NZ.
- A Schedule 6 entry for quinine with ready for use cut-off levels (rinse-off products 0.5% and leave-in products 0.2%) would bring Australia in line with international restrictions on its use.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for quinine in the Poisons Standard. The proposed Schedule entry is as follows:

Schedule 6 – New Entry

QUININE in cosmetic preparations **except**:

- a) in rinse-off hair preparations containing 0.5 per cent or less of quinine; or
- b) in leave-on hair preparations containing 0.2 per cent or less of quinine.

Appendix F, Part 3 – New Entry

QUININE

Warning Statement: 28 (Repeated exposure may cause sensitisation).

Index – Amend Entry

QUININE

cross reference: QUININE (CAS No. 130-95-0), QUININE SULFATE (1:1) (CAS No. 549-56-4), QUININE SULFATE (2:1) (CAS No. 804-63-7), QUININE SULFATE (2:1) DIHYDRATE (CAS No. 6119-70-6), QUININE SULFATE (1:1) HEPTAHYDRATE (CAS No. 6183-68-2), QUININE DIHYDROCHLORIDE (CAS No. 60-93-5), QUININE MONOHYDROCHLORIDE (CAS No. 130-89-2), QUININE HYDROCHLORIDE DIHYDRATE (CAS No. 6119-47-7), QUININE HYDROCHLORIDE (UNSPECIFIED) (CAS No. 7549-43-1)

Schedule 7

Schedule 6

Schedule 5

Schedule 4

Appendix F, Part 3

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

- The potential risks of quinine are skin sensitisation and moderate acute oral toxicity.
- Other than therapeutics and its use as a food additive, the only reported use of quinine is in hair cosmetics (both leave-on and rinse-off).
- No cosmetic products are reported to exceed the proposed cut-off concentrations of quinine or its salts. Schedule 6 would allow for appropriate labelling and packaging of the product to provide appropriate protections for users and consumers.
- The proposed exemption concentration cut-offs will align with the maximum permitted concentrations in comparable countries, many of which are among our major trading partners – EU, ASEAN and NZ.
- A Schedule 6 entry for quinine with ready for use cut-off levels (rinse-off products 0.5% and leave-in products 0.2%) would bring Australia in line with international restrictions on its use.

2.3. Phenibut

Referred scheduling proposal

A delegate from the Therapeutic Goods Administration has referred a scheduling proposal to create a new Schedule 9 or Schedule 4 with an Appendix D, Part 5 entry for phenibut in the Poisons Standard.

Scheduling application

This was a delegate initiated application. The delegate's proposed amendments to the [Poisons Standard](#) are:

Schedule 9 – New Entry

PHENIBUT.

OR

Schedule 4 – New Entry

PHENIBUT.

Appendix D, Part 5 – New Entry

PHENIBUT.

AND

Index – New Entry

PHENIBUT

cross reference: BETA-PHENYL-GAMMA-AMINO BUTYRIC ACID

Schedule 4/9

Appendix D, Part 1

The reasons for the request are:

- Case reports of significant toxicity have emerged, as well as evidence of dependence; and
- One state has raised concerns regarding the potential for tolerance and withdrawal symptoms from the use of Phenibut. Specific toxicity is related to these symptoms.

Current scheduling status and relevant scheduling history

Phenibut is currently not captured by any schedule entry in the current [Poisons Standard](#).

The pharmacologically similar substance, Baclofen, is in Schedule 4 and Appendix K of the current [Poisons Standard](#).

Phenibut has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Australian regulatory information

Phenibut is not listed as an ingredient in products on the [ARTG](#) and cannot be legally sold in Australia as a Therapeutic Good. However, information received from one Australian state health department indicates that phenibut is marketed to relieve anxiety and depression, improve sleep and enhance cognition.

Despite phenibut not being in products on the ARTG, the [Database of Adverse Events Notification \(DAEN\) - Medicines](#) has returned 1 report of an adverse event suspected to be related to phenibut in an unregistered product.

Phenibut is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#).

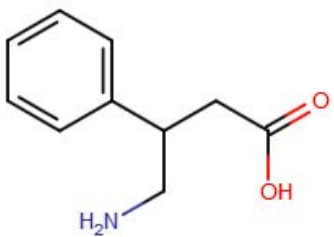
International regulations

No evidence of scheduling in New Zealand, EMA, US FDA or Canada.

Substance summary

Phenibut is a neuropsychotropic drug with anxiolytic and nootropic (cognition enhancing) effects. It acts as a GABA mimetic, primarily at GABA_B and to some extent at GABA_A receptors.

Table 2.3.1: Chemical information for phenibut

Property	Phenibut
Chemical structure	
Molecular formula	C ₁₀ H ₁₃ NO ₂
Molecular weight	179.2 g/mol
CAS number	1078-21-3

Property	Phenibut
IUPAC and/or common and/or other names	4-amino-3-phenylbutanoic acid (IUPAC); Commonly known as beta-phenyl-gamma-aminobutyric acid.

Pre-meeting public submissions

Eleven (11) public submissions were received, two (2) in support, eight (8) opposed (four (4) to the Schedule 9 proposal and four (4) showing some agreement with a Schedule 4 entry to allow access via a prescription) and one (1) did not state their position.

Main points in support:

- There are no established therapeutic uses for phenibut.
- In Australia there are confirmed cases of phenibut poisoning and an increase in the number of suspected cases of phenibut use, misuse and harm.
- Phenibut is marketed on the internet as a dietary supplement to treat anxiety and sleep disorders. However, there is strong evidence to indicate that it is predominantly used as a recreational drug.
- The medical conditions phenibut is reportedly being used to treat (including anxiety and sleep disorders) are better managed by a medical practitioner.
- Phenibut represents a significant risk of harm, including overdose (intentional and accidental). Complications of overdose include coma requiring admission to an Intensive Care Unit (ICU) for advanced life support.
- Withdrawal symptoms result when phenibut is stopped.
- No preference between Schedule 4/Appendix D or Schedule 9 was indicated in the submissions.

Main points opposed:

- Personal stories indicate that where other medicines have failed phenibut has:
 - provided improvement to sleep and symptoms of anxiety, depression, idiopathic hypersomnia and Post-Traumatic Stress Disorder (PTSD); and
 - been used to treat addiction to alcohol and benzodiazepine use.
- Claims that suppliers of phenibut provide adequate information on its safe use.
- Consumers have had no problems with toxicity or dependence and believe phenibut is very safe.
- Scheduling phenibut may cause an increase in alcohol consumption, use of stronger anti-anxiety medicines or black-market drug purchasing.
- Internationally phenibut is only regulated in Russia. No evidence for scheduling in other countries.
- Submissions indicate some preference for:
 - Schedule 4 without an appendix entry to allow access via a prescription; and
 - Schedule 3 to allow access by a pharmacist.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that new Schedule 9 and index entries be created in the Poisons Standard for phenibut as follows:

Schedule 9 – New Entry

PHENIBUT.

Index – New Entry

PHENIBUT

cross reference: BETA-PHENYL-GAMMA-AMINO BUTYRIC ACID

Schedule 9

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- Risks of phenibut include tolerance, dependence, abuse, accidental and intentional overdose resulting in significant toxicity requiring hospitalisation, with severity potentially requiring ICU admission.
- There are anecdotal reports of the therapeutic benefit of phenibut based on public submissions.
- Although phenibut is used therapeutically in Russia, the associated clinical trial literature is unable to be evaluated critically at this time due to translation issues. Furthermore, there has been no established therapeutic benefit of phenibut in regulatory comparable countries.
- Taking into consideration the danger to the health of individuals and of the community (both immediate and imminent) associated with the use of phenibut and the high risk of dependency, abuse, misuse and illicit, the perceived benefits (as indicated in public submissions) are substantially outweighed by the risks.
- The substance is not currently permitted in Australia to be marketed for therapeutic reasons but is widely available on the internet for purchase. International websites make significant therapeutic claims for cognition enhancement, anxiety and depressive disorders. Prevalence of use is not established but is clearly across the country and increasing.
- Phenibut is a neuropsychotropic drug with anxiolytic and cognition enhancing effects. It acts as a GABA mimetic, primarily at GABAB and to some extent at GABAA receptors. Published reports of ED presentations, acute intoxication with delirium, and dependence treated with baclofen. These reports include reports from Australia. Descriptions of withdrawal include tremors, anxiety, insomnia, hypertension, hyperhidrosis, psychosis, tachycardia, widening of QRS complex and convulsions. There is significant risk of harm. Effects include CNS depression, delirium, seizures – potentially requiring intubation and ventilation.
- Rapid development of tolerance and dependence with a withdrawal syndrome consisting of hallucinations, agitation, tremor, insomnia, abdominal pain, vomiting.
- The availability as a powder increases risks of toxicity.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create new Schedule 9 and index entry in the Poisons Standard for phenibut. The proposed Schedule entry is as follows:

Schedule 9 – New Entry

PHENIBUT.

Index – New Entry

PHENIBUT

cross reference: BETA-PHENYL-GAMMA-AMINO BUTYRIC ACID

Schedule 9

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

(a) the risks and benefits of the use of a substance:

- There are anecdotal reports of the therapeutic benefit of phenibut based on public submissions.
- Although phenibut is used therapeutically in Russia, the associated clinical trial literature is unable to be evaluated critically at this time due to translation issues. Furthermore, there has been no established therapeutic benefit of phenibut in regulatory comparable countries.
- International websites make significant therapeutic claims for cognition enhancement, anxiety and depressive disorders.
- Risks of phenibut include tolerance, dependence, abuse, accidental and intentional overdose resulting in significant toxicity requiring hospitalisation, with severity potentially requiring ICU admission.
- The perceived benefits (as indicated in public submissions) are substantially outweighed by the risks.

(b) the purposes for which a substance is to be used and the extent of use of a substance:

- The substance is not currently permitted in Australia to be marketed for therapeutic reasons but is widely available on the internet for purchase. International websites make significant therapeutic claims for cognition enhancement, anxiety and depressive disorders. Prevalence of use is not established but is clearly across the country and increasing.
- Prevalence of use is not established but is clearly across the country and increasing.

(c) the toxicity of a substance:

- Phenibut is a neuropsychotropic drug with anxiolytic and cognition enhancing effects. It acts as a GABA mimetic, primarily at GABAB and to some extent at GABAA receptors.
- Published reports of ED presentations, acute intoxication with delirium, and dependence treated with baclofen. These reports include reports from Australia.
- Descriptions of withdrawal include tremors, anxiety, insomnia, hypertension, hyperhidrosis, psychosis, tachycardia, widening of QRS complex and convulsions. There is significant risk of harm.
- Effects include CNS depression, delirium, seizures – potentially requiring intubation and ventilation.
- The availability as a powder increases risks of toxicity.

(d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Packaged as a supplement in 250 and 500mg capsules.
- No restrictions at present, currently available in powder and capsules with variable labelling.
- The availability as a powder increases risks of toxicity. Loose powders pose particular risk of accidental overdose.

(e) the potential for abuse of a substance:

- Rapid development of tolerance and dependence with a withdrawal syndrome consisting of hallucinations, agitation, tremor, insomnia, abdominal pain, vomiting.
- Cases of recreational abuse have been described.
- Rapid development of tolerance is established.

(f) any other matters that the Secretary considers necessary to protect public health:

- Taking into consideration the danger to the health of individuals and of the community (both immediate and imminent) associated with the use of phenibut and the high risk of dependency, abuse, misuse and illicit, the perceived benefits (as indicated in public submissions) are substantially outweighed by the risks.

2.4. Docusate sodium

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for docusate sodium in the Poisons Standard to restrict its use in cosmetic and domestic products.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Appendix B, Part 3 – Delete Entry

DOCUSATE SODIUM (DIOCTYL SODIUM SULFOSUCCINATE)

Schedule 6 – New Entry

DOCUSATE SODIUM **except:**

- a) in wash-off preparations containing 30 per cent or less of docusate sodium and, if containing more than 5 per cent of docusate sodium, when labelled with a warning to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER;

- b) in leave-on preparations containing 1.5 per cent or less of docusate sodium;
- c) in toothpaste and oral hygiene preparations containing 5 per cent or less of docusate sodium;
- d) in other preparations for animal use containing 2 per cent or less of docusate sodium; or
- e) in other preparations containing 30 per cent or less of docusate sodium and, if containing more than 5 per cent of docusate sodium, when labelled with warnings to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

IF SKIN OR HAIR CONTACT OCCURS, REMOVE CONTAMINATED CLOTHING
AND FLUSH SKIN AND HAIR WITH RUNNING WATER.

Appendix E, Part 2 – New Entry

DOCUSATE SODIUM

Standard Statements: E1 (If in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

DOCUSATE SODIUM

Warning Statements: 5 (Irritant); 72 (Do not use in the eyes); 79 (Will irritate eyes).

Safety Directions: 1 (Avoid contact with eyes); 4 (Avoid contact with skin).

Index – Amend Entry

DOCUSATE SODIUM

cross reference: DIOCTYL SODIUM SULFOSUCCINATE

~~Appendix B, Part 3~~

Schedule 6

The applicant's reasons for the request are:

- While the US CIR Expert Panel concluded in 2013 that surfactant formulations containing docusate sodium would most likely produce irritation effects and recommended that products containing dialkyl sulfosuccinate salts (including docusate sodium) be formulated to be non-irritating, the available data do not provide sufficient evidence to determine a cut-off concentration at which exemptions may apply for either leave-on or rinse-off cosmetic formulations;
- An exemption cut-off for domestic uses and rinse-off cosmetics could be assigned similar to that used for lauryl sulfate salts;

- Inclusion of docusate sodium in Appendix B of the Poisons Standard is considered inappropriate, as docusate sodium cannot be considered to be of low toxicity based on the results of the NICNAS IMAP assessment;
- Docusate sodium is reported to be used in domestic products in Australia;
- Docusate sodium is reported to be used in cosmetic and domestic products overseas (CIR, 2013) that are potentially available for use in Australia; the updated REACH Dossier (December 2016) indicates consumer uses in cleaning applications, laundry detergents, paints and coatings;
- Although there is no information to confirm the maximum use concentration of docusate sodium in cosmetic and domestic products in Australia, it is reported to be used in cosmetic and domestic products overseas at concentrations up to 4.4 and 5.0%, respectively (CIR, 2013);
- Docusate sodium is a skin irritant and a severe eye irritant;
- Docusate sodium is also reported to be a cumulative skin irritant based on effects observed in human irritation and skin sensitisation studies. In several four-day cumulative irritancy tests, application of products containing docusate sodium resulted in a primary irritation index (PII) range of 0.25-0.80 at 2.94% concentration, a PII range of 1.78-1.85 at 0.21% concentration and a PII of 0.04 at 0.084% concentration. In a 21-day cumulative irritancy test in seven volunteers, daily application of a product containing 1.13% of docusate sodium (84% purity) under occlusive conditions resulted in a total irritation score of 324/578, with the average score of 46.3/84 per subject (CIR, 2013; CIR, 1998);
- Dermal irritation has been observed in humans (studies and case reports) following repeated application of products containing docusate sodium at <5% (CIR, 2013); and
- The US CIR (2013) report stated, 'Diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate) was reviewed by the CIR Expert Panel (Panel) in 1994, and a safe concentration limit of 0.42% was established. A petition to open the report to review new clinical data was received, and in 1998, the Panel amended the report to conclude that this ingredient is safe as used in cosmetic formulations. In the discussion, the Panel stressed that care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin.' (CIR, 2013).

Current scheduling status and relevant scheduling history

Docusate sodium is currently listed in Appendix B of the [Poisons Standard](#) as follows:

Appendix B, Part 3: Substances considered not to require control by scheduling

DOCUSATE SODIUM (DIOCTYL SODIUM SULFOSUCCINATE)

Date of entry: February 1970

Reason for Entry – a, low toxicity

Area of Use – 7.1, general, any use

Docusate sodium (as dioctyl sodium sulphosuccinate) was considered for scheduling at the February 1970 meeting of the National Health and Medical Research Council Poisons Schedule Sub-committee. The product presented to the committee was a combination of bisacodyl and docusate sodium and was intended for use as a general purpose laxative. The sub-committee agreed that neither of the well-known actives required scheduling due to their low toxicity.

Australian regulatory information

Docusate sodium is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as follows:

Table 2.4.1: Permissible ingredients and requirements applying to docusate sodium when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
1900	DOCUSATE SODIUM	E	-

Docusate sodium is in 186 products on the ARTG, including medicines for constipation, pain relief, Parkinson's disease, anxiety, benign prostatic hyperplasia. Four (medicines to treat constipation) of the 186 products are listed medicines and 95 are non-prescription medicines (includes medicines for constipation and pain relief).

According to the [TGA Ingredient Database](#), docusate sodium is available for use as an:

- Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines; and
- Excipient Ingredient in: Biologicals, Devices, Export Only, Listed Medicines, Over the Counter, Prescription Medicines.

In the last 20 years, there have been 81 reported adverse events related to docusate sodium in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#): 22 cases with a single suspected medicine (*application site reaction* (22), *otitis externa* (18) and *ear pain* (16)) and 1 case of death as a reported outcome.

Docusate sodium is present in 2 products registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA), to treat the alimentary systems of dogs, cats and horses, containing up to 2.1% (21 mg/mL) docusate sodium.

International regulations

EU

Docusate sodium was registered under REACH as of 15 June 2012. The registration dossier was updated on 17 December 2016, following compliance checks by ECHA.

Docusate sodium is used in the following products in the EU: washing & cleaning products, lubricants and greases, polymers, metal working fluids, textile treatment products and dyes, pH regulators and water treatment products, hydraulic fluids and leather treatment products. This substance is also used as an intermediate in the manufacture of another substance.

Docusate sodium is used in the following areas: mining, agriculture, forestry and fishing, formulation of mixtures and/or re-packaging and municipal supply (e.g. electricity, steam, gas, water) and sewage treatment. It is used for the manufacture of: chemicals, textile, leather or fur, plastic products and food products.

USA-FDA

Docusate sodium is an approved ingredient for use in certain over-the-counter products including weight control and pediculicide drugs.

Canada

Docusate sodium is in 59 marketed over-the-counter products in Canada. Products include treatments for bloat and constipation.

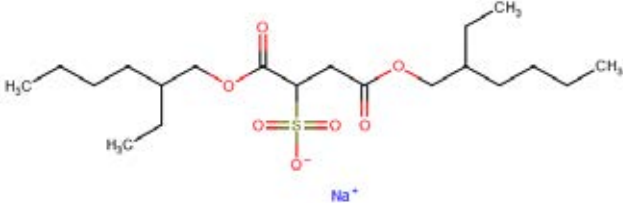
New Zealand

Docusate sodium (as dioctyl sodium sulfosuccinate) is available for General Sale in NZ.

Substance summary

Docusate sodium is used in cosmetics, domestic products and in human therapeutic products (primarily as a laxative to treat constipation and as an ear wax remover) and animal therapeutic products (used to treat constipation and bloat).

Table 2.4.2: Chemical information for docusate sodium

Property	Docusate sodium
Chemical structure	
Molecular formula	$C_{20}H_{37}NaO_7S$
Molecular weight	444.6 g/mol
CAS number	577-11-7
CAS name	butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt
IUPAC and/or common and/or other names	<p>Sodium;1,4-bis(2-ethylhexoxy)-1,4-dioxobutane-2-sulfonate (IUPAC);</p> <p>Diethylhexyl sodium sulfosuccinate (INCI);</p> <p>Dioctyl sodium sulfosuccinate; succinic acid, sulfo-1,4-bis(2-ethylhexyl)ester, sodium salt.</p>

The following information was extracted from the [IMAP Human Health Tier II assessment report for docusate sodium](#) publicly available from the NICNAS website. [The US Cosmetic Ingredients Review \(CIR\)](#) report is also publicly available.

Table 2.4.3: Acute toxicity end-points for docusate sodium

Toxicity	Species	Docusate Sodium	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	1900 - 4200	Schedule 5
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rabbit (New Zealand White)	>2000	Schedule 5

Toxicity	Species	Docusate Sodium	SPF (2015) Classification
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rat	20 mg/L However, only very limited data available	Schedule 7
Skin irritation	Rabbit (Russian and New Zealand White) Human	Severe skin irritant Cumulative skin irritant	Schedule 6
Eye irritation	Rabbit (Russian and New Zealand White)	Severe eye irritant	Schedule 6
Skin sensitisation (human repeated insult patch tests - HRIPTs)	Human	Not skin sensitising	N/A

Acute oral toxicity

Based on the weight of evidence of results from animal tests following oral exposure, docusate sodium is considered to have low acute oral toxicity.

In a study in rats conducted according to Organisation for Economic Co-operation and Development (OECD) test guidelines, the median lethal dose (LD₅₀) reported was >2100 mg/kg bw. In several other acute toxicity studies in rats, the oral LD₅₀ values were reported to be between 3080 - 4200 mg/kg bw. In 2 other studies, no mortalities were reported up to the highest doses tested (LD₅₀ values of >1300 and >1400 mg/kg bw, respectively). Although an LD₅₀ value in rats of 1900 mg/kg bw was reported in 1 early study, only limited study details are available.

Acute dermal toxicity

Docusate sodium has low acute toxicity based on results from animal tests following dermal exposure.

In a study in New Zealand White (NZW) rabbits, the dermal LD₅₀ value was reported to be >10000 mg/kg bw. No mortalities were reported. Local effects of skin irritation were noted. In another study of limited reliability (due to low numbers of animals), the dermal LD₅₀ in rabbits was reported to be 2525 mg/kg bw.

Acute inhalation toxicity

Limited inhalation data are available. Docusate sodium is reported to have a median lethal concentration (LC₅₀) value of 20 mg/L in rats following 96-hours exposure. No further study details are available.

Skin irritation

Based on available experimental data, docusate sodium is considered to be a skin irritant. While effects indicative of corrosivity have been reported in several studies, these followed co-exposure to other substances, or exposure for prolonged exposure times.

In a skin irritation study conducted according to relevant OECD test guidelines, 0.5 mL of a 70% solution of docusate sodium was applied, under occlusive conditions, to the shaved skin of 3 white

Russian rabbits for a 4 hour exposure period. A mean irritation score of 7.8 (out of a maximum score of 8) was reported based on observations recorded at 1, 24, 48 and 72 hours after exposure. Severe erythema and oedema were still observed in all animals after 14-days' observation, with formation of scars reported in 2/3 animals. While scar formation may indicate corrosive effects, the presence of 15% ethanol (denatured with 5% methanol) in the solution potentially increased the irritancy of the test substance was reported.

In another study conducted according to test guidelines, 0.5 mL of docusate sodium (>97% purity) was applied under occlusive conditions, to the shaved and intact skin of 6 NZW rabbits for 24-hours exposure. A primary irritation score of 3.83/4 was reported, with docusate sodium considered to be strongly irritating to the skin. Erythema and oedema were still observed after 72-hours observation. Reversibility was not assessed in this study.

In other studies, docusate sodium applied as a 2% patch on the skin of rabbits for 24 hours resulted in irritation scores of 3.7/8 (intact skin) and 1.7/8 (abraded skin), while 5% of docusate sodium applied to intact abdominal skin in rabbits produced a burn after two to four 24-hour applications, and 25% produced a burn after one 24-hour application. Additionally, application of 1, 5 and 25% of docusate sodium to abraded rabbit skin for three days caused moderate to severe irritation.

Eye irritation

Based on the available experimental data, docusate sodium is considered to be a severe eye irritant.

In an eye irritation study conducted according to relevant OECD test guidelines, 0.1 mL of a 70% solution of docusate sodium was applied to the right eye of 3 white Russian rabbits; the left eye served as the control. The test substance was washed out of the eye after 72-hours' exposure. An irritation index of 46.67/110 was reported based on mean irritation scores recorded at 1, 24, 48 and 72 hours after application. Effects, including turbidity of the cornea (reported as irreversible damage), were still visible after 21-days.

In another eye irritation study, 0.1 mL (equivalent to 0.1 g) of docusate sodium (>97% purity) was applied to the eyes of 3 NZW rabbits (exposure period not specified). Docusate sodium was reported to cause moderate eye irritation based on observations at 24, 48 and 72 hours after application. Effects on the cornea, iris and conjunctivae were still present after 72-hours observation. Reversibility was not assessed in this study.

A 10% solution of docusate sodium was also reported to have been used as a positive control in an eye irritancy test in rabbits, with severely irritating effects.

Sensitisation

While no skin sensitisation studies in animals are available, several repeat insult patch tests have been conducted in humans, with no significant effects indicative of skin sensitisation observed. However, skin irritation was reported in these studies, resulting from repeated exposure to docusate sodium.

Repeat-dose toxicity

Based on the available information from experimental studies, repeated oral exposure to docusate sodium is not considered to cause serious damage to health.

Based on the limited data available, repeated dermal exposure to docusate sodium is not considered to cause serious systemic health effects.

While several repeated inhalation toxicity studies in animals are available, these were conducted using formulated products containing docusate sodium, with very little information regarding the composition of the product. Therefore, any adverse effects reported in these studies cannot be solely attributed to docusate sodium being assessed in this report.

Genotoxicity

Although 2 well-conducted *in vitro* experimental studies are available, the results are inconclusive, and as no *in vivo* studies are available, there is insufficient evidence to determine the genotoxic potential of docusate sodium.

In an *in vitro* bacterial reverse mutation assay (Ames test), docusate sodium did not induce mutations in several strains of *Salmonella typhimurium*, either with or without metabolic activation, at test concentrations up to 5000 µg/plate.

In an *in vitro* mammalian chromosome aberration test in Chinese hamster ovary (CHO) cells, a significantly increased frequency of cells with chromosomal aberrations was reported at concentrations ≥120 µg/mL, only in the presence of metabolic activation. No significant difference was observed in the absence of metabolic activation. While the study concluded that docusate sodium was able to induce chromosome aberrations in CHO cells, the authors noted that effects were observed at doses very close to the threshold of toxicity, and that aberration induction is likely to be associated with an indirect mechanism.

Carcinogenicity

No reliable data are available.

The only available carcinogenicity information is from a 6 month study investigating colorectal carcinogenesis in male rats. Animals were administered docusate sodium in the diet at 0 or 1%, in addition to a weekly single subcutaneous injection of 1,2-dimethylhydrazine (a chemical known to induce colon tumours in experimental animals). No statistically significant difference between test and control group animals were reported in regards to frequency or progression of tumours. However, due to the study design and the very limited study details available, these results are insufficient to determine the carcinogenic potential of docusate sodium.

Reproduction and developmental toxicity

Docusate sodium is the sodium salt of the diester of 2-ethylhexanol (2-EH) and sulfosuccinic acid, with hydrolysis of docusate sodium resulting in formation of 2-EH at a ratio of 2:1. Docusate sodium 2-EH has been assessed by NICNAS and is reported to cause developmental toxicity, but not teratogenicity, in rats following treatment via the oral route. These effects were noted in the absence of signs of marked maternal toxicity. The NOAEL for developmental toxicity was reported to be 130 mg/kg bw/day. Docusate sodium 2-EH is also classified as a Category 3 hazardous substance toxic to reproduction, with the risk phrase 'Possible risk of harm to the unborn child' (Xn; R63) in the HSIS (Safe Work Australia).

Available data on docusate sodium indicate that it is not a specific reproductive or developmental toxin. While some developmental effects were seen in a study using a very high dose of docusate sodium, this dose is outside the dose range considered relevant for developmental toxicity studies.

Observation in humans

In addition to being a potential skin and eye irritant following a single exposure, docusate sodium is reported to be a cumulative irritant based on effects observed in human irritation and skin sensitisation studies.

In 'mini-cumulative irritancy tests' in humans with 4 products containing docusate sodium at different concentrations, the following primary irritation index (PII) ranges were reported (CIR, 2013):

- 0.25-0.80 for a product containing 3.5% solution of 84% of docusate sodium (chemical concentration = 2.94%);
- 1.78 and 1.85 for two products containing 0.25% solution of 84% of docusate sodium (chemical concentration = 0.21%); and

- 0.04 for a product containing 0.1% solution of 84% of docusate sodium (chemical concentration = 0.084%).

These PII's indicate only mild skin irritation with cumulative exposure at concentrations up to ~3%.

In a 21-day cumulative irritancy test in 7 volunteers, daily application of a product containing 1.13% of docusate sodium (of 84% purity) under occlusive conditions resulted in a total irritation score of 324/578, with the average score of 46.3/84 per subject (CIR, 2013; CIR, 1998).

Skin irritation reactions were also reported in 6 patients following application of an orthopaedic plaster cast lined with a wool containing docusate sodium solution (CIR, 2013; CIR, 1998). Subsequent patch testing was conducted in these patients using the 4 chemicals used to manufacture the wool (the other three chemicals are not identified) at concentrations of 1, 10, and 100%. Application of docusate sodium produced positive irritancy reactions in all patients. The other 3 chemicals did not cause irritation. In a follow-up patch testing study, a product containing docusate sodium was applied to the skin of 18 volunteers (8 with normal skin and 10 with non-inflammatory skin disease). No irritation or allergic reactions were reported in any of the subjects exposed to docusate sodium at 1 and 10%. However, at 100%, docusate sodium produced skin irritation reactions in 12/18 volunteers.

In a separate study with 50 subjects, no irritation effects were reported following a single application of a formulation containing docusate sodium at 2.5% (occlusive patch) for a 24-hour period (CIR, 2013).

In a skin sensitisation patch test in humans, 0.3 g of a 2.5% solution of docusate sodium was applied to the back or forearms of 100 volunteers for 24-hour periods over 10 alternate days (induction phase). After one-week's rest, 0.3 g of a 1% solution was applied to different sites on the back or forearms of the volunteers for 24-hours (challenge phase). Observations were recorded after removal of the challenge patch. No sensitisation reactions were reported in any of the subjects at the challenge sites. However, mild erythema was reported in 19/100 individuals during the induction phase (REACH).

Docusate sodium was also reported not to induce skin sensitisation effects in several human repeated insult patch tests (HRIPTs) at concentration up to 5%. However, mild irritation reactions were reported in some individuals during the induction phase (CIR, 2013). Similar results were observed in a HRIPT of a 50/50 dilution in distilled water of an eyebrow pencil containing 2.5% of docusate sodium and another HRIPT of a product containing 0.1% of docusate sodium (reported as 84% purity) (CIR, 2013; CIR, 1998).

Public exposure

Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products.

Considering the range of domestic, cosmetic and personal care products that may contain docusate sodium, the main route of public exposure is expected to be through the skin, inhalation from products applied as sprays or aerosols, and potential eye exposure from eye make-up products. Docusate sodium is also reported to be used in a cosmetic product that is likely to result in exposure to the mucous membrane. No further details on the product are available. Reported use of docusate sodium in a bath oil is also a potential concern in regards to all routes of exposure. Although concentration levels of docusate sodium used in consumer products in Australia are not known, docusate sodium is reported to be used in domestic products overseas at concentrations ranging from 0.01 - 5.0%. The maximum reported use concentration in cosmetic products overseas is at 4.4% in a leave-on eye make-up product. Docusate sodium is also reported to be used in leave-on skin moisturising products. Although use concentrations of docusate sodium are not specifically reported for these products, a concentration range of 0.0002 - 4.4% is reported for cosmetic products that are expected to result in dermal exposure. The concentration of docusate sodium used in bath oil is not reported (CIR, 2013).

The US Cosmetic Ingredients Review (CIR) Expert Panel evaluated the use of docusate sodium in cosmetic products in 1998 and 2013. Both reviews acknowledged that docusate sodium is a

cumulative irritant and that 'care should be taken to avoid irritancy in formulations intended for prolonged contact with the skin', concluding that use of docusate sodium in cosmetics is 'safe in the present practices of use and concentration in cosmetics described...' and '...when formulated to be non-irritating' (CIR, 2013).

While docusate sodium is reported to be used at concentrations up to 0.25% in cosmetic products that may be aerosolised, there are insufficient data from inhalation exposure studies to determine the risk from use of these products. However, the CIR panel evaluated the risk of incidental inhalation exposure of docusate sodium from hair sprays, and concluded that, based on the available information (including docusate sodium and biological properties of docusate sodium), incidental inhalation is not considered to be a significant route of exposure that could lead to local respiratory or systemic effects.

Docusate sodium is a severe eye and skin irritant. Docusate sodium at 10% concentration was reported to cause severe eye irritation in rabbits. As the rinse off cosmetic products may lead to ocular exposure, concentration of docusate sodium in these products should be lowered to mild or non-irritating concentrations.

Docusate sodium is not a skin irritant at 2.5% concentration but a mild irritant at 5% concentration in humans. However, in a human patch test, a 2.5% solution of docusate sodium applied for 10 days produced mild erythema in 19/100 individuals. Docusate sodium caused mild skin irritation with cumulative exposure at concentrations up to ~3%, indicating concerns for use in leave-on cosmetic products at higher concentrations.

Pre-meeting public submissions

Two (2) public submissions were received, one (1) opposed and one (1) did not state a position.

Main points opposed:

- Scheduling of this surfactant will not lead to a better risk management outcome;
- The risks of surfactants are already well managed;
- The public have a good understanding that surfactant based products such as shampoos, soaps and detergents are irritating to skin and eyes and will wash their hands and rinse their eyes in case of accidental contact, without being prompted by the label; and
- If accidental eye contact did occur, attempting to read any instructions on the product label may prove to be problematic.

The other submission noted that more clarity was needed regarding restrictions for docusate sodium so that industry may comment. The submitter supported the current CIR recommendations that products containing dialkyl sulfosuccinate salts (including docusate sodium), be used in cosmetic products at concentrations up to 5.0% with the caution that manufacturers are aware that 'care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin' (CIR, 2013).

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that the current Appendix B (7.1 – any use) entry for docusate sodium in the Poisons Standard remained appropriate, and suggested that a review into the scheduling of all surfactants should take place.

Members agreed that the relevant matter under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance.

The reasons for the advice were:

- There is no evidence of a public health risk.

- Appendix B remains appropriate for docusate sodium in the absence of evidence relating to the human safety issues.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is that the current Appendix B (7.1, any use) entry for docusate sodium in the Poisons Standard remains appropriate.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance.

The reasons for the interim decision are:

- There is no evidence of a public health risk.
- Appendix B remains appropriate for docusate sodium in the absence of evidence relating to the human safety issues.

2.5. Vinyl acetate

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create new entries for vinyl acetate in Schedules 6 and 10 of the Poisons Standard.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – New Entry

VINYL ACETATE (if appropriate, exempt up to 1% concentration in domestic products).

Schedule 10 – New Entry

VINYL ACETATE for cosmetic use.

Appendix E, Part 2 – New Entry

VINYL ACETATE

Standard Statement: A (For advice, contact a Poisons Information Centre or a doctor).

Appendix F, Part 3 – New Entry

VINYL ACETATE

Warning Statement: 6 (May cause cancer).

Safety Directions: 4 (Avoid contact with skin); 8 (Avoid breathing vapour); 9 (Use only in well ventilated area).

The applicant's reasons for the request are:

- Vinyl acetate is highly volatile, a respiratory irritant, and may have genotoxic and carcinogenic potential;
- Domestic uses of vinyl acetate in Australia were identified in paints, lacquers, varnish, adhesives and possibly in automotive products;
- Domestic uses identified overseas include products containing vinyl acetate up to 67% in a home maintenance paste (US Household Products Database). However, available data suggest that most products contain 1% or less; glues/adhesives (0-1%), foam sealants (0.1-2%), or paints/varnish/primer (0.1-0.5%) (US Household Products Database);
- Previously allowed cosmetic use was for a film forming substance (in 2006) in the European Union (EU); this use has been prohibited from 1 January, 2015 under Reg 944/2013 (CosIng); and
- When vinyl acetate is used in domestic products, the potential for respiratory irritation, mutagenicity and carcinogenicity from vapours clearly presents a risk. The risk can be controlled by imposing concentration restrictions and warning labels for domestic uses. If there is any cosmetic use of vinyl acetate in Australia, it should be prohibited.

Current scheduling status and relevant scheduling history

Vinyl acetate is not currently scheduled and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Australian regulatory information

Vinyl acetate is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as follows:

Table 2.5.1: Permissible ingredients and requirements applying to vinyl acetate when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
5014	VA/BUTYL MALEATE/ISOBORNYL ACRYLATE COPOLYMER	E	Vinyl acetate is a mandatory component of VA/butyl maleate/isobornyl acrylate copolymer. The concentration of vinyl acetate in the medicine must be no more than 0.01% or 100 ppm. Only for use in topical medicines for dermal application and not to be

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
			included in medicines intended for use in the eye. The concentration in the medicine must be no more than 5%.

According to the [TGA Ingredient Database](#), vinyl acetate is available for use as an:

- Excipient only in biologicals, devices and prescription medicines; and
- Equivalent ingredient in devices, listed medicines and prescription medicines.

Vinyl acetate is in 59 products listed on the [Australian Register of Therapeutic Goods \(ARTG\)](#):

- 1 Medical device (Class IIa);
- 24 Non-prescription medicines; and
- 34 Prescription medicines.

Vinyl acetate is not listed in the [Database of Adverse Events Notification \(DAEN\) - Medicines](#).

International regulations

EU

Vinyl acetate is classed as a CMR 2 (carc.2) substance⁶ and is prohibited for use in cosmetics and personal care products in the European Union (EU) from 1 January 2015, as per EU Regulation No 944/2013.

USA

The Food and Drug Administration (FDA) has determined that vinyl acetate may be safely used as a coating or a part of a coating (e.g. an adhesive) that is used in plastic films for food packaging, and as a modifier of food starch.^{7, 8}

The American Conference of Governmental Industrial Hygienists (ACGIH) has established an exposure limit of 10 parts of vinyl acetate per million parts of workplace air (10 ppm) for an 8-hour workday, 40-hour workweek.⁷

The National Institute for Occupational Safety and Health (NIOSH) recommends that exposure to vinyl acetate in the workplace not exceed 4 ppm over a 15-minute period.⁷

⁶ CMR 2 (carc 2): suspected to have CMR (Carcinogenic, Mutagenic, Reprotoxic) potential for humans

⁷ [ToxFAQsTM for Vinyl Acetate](#)

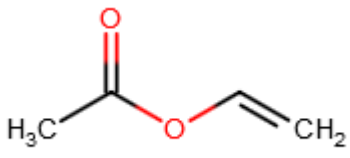
⁸ [Electronic Code of Federal Regulations, Part 175-Indirect Food Additives: Adhesives and Components of Coatings.](#)

Substance summary

Vinyl acetate is a clear, colourless liquid. It has a sweet, pleasant, fruity smell, but the odour may be sharp and irritating to some people. Vinyl acetate can be smelt when it is in the air at levels around 0.5 ppm. It readily evaporates into air and dissolves easily in water.

Vinyl acetate is flammable and may be ignited by heat, sparks, or flames. Vinyl acetate is used to make other industrial chemicals (such as polyvinyl acetate polymers and ethylene-vinyl acetate copolymers). These are used mainly to make glues for the packaging and building industries. These are also used to make paints, textiles, and paper.⁹

Table 2.5.2: Chemical information for Vinyl acetate

Property	Substance
Chemical structure	
Molecular formula	C ₄ H ₆ O ₂
Molecular weight	86.1 g/mol
CAS name	Acetic acid ethenyl ester
CAS number	108-05-4
IUPAC and/or common and/or other names	Ethenyl acetate (IUPAC); Vinyl acetate (INCI, AAN).

The following information was extracted from the [NICNAS Inventory Multi-tiered Assessment Prioritisation \(IMAP\) human health Tier II assessment report for Acetic acid, ethenyl ester](#), publicly available on the NICNAS website.

Table 2.5.3: Acute toxicity end-points for vinyl acetate

Toxicity	Species	Vinyl acetate	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	2500-3500	Schedule 5
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rabbit	2335	Schedule 5
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rat	4490 ppm or ~15810 mg/m ³ (vapour)	Schedule 5

⁹ [ATSDR – Public Health Statement: Vinyl Acetate](#)

Toxicity	Species	Vinyl acetate	SPF (2015) Classification
Skin irritation	Rabbit	Slight	Schedule 5
Eye irritation	Rabbit	Slight	Schedule 5
Skin sensitisation (LLNA)	Mouse	Negative	N/A

Acute toxicity

Vinyl acetate has low acute oral and dermal toxicity in animals (LD₅₀ >2000 mg/kg bw).

Based on the available data, vinyl acetate (as a vapour) has moderate acute inhalation toxicity in rats.

Irritation

Vinyl acetate has been classified by NICNAS as a respiratory irritant based on: effects observed in humans following exposure to vinyl acetate; necropsy findings from acute inhalation studies in animals and clinical signs of toxicity observed in repeat dose inhalation studies in animals.

In male Sprague Dawley (SD) rats exposed (whole body) to vinyl acetate vapour on either one, five or 20 occasions (for six hours per day, five days per week) at concentrations of 50, 200, 600 or 1000 ppm (whole body), a dose related increase in the severity of microscopic lesions in the olfactory epithelium was observed at 600 ppm and above. Following a single exposure, degeneration, necrosis and exfoliation of olfactory epithelial cells were observed (REACH).

In three-month inhalation studies conducted in rats and mice, clinical signs of toxicity included intermittent symptoms of respiratory distress, hunched posture and ruffled fur in animals exposed to vinyl acetate at 200 – 1000 ppm concentrations. Increased lung weight observed in rats and mice exposed to vinyl acetate at 1000 ppm was attributed to lung congestion arising from respiratory irritation. Treatment-related lesions were observed at necropsy in the lungs, trachea and nasal epithelium of mice exposed to vinyl acetate at 1000 ppm (REACH).

Vinyl acetate may cause slight eye and skin irritation.

Sensitisation

Based on the negative results observed for vinyl acetate in a well conducted (OECD TG 429 compliant) local lymph node assay (LLNA) in CBA/CaOlaHsd mice, vinyl acetate is not considered to be a skin sensitiser.

Repeat-dose toxicity

Vinyl acetate is not considered to cause severe effects following repeated oral exposure. No data are available on repeated dermal exposure.

Repeated inhalation exposure to vinyl acetate may cause symptoms consistent with respiratory irritation and inflammation. Based on the available data, vinyl acetate is not considered to cause severe systemic effects following repeated inhalation exposure, apart from causing histopathological changes in the olfactory epithelium and respiratory system, which are considered possible evidence of precursor events to tumour formation (see [Carcinogenicity](#)).

Genotoxicity

Vinyl acetate showed positive results for genotoxicity, both *in vitro* and *in vivo*. Based on the weight of evidence from the available genotoxicity data, vinyl acetate may have genotoxic potential and NICNAS

classified it as a Category 3 Mutagen according to the Approved Criteria for Classifying Hazardous Substances.

Although *in vitro* assays utilising bacterial cells have shown negative results for mutagenicity, positive results have been obtained using mammalian cells (*in vitro* and *in vivo*), particularly for chromosome effects (ACGIH, 2001; IARC, 1995; Norppa *et al.*, 1985; REACH). It has been hypothesised that the genotoxicity of vinyl acetate may be attributable to the formation of acetaldehyde, although the lowering of cell pH that occurs when large doses of vinyl acetate are metabolised to acetic acid may also be a contributing factor (Albertini, 2013).

Vinyl acetate undergoes hydrolysis under aqueous conditions to form acetaldehyde and acetic acid, which both have a negative effect on cells. Genotoxicity of vinyl acetate may be attributable to the formation of acetaldehyde, which is a Category 3 mutagen. Acetic acid that acts to lowering cell pH may also be a contributing factor.

Vinyl acetate vapour or liquid tested negative for mutagenicity in *Salmonella typhimurium* strains TA 98, 100, 1535, 1537 and 1538, in the presence or absence of metabolic activation (ACGIH, 2001).

All other *in vitro* assays showed positive results with vinyl acetate:

- A dose-dependent and statistically significant increase in sister chromatid exchange (SCE) was observed in human lymphocytes (whole blood culture) following exposure for 48 hours to concentrations of 0.1 mM of vinyl acetate and above. A dose-dependent increase in chromosome aberrations was also observed. An increased number of aberrant cells (gaps included or excluded), number of cells carrying chromatid-type aberrations or chromatid-type exchanges was statistically significant at 0.5 mM (Norppa *et al.*, 1985).
- A dose-dependent increase in SCE was observed in Chinese hamster ovary (CHO) cells following exposure to vinyl acetate for 24 hours at doses of 0.125-1 mM or exposure to vinyl acetate for 4 hours at doses of 0.3-5 mM (Norppa *et al.*, 1985).
- Induced DNA cross links in isolated human lymphocytes and rat nasal epithelial cells at 860 µg/mL (IARC, 1995).
- Increased numbers of micronuclei in human lymphoblastoid cells (TK6) following a 4-hour exposure to concentrations of 0.25, 0.5, 1 or 2 mM in a micronucleus assay (a similar protocol to OECD TG 487). Acetaldehyde, a metabolite of vinyl acetate, was also found to be positive in this same assay at concentrations of 0.25, 0.5 and 1 mM (REACH).
- Increased chromosome aberrations in human whole blood and isolated human lymphocytes after exposure (similar to OECD TG 473) to concentrations of 0.25, 0.5, 1 or 2 mM for 24 hours, without metabolic activation (REACH).

Three *in vivo* genotoxicity studies showed positive results with vinyl acetate (REACH):

- A dose-dependent increase in micronuclei was observed in C57BL mice that received an intraperitoneal injection of vinyl acetate at 250, 500, 1000 or 2000 mg/kg bw (similar to OECD TG 474). Increases were statistically significant at the 2 high doses that caused increased mortality.
- Male mice that received vinyl acetate for 5 days at 125, 250, 500 or 750 mg/kg bw/day via i.p. injection showed effects on testicular weight (reduced at 125 and 500 mg/kg bw/day), sperm count (decreased with increased dosing) and morphology (5 weeks after treatment 3/7 had sperm abnormalities at 500 mg/kg bw/day). One mouse (1/5) survived at the highest dose, and showed an increased level of abnormal sperm.
- There was an increased frequency of chromosomal aberrations in cultured lymphocytes of humans following occupational exposure (IARC, 1995). No additional details were available.

Carcinogenicity

According to the International Agency for Research on Cancer (IARC), vinyl acetate is a Group 2B carcinogen 'possibly carcinogenic to humans' (IARC, 1995). The IARC classification was based on limited evidence in experimental animals, although the evidence in humans was considered to be insufficient to establish carcinogenicity (IARC, 1995). Vinyl acetate has a harmonised GHS classification in the EU as a Category 2 carcinogen (suspected of causing cancer).

Based on the positive carcinogenicity findings in animals following both oral and inhalation exposure to vinyl acetate, NICNAS classified vinyl acetate as a Category 3 carcinogen according to the Approved Criteria for Classifying Hazardous Substances.

Groups of Swiss mice and SD rats (n = 60/sex/dose) exposed (via inhalation) to vinyl acetate at 0, 50, 200 or 600 ppm, six hours per day, five days per week, for 104 weeks showed evidence of carcinogenicity. One lung squamous cell carcinoma was reported in a high dose male mouse. Several non-neoplastic lesions in mice were reported in the respiratory tract (olfactory epithelium atrophy, respiratory metaplasia, squamous metaplasia of respiratory epithelium in nasal cavity, tracheal epithelial hyperplasia). There was an increased incidence of squamous cell carcinoma in the nasal cavity in high dose female rats (4/59) compared with controls. There was a statistically significant increase in the total number of nasal tumours (benign and malignant) in high dose male rats. Non-neoplastic observations in rats included thinning of the olfactory epithelium of the nasal cavity, accompanied by basal cell hyperplasia (IARC, 1995).

There is additional evidence of carcinogenicity in animals since the IARC decision in 1995. Vinyl acetate administered to Wistar rats and Swiss mice at 5000 ppm in drinking water resulted in statistically significant increases in the percentage of animals with malignant tumours (cancers in the oral cavity, tongue, oesophagus and fore-stomach, and upper gastrointestinal tract). Female mice also showed tumours in the uterus at 5000 ppm (Soffritti *et al.*, 2008).

Reproduction and developmental toxicity

Based on the available data following oral and inhalation exposure in animals, vinyl acetate is not considered to cause reproductive or developmental toxicity. Developmental effects in rats were only observed at maternally toxic doses.

Observation in humans

Respiratory irritation: Volunteers exposed to vinyl acetate at 19.4-71 ppm for 0.5-4 hours reported respiratory irritation. In workers exposed to vinyl acetate at average levels of 5-10 ppm (with possible acute exposures of 300 ppm), irritation of the throat and eyes was reported at levels of 21 ppm, but eye irritation was not reported under 10 ppm (ACGIH, 2001).

Carcinogenicity: In a cohort study of 4806 men employed at a chemical manufacturing plant in the US between 1942-1973, the cohort had an excess risk of cancer (as compared to national rates) in the respiratory system. One subgroup, with undifferentiated large-cell lung cancer, had higher exposure to vinyl acetate (IARC, 1995).

A nested case-control study in the US investigated individuals who had died between 1940 and 1978 from certain cancers following exposure to 21 chemicals, including vinyl acetate. Potential exposure to vinyl acetate was reported for 7/52 deaths associated with non-Hodgkin's lymphoma, 3/20 deaths associated with multiple myeloma, 2/18 deaths associated with lymphocytic leukaemia and 2/39 deaths associated with non-lymphocytic leukaemia (IARC, 1995).

Public exposure

The critical health effects for vinyl acetate include local effects (respiratory irritation) and systemic long term effects (carcinogenicity and genotoxicity).

Vinyl acetate has domestic uses identified in Australia in adhesives, paints, lacquers and varnish, and possibly in automotive products. No use concentrations of vinyl acetate in these products are available. Based on these uses, the general public may be exposed to vinyl acetate via inhalation and/or dermal contact.

Vinyl acetate is highly volatile (vapour pressure = 90.2 mm Hg at 20°C; ChemIDplus). Reducing the concentration in domestic products to result in vapour pressure similar to or below the assigned exposure standard for vinyl acetate (10 ppm time-weighted average (TWA); HSIS, SWA) may eliminate the risk of respiratory irritation from inhalation of chemical vapour.

From the calculation below, a concentration limit of about up to 1% in domestic products is estimated to generate vapour concentration similar to the assigned TWA exposure standard for vinyl acetate:

$$\begin{aligned}\text{Saturated vapour concentration for vinyl acetate at 100\%} &= 90.2/760 \times 100\% \\ &= 11.87\% \text{ or } 118,700 \text{ ppm}\end{aligned}$$

$$\begin{aligned}\text{Concentration required generating vapour pressure} &= 100\%/118,700 \text{ ppm} \times 10 \text{ ppm} \\ \text{similar to 10 ppm TWA} &= 0.84\%\end{aligned}$$

It is possible that vinyl acetate may be used in cosmetics in Australia, as it was allowed to be used as a film forming agent (concentration not available) in cosmetics in the EU until January 2015.

Pre-meeting public submissions

Two (2) public submissions were received and both supported the proposal. One submissions also noted that specifying cosmetic use in the Schedule 10 entry, and domestic use in the Schedule 6 entry would ensure that industrial uses, including as a manufacturing intermediate, would be unaffected.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that a new Schedule 6 entry be created for vinyl acetate, and Appendix E, Part 2 and Appendix F, Part 3 entries as follows:

Schedule 6 – New Entry

VINYL ACETATE MONOMER (excluding its derivatives) except:

- a) in preparations for therapeutic use; or
- b) in preparations for domestic use containing 1 per cent or less of vinyl acetate; or
- c) in preparations containing 0.01 per cent or less of vinyl acetate as residual monomer in a polymer.

Appendix E, Part 2 – New Entry

VINYL ACETATE

Standard Statements: **A (For advice, contact a Poisons Information Centre or a doctor); R1 (If inhaled, removed from contaminated area. Apply artificial respiration if not breathing).**

Appendix F, Part 3 – New Entry

VINYL ACETATE

Warning Statement: 11 (Vapour may be harmful).

Safety Directions: 8 (Avoid breathing vapour); 9 (Use only in well ventilated area).

The committee also recommended an implementation date of **1 June 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; and (c) the toxicity of a substance.

The reasons for the advice were:

- Vinyl acetate is a monomer and industrial chemical used in the manufacture of products, e.g. paints, adhesives and possibly in automotive products.
- Vinyl acetate is useful in a number of domestic formulations that require liquid consistency which polymerises or “sets” to give a solid finish e.g. paints, sealants, adhesives, etc. It is not expected to be a simple matter to replace this technology.
- Vinyl acetate is a respiratory irritant and in high doses has genotoxic potential.
- Based on limited evidence of carcinogenicity in experimental animals, vinyl acetate is a potential carcinogen. This may be due to formation of acetaldehyde (hydrolysis under aqueous conditions).

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for vinyl acetate, with supporting Appendix E, Part 2 and Appendix F, Part 3 entries. The proposed Schedule entry is as follows:

Schedule 6 – New Entry

VINYL ACETATE MONOMER (excluding its derivatives) **except:**

- a) in preparations for therapeutic use; or
- b) in preparations for domestic use containing 1 per cent or less of vinyl acetate; or
- c) in preparations containing 0.01 per cent or less of vinyl acetate as residual monomer in a polymer.

Appendix E, Part 2 – New Entry

VINYL ACETATE

Standard Statements: A (For advice, contact a Poisons Information Centre or a doctor); R1 (If inhaled, removed from contaminated area. Apply artificial respiration if not breathing).

Appendix F, Part 3 – New Entry

VINYL ACETATE

Warning Statement: 11 (Vapour may be harmful).

Safety Directions: 8 (Avoid breathing vapour); 9 (Use only in well ventilated area).

The proposed implementation date is **1 June 2018**. A later implementation date is proposed in order to allow for industry alignment.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are:

- Vinyl acetate is a monomer and industrial chemical used in the manufacture of products, e.g. paints, adhesives and possibly in automotive products.
- Vinyl acetate is useful in a number of domestic formulations that require liquid consistency which polymerises or “sets” to give a solid finish e.g. paints, sealants, adhesives, etc. It is not expected to be a simple matter to replace this technology.
- Vinyl acetate is a respiratory irritant and in high doses has genotoxic potential.
- Based on limited evidence of carcinogenicity in experimental animals, vinyl acetate is a potential carcinogen. This may be due to formation of acetaldehyde (hydrolysis under aqueous conditions).

2.6. Methylothiazolinone

Referred scheduling proposal

A delegate from the Therapeutic Goods Administration has referred a scheduling proposal to amend the Schedule 6 entry for methylothiazolinone.

Scheduling application

This was a delegate initiated application. The delegate’s proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – Amend Entry

METHYLISOTHIAZOLINONE **except:**

- a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing **0.0015** ~~0.01~~ per cent or less of MI; or
- b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of MI.

Appendix F, Part 3 – Current Entry

METHYLISOTHIAZOLINONE

Warning Statement: 28 (Over) (Repeated) exposure may cause sensitisation.

The reasons for proposal include:

- Methylisothiazolinone (MI) has exhibited skin sensitisation effects and may also cause systemic acute toxicity and local effects such as eczema and contact allergy reactions.
- On the basis of the December 2015 SCCS Opinion Report on MI, the EU have proposed a change to the MI restrictions at the time (maximum concentration of 0.01% of MI). The report stated that:
 - the information provided does not support the safe use of MI as a preservative in rinse-off cosmetic products up to a concentration limit of 100 ppm (0.01%) from the view of induction of contact allergy;
 - for rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the point of view of induction of contact allergy; and
 - it is also not safe to use MI as a preservative in leave-on hair cosmetic products up to a concentration limit of 100 ppm (0.01%) from the point of view of induction of contact allergy.
- At the time of the [December 2015 delegate's final decision](#), the committee noted that should the EU confirm its proposed cut-off for rinse-off products at 0.0015%, there will be sufficient time prior to the proposed implementation date of 1 October 2017 for the current scheduling decision to be revised accordingly.

Current scheduling status and relevant scheduling history

Methylisothiazolinone is currently listed in the [Poisons Standard](#) as follows:

Schedule 6

METHYLISOTHIAZOLINONE in leave-on cosmetic products or therapeutic goods intended for leave-on topical application, **except** in preparations containing 0.01 per cent or less of methylisothiazolinone.

Appendix F, Part 3

METHYLISOTHIAZOLINONE

Warning Statement: 28 (Over) (Repeated) exposure may cause sensitisation.

The delegate's [final decision for methylisothiazolinone](#) referred to the August 2015 Joint ACCS-ACMS meeting, due to be implemented on **1 October 2017**, is to amend the current Schedule 6 entry for methylisothiazolinone as follows:

Schedule 6 – Amend Entry

METHYLISOTHIAZOLINONE **except**:

- a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.01 per cent or less of methylisothiazolinone; or
- b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone.

Advisory Committee on Chemicals Scheduling (ACCS) (July 2014)

In July 2014, the Advisory Committee on Chemicals Scheduling (ACCS), considered toxicological data on methylisothiazolinone (MI) and noted that its toxicological profile met the Schedule 6 factors of the Scheduling Policy Framework (SPF). MI is not a carcinogen or genotoxic. Based on the toxicity profile of MI, the committee considered that a Schedule 6 entry was warranted. The committee noted the maximum use concentration levels in both leave-on and rinse-off products (0.01%) overseas. In cleaning preparations the concentration level is typically reported to be <1% of MI. However, the committee proposed that a low concentration exemption cut-off to exclude MI from the schedules is not warranted.

The committee was concerned about the reports that indicate an increased number of incidents of clinical sensitisation to MI. They also noted a pre-meeting public submission that proposed deferral of the scheduling decision for cosmetic and domestic products intended for skin contact until the finalisation of the US Cosmetic Ingredients Review (CIR) report, which was expected to be published later that year.

The committee recommended that a new Schedule 6 entry be created for MI and that the delegate seek further information on non-cosmetic uses and possible exemptions. The committee agreed that the name MI should be used in the Poisons Standard.

The delegate noted the committee's recommendation and public submissions. It was agreed that the sensitising potential was the key driver for scheduling MI in Schedule 6 with an appropriate exemption for cosmetics and other products containing a low concentration of MI. The delegate agreed with the proposal to defer further consideration of scheduling MI pending the publication of the final US CIR decision.

Joint ACCS-ACMS (August 2015)

In August 2015, the Joint ACCS-ACMS considered new information on MI and noted that MI was a preservative with increasing prevalence for skin sensitisation due to its increased use pattern in cosmetics, therapeutic goods, industrial and household products. The joint committee recommended that a new Schedule 6 entry for MI be created with certain exemption cut-offs. The delegate agreed and made an interim decision to create a new Schedule 6 entry for MI with a 0.0015 per cent exemption cut-off for rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application and an exemption cut-off of 0.1 per cent in other preparations that are not intended for human use.

In December 2015, the [delegates' final decision](#) was to vary the interim decision, raising the exemption cut-off from 0.0015% to 0.01% (clause (a)) and clarifying that the exemption cut-off of 0.1% only applied to products that are not intended for direct skin contact (clause (b)). The delegate also proposed a staged implementation to allow for an earlier date to control all cosmetics and therapeutic goods applied directly to the skin, with a longer period allowed to phase in scheduling that allows for exemptions on only those products intended to be rinsed off.

The reason for raising the cut-off in clause (a) to 0.01% was to align with current international standards for such products. The committee based its advice on an appropriate cut-off for rinse-off preparations on a proposal from the EU SCCS that was yet to be ratified. The submissions received as part of the interim decision consultation period included comment that industry has submitted data on quantitative risk assessments (QRA) for different product types that demonstrate an adequate safety profile at up to 0.01% MI for some types of cosmetic products. At the time of the December 2015 delegate's final decision the committee noted that should the EU reject these industry submissions and confirm its proposed cut-off for rinse-off products at 0.0015%, there will be sufficient time prior to the proposed implementation date of 1 October 2017 for the current scheduling decision to be revised accordingly.

Australian regulatory information

According to the [TGA Ingredient Database](#), methylisothiazolinone (MI) is available for use as an:

- Excipient in biologicals, devices, export only, listed medicines, over-the-counter and prescription medicines; and
- Active pharmaceutical ingredient in biologicals and prescription medicines.

The following restrictions for MI apply to listed medicines:

*Only for use in topical medicines for dermal application.
The concentration of methylisothiazolinone in the medicine must be no more than 0.01%.*

The total concentration of methylchloroisothiazolinone and methylisothiazolinone in the medicine must be no more than 0.0015%.

MI is in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as follows:

Table 2.6.1: Permissible ingredients and requirements applying to methylisothiazolinone when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
3303	METHYLISOTHIAZOLINONE	E	<p>Only for use in topical medicines for dermal application.</p> <p>The concentration of methylisothiazolinone in the medicine must be no more than 0.01%.</p> <p>The total concentration of methylchloroisothiazolinone and methylisothiazolinone in the medicine must be no more than 0.0015%.</p>

Methylisothiazolinone is used in 5 proprietary ingredient (PI) formulations and is in 97 [Australian Register of Therapeutic Goods \(ARTG\)](#) entries:

- 21 Export Only products;
- 59 Listed Medicines;
- 14 Medicinal Devices;
- 2 Non-Prescription Medicines; and
- 1 Other Therapeutic Good (OTG) Devices.

Products that contain MI include domestic cleaners, sunscreen, mouth wash, cleansing gels, antiseptic wipes and shampoo.

International regulations

The Korean Ministry of Food and Drug Safety (MFDS) has amended the usage limit of compounds of methylchloroisothiazolinone (MCI) and MI. The compounds are used as preservatives in rinse-off products at maximum level of 0.0015% in a ratio 3:1 of the two substances. In Japan, MI is restricted to a maximum level of 0.01 g/100 g (100 ppm [0.01%]) in both wash-off and leave-on cosmetics.

MI has been reviewed and approved for use up to 0.01% (100 ppm) in both leave-on and rinse-off products by the following nations: the Association of South East Asian Nations (ASEAN) (Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, Vietnam), Argentina, Brazil, Canada, Iceland, Israel, Korea, Mexico, Norway, Russia, Switzerland, and Turkey.¹⁰

China

According to Hygienic Standard for Cosmetics 2007, the limit level and requirements are same as the original version of (EC) No. 1223/2009. From 1 Dec 2016, Technical Safety Standard for Cosmetics will come into force to replace Hygienic Standard for Cosmetics 2007. The limit level of MI is still 0.01% in cosmetics. The mixture of methylchloroisothiazolinone (MCI) and MI is only available to rinse-off products with the limit level of 0.0015% in a ratio 3:1 of the two substances. For rinse-off products, the mixture of MCI and MI could not be used with additional MI in cosmetics. The requirements are the same as revised (EC) No. 1223/2009 (COMMISSION REGULATION (EU) No 1003/2014 of 18 September 2014).¹⁰

USA and the EU

The use of MI in wash-off and leave-on cosmetics in the EU and in the USA is restricted to a maximum concentration of 0.01%.

In 2010, the Cosmetic Ingredient Review expert panel concluded that 'MI is safe for use in cosmetic formulation at concentrations up to 100 ppm (0.01%)' (Cosmetic Ingredient Review (CIR), 2010).

The Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) is also of the opinion that 'the proposed use of MI as a preservative at a maximum concentration of 0.01% (100 ppm) in the finished cosmetic product does not pose a risk to the health of the consumer' (SCCS, 2003).

MI was authorised as a preservative in cosmetics products through Annex V, entry 57, of Regulation (EC) No 1223/2009 ("Cosmetics Regulation") at a maximum concentration of 0.01% (100 ppm). The Cosmetics Regulation also authorised the mixture of methylchloroisothiazolinone (MCI) and MI as a preservative in rinse-off cosmetic products at a maximum concentration of 0.0015% (15 ppm) in a ratio 3:1 of the two substances (since 16 July 2015).

The first SCCS opinion related to MI was adopted by the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) in March 2003.

A second SCCS opinion on MI adopted in April 2004 concluded that MI, as a preservative at a maximum concentration of 0.01% (100 ppm) in the finished cosmetic product, does not pose a health risk to the consumer. However, there is an increasing problem all over Europe of sensitization in young children from moist toilet tissue/hygiene moist tissues (wet wipes) and cosmetics. Due to this, the Commission requested that the SCCS reassess the safety of MI at concentrations of 100 ppm.

A third SCCS opinion was adopted in December 2013. The conclusions include but are not limited to:

- Current clinical data indicate that 100 ppm MI in cosmetic products is not safe for the consumer.
- For leave-on cosmetic products (including 'wet wipes'), no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated.
- For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the view of induction of contact allergy. However, no information is available on elicitation.
- Information on the actual concentration of MI present in individual cosmetic products will allow future evaluation of safe concentrations.

¹⁰ [EU Public Consultation on Methylisothiazolinone \(MI\) Ban for Leave-on Cosmetic Products Launched](#), 11 May 2016

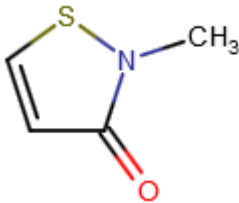
- Labelling is only helpful to a consumer who has a known (established by diagnostic patch test investigations) allergy. It is unknown what proportion of the general population is now sensitised to MI and has not been confirmed as sensitised
- Consumers cannot find information on the presence of MI in products except in cosmetics and household detergents because, as yet, there is no harmonised classification of MI as a skin sensitiser. The risk for skin sensitisation by MI is at least equivalent to that of other substances which have received a harmonised classification according to the CLP Regulation

In December 2015, the SCCS adopted the fourth opinion. It was concluded that the information provided does not support the safe use of MI as a preservative in rinse-off cosmetic products up to a concentration limit of 100 ppm from the view of induction of contact allergy. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the point of view of induction of contact allergy. It was not safe to use MI as a preservative in leave-on hair cosmetic products up to a concentration limit of 100 ppm (0.01%) from the point of view of induction of contact allergy.

Substance summary

Methylisothiazolinone (MI) is used in domestic (e.g. car wash soaps, floor finishing/protection products), industrial (e.g. coatings and paint), and cosmetic (e.g. baby wipes, hand and body lotions, shampoos, surfactants and conditioners) products.

Table 2.6.2: Chemical information for methylisothiazolinone

Property	Methylisothiazolinone
Chemical structure	
Molecular formula	C ₄ H ₅ NOS
Molecular weight	115.2 g/mol
CAS name	3(2 <i>H</i>)-Isothiazolone, 2-methyl
CAS number	2682-20-4
IUPAC and/or common and/or other names	2-methyl-1,2-thiazol-3-one (IUPAC); 2-methylisothiazol-3(2 <i>H</i>)-one.

The following information was extracted from the [NICNAS Inventory Multi-tiered Assessment Prioritisation \(IMAP\) human health Tier II assessment report for 3-isothiazolone, 2-methyl-](#), publicly available on the NICNAS website.

Table 2.6.3: Acute toxicity end-points for methylisothiazolinone

Toxicity	Species	Methylisothiazolinone	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	209 (183-235)	Schedule 6
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rat	242	Schedule 6
Acute inhalational toxicity LC ₅₀ (mg/L/4h)	Rat	0.11	Schedule 7
Skin irritation	Animal and Human	1.7% not corrosive 51.1%-100% corrosive	Schedule 7
Eye irritation	Bovine	100 ppm found as non-irritating. Expectation is that undiluted MI will be severely damaging to the human eye – classification: severely damaging.	Schedule 7
Skin sensitisation (LLNA)	Mouse	Buehler test positive at 1000 ppm or higher GPMT not a sensitiser at concentrations up to 800 ppm EC3 0.4% (acetone and olive oil) EC3 2.2% PG solution HRIPT up to 600 ppm did not cause dermal sensitisation, but once sensitised, the lowest eliciting dose of 49ppm has been observed (CIR, 2010) Strong sensitising potential	Schedule 6

Toxicokinetics

Toxicokinetic studies in rats using the chemical and its analogue (CAS No. 55965-84-9) show that it is readily absorbed and metabolised. The major metabolic products of the chemical are *N*-methyl malonamic acid (NMMA) and the 3-mercaptopuric acid conjugate of 3-thiomethyl-*N*-methyl-propionamide. These studies did not report accumulation of the chemical or its metabolites in tissues. It is widely distributed to all tissues in the body, with the highest level seen in the liver and lowest in the bone. The chemical is eliminated within 24 hours through urine > bile > faeces. In an *in vitro* human skin absorption study conducted in accordance with OECD Test Guideline (TG) 428, aqueous solutions of products containing the chemical were applied by occlusion for 24 hours at concentrations of 52.2, 104.3 or 313 µg/mL. Potential systemic bioavailability was estimated as a maximum of 75.5% of the applied dose (SCCS, 2009).

Acute oral toxicity

MI had high acute toxicity in animal tests following oral exposure. The median lethal dose (LD₅₀) in rats (CrI:CD®BR strain) was 209 mg/kg bw (235 for male and 183 mg/kg bw for female rats). MI (99.7%) was administered as a single dose through gavage at concentrations of 75, 150, 180, 225 and 300 mg/kg bw. Observed sub-lethal effects included passivity, ataxia, scant or no faeces, mucus in faeces, yellow or brown stained anogenital area, red-stained muzzle and/or lacrimation. Additionally, at necropsy reddened intestines and/or stomach mucosa, reddened glandular portion of the stomach, and distended stomachs were observed (CIR, 2010; SCCNFP, 2003).

Based on the available data, MI is recommended for classification as hazardous with the risk phrase 'Toxic if swallowed' (T; R25) in HSIS (Safe Work Australia).

Acute dermal toxicity

MI had high acute toxicity in animal tests following dermal exposure. The median lethal dose (LD₅₀) in rats (CrI:CD®BR strain) was 242 mg/kg bw for both sexes. MI (97.5%) was administered undiluted at a single 24-hour occluded topical application on shaved intact skin. Observed sub-lethal effects included decrease in body weight in both sexes at higher dose groups (200 mg/kg and above). Local effects included blanching, oedema, erythema, desiccation, darkened or reddened areas, scabs, eschar, and/or sloughing (CIR, 2010).

Based on the available data, MI is recommended for classification as hazardous with the risk phrase 'Toxic in contact with skin' (T; R24) in HSIS (Safe Work Australia).

Acute inhalation toxicity

MI had high acute toxicity in animal tests following inhalation exposure. The median lethal concentration (LC₅₀) for aerosol in rats (CrI:CD®BR strain, 6 animals/group) after four-hour exposure was 0.11 mg/L. The necropsy showed signs of slight to severe redness in all lobes of the lung in all treatment groups (CIR, 2010).

In another study, the LC₅₀ in rats (CrI:CD®BR strain, 5 animals/group) after four-hour aerosol exposure was reported at 0.33 mg/L. Observed sub-lethal effects included body weight reduction in females at higher dose groups (0.25 mg/kg and above). Signs of pale and/or reddened lungs, distended intestines, and/or wet muzzles were observed at necropsy (CIR, 2010).

Based on the available data, MI is recommended for classification as hazardous with the risk phrase 'Very toxic by inhalation' (T; R26) in HSIS (Safe Work Australia).

Skin irritation

Based on the available data, MI is recommended for classification as hazardous with the risk phrase 'Causes burns' (R34) in HSIS (Safe Work Australia).

MI was applied undiluted as a single semi-occluded application of 0.5 mL to shaved intact skin of New Zealand White rabbits for 3 minutes, 1 hour, and 4 hours. The 3-minute exposure resulted in a very slight to well-defined erythema through to day 7 and slight oedema at 1 and 48 hour observations. At 1 and 4 hour exposures to MI, skin irritation indicative of corrosivity (concave eschar) was observed on days 7 and 14, respectively (CIR, 2010; SCCNFP, 2003). In an *in vitro* study with skin constructs, exposure to 1.7% of MI for three or 60 minutes was not corrosive to the skin. However, MI was corrosive at higher concentration of 51.1% at an exposure period of 60 minutes (CIR, 2010).

Eye irritation

MI is recommended for classification as corrosive. It is expected that undiluted MI will be severely damaging to the eyes.

MI (undiluted) was found to be an irritant in a bovine cornea study measuring opacity and permeability. Eye irritation studies using formulations containing MI at 100 ppm (body lotion, shampoo and sunscreen) were found non-irritating (CIR, 2010).

Skin sensitisation

MI produced skin sensitisation effects in several animal and human studies. Although the potency of these effects varied across the studies, skin sensitisation was sufficiently noted across all the studies to support the classification (SCCS, 2009; CIR, 2010; Lundov *et al.*, 2011; Yazar *et al.*, 2011; Boyapati *et al.*, 2013; Cahill *et al.*, 2014; SCCS, 2013; Lammintausta *et al.*, 2014).

MI, in combination with methylchloroisothiazolinone (MCI) in a ratio of 1:3, has been used in industrial and consumer products as a preservative since the beginning of the 1980s. The first cases of contact allergy caused by these chemicals were published in 1985. Although MCI has been considered a more potent sensitiser than MI, it is still classified as a strong sensitiser. As a result of the sensitising potential of these chemicals, the maximum permitted concentration in the EU of the mixed preservative in cosmetics in the ratio of 1:3 (MI:MCI) is 15 ppm (0.0015%); the allowed concentration of MI in the mixture is 3.75 ppm. Following a review of the safety of MI, MI was allowed in cosmetic products in the EU at a maximum concentration of 100 ppm in 2005 (SCCNFP, 2003; Lundov *et al.*, 2011). The CIR expert panel recommended that the United States cosmetic manufacturers use the chemicals at the same concentrations as allowed in the EU (CIR, 2010).

Following its approval for use as a preservative in cosmetic products in 2005 at a maximum concentration of 100 ppm, several reports have indicated the emergence of the issue of contact allergy to MI (see [Sensitisation: observation in humans](#)). The permitted use of MI at 100 ppm in cosmetic products is approximately 25-fold the permitted concentration of MI in the MI/MCI combination (3.75 ppm MI in 15 ppm of MI/MCI).

MI, in a combination with MCI (1:3 ratio), is also used as a preservative in industrial products and there are no restrictions on the use of MI in industrial products. MI-induced occupational contact allergy and dermatitis were also reported after contact with wall covering glue and in a paint factory (Lundov *et al.*, 2011; Boyapati *et al.*, 2013; SCCS, 2013).

Although several reports on the sensitisation potential of the mixture (MI:MCI) are available in animals, the most comprehensive studies conducted on MI are reported below.

The potential for MI to cause skin sensitisation was investigated in an OECD Test Guideline (TG) 406 study (Buehler test). In this study, four groups of Hartley guinea pigs (five/sex/group) were treated with MI in the form of 6 hours' induction with three doses each week for 3.5 weeks under an occlusive condition. MI was administered at 0.4 mL/dose containing concentrations of 1000, 5000, 15000 and 30000 ppm suspended in distilled water on shaved intact skin. The animals were allowed to rest for two weeks before the challenge application. During the challenge phase, the animals were patched with MI at doses 1000, 5000, or 15000 ppm in distilled water. The treated animals were monitored for erythema for 24 or 48 hours following the application. Appropriate controls were also used in this study. The results showed no erythema reactions in the non-induced control animals at any challenge concentration. However, incidences of erythema were observed in animals induced and challenged with MI at 1000 ppm or higher (Burnett *et al.*, 2010; SCCS, 2013).

In another study (maximisation test), 60 female Hartley guinea pigs received six intradermal injections containing induction doses of 500 ppm or 800 ppm of MI. After a week, the treated animals were given a single 24-hour topical exposure to 0.1 mL of MI under occlusive conditions. The animals were challenged with 500 ppm or 800 ppm after two weeks and were evaluated for reactions at 24 and 48 hour periods. The animals were also subjected to rechallenge with 1000 ppm. The results showed that 500 ppm did not cause dermal reactions. Only one reaction was noted at 800 ppm dose challenge after the 48-hour observation. During the rechallenge, less than 30% of the animals displayed grade one erythema. Based on these results, MI was not considered a sensitiser at concentrations up to 800 ppm (Burnett *et al.*, 2010).

Furthermore, several mouse local lymph node assay (LLNA) studies have reported evidence suggesting that MI is a potential skin sensitiser. In one study, female CBA/Ca mice were treated with MI (19.7% purity in water) at the concentrations of 0.049, 0.099, 0.197, 0.493, 0.985% in acetone and olive oil (4:1; v/v) and also at the concentrations of 0.99, 1.97, 4.93, 9.85% in propylene glycol (PG). The induction phase consisted of applying MI, positive controls (formaldehyde, glutaraldehyde, MCI/MI mixture) or vehicles over the ears (25 µL/ear) for three consecutive days (days one, two and three). After two rest days, the proliferation of lymphocytes in the lymph node draining the application site was measured by incorporating tritiated methyl thymidine (day six) for five hours. A linear interpolation of the dose-response data was used to estimate concentrations required to induce stimulation indices (SI) of 3, relative to concurrent vehicle-treated controls (the EC3 value). The EC3 values of 0.4 and 2.2% were calculated for MI for acetone and olive oil (4:1; v/v) and PG solutions, respectively. It was concluded that MI has strong sensitising potential, with potency being comparable to that of the formaldehyde although much lower than the mixture of MI with MCI in 1:3 ratio. Similar findings were noted in another study, indicating that MI is a sensitiser at concentrations greater than 0.76% in acetone/olive oil (4:1) with a reported EC3 value of 0.86% (SCCS, 2013).

Overall, these data suggest that MI is a potential skin sensitiser.

Observation in humans

Contact allergy to MI and the mixed preservative (MI:MCI) has been commonly reported following its approval for use in cosmetics in 2005. Increased incidence of clinical sensitisation to MI was more evident following the introduction of patch test for MI alone. The prevalence of sensitisation increased from 1.94% of all dermatological clinic patients in 2009 to 6.02% in 2012 in Germany. This increase was mainly stated to be driven by female patients aged ³ 40 years, patients with facial dermatitis, and the use of cosmetics. Additionally, MI was named the 2013 "Contact Allergen of the Year" by the American Contact Dermatitis Society, indicating increased incidence of MI-induced contact dermatitis (Cahill *et al.*, 2014). Painters, beauticians, and patients with ano-genital dermatitis were identified as being potentially at risk for sensitisation to MI (Lundov *et al.*, 2011; Uter *et al.*, 2013; Gameiro *et al.*, 2014; Lammintausta *et al.*, 2014).

In a series of repeat insult patch tests (RIPT) in human volunteers, exposure to MI at doses 200, 300, 400, 500, or 600 ppm did not cause dermal sensitisation (CIR, 2010; Burnett *et al.*, 2010). Conversely, cases of allergic contact dermatitis were also reported in patients who had come into contact with coolant solutions containing biocides and those who were exposed to paint additives containing 7-10% of MI. In addition, a lowest eliciting dose of 1.47 µg of MI (49 ppm) was observed in a sensitisation studies conducted in 11 MI-allergic patients (CIR, 2010).

MI has been reported to be an emerging and important allergen in both cosmetic and occupational settings in Australia. Baby wipes and facial wipes containing MI were reported to be an important cause of hand dermatitis in carers. Facial dermatitis in children was also noted following the use of moist wipes containing MI. It was concluded that the continued use of MI in baby wipes and facial wipes will lead to increased rates of allergy to these preservatives in adults. The present study also noted three cases of contact allergy as occupational exposure from hand cleansers containing MI (Boyapati *et al.*, 2013). Based on the results of a series of patch test conducted from 2011-2013, the Medical Journal of Australia reported a significant increase in the incidence of contact dermatitis in adult patients from the use of the baby wipes which contain MI (Cahill *et al.*, 2014). In this report, the authors highlighted this remarkable rise of contact dermatitis from 3.5% in 2011 to 11.3% in 2013 among their patient population. The authors also noted that MI is now the most common cause of allergic contact dermatitis in their patient population (Cahill *et al.*, 2014).

The SCCS presented its opinion on the safety of MI in consumer products. The committee concluded that, on the basis of current clinical data, the use of MI at 100 ppm in cosmetic products is not safe for the consumer. The committee also concluded that, for leave-on cosmetic products (including wet wipes), safe concentrations of MI for induction of contact allergy or elicitation have not been adequately demonstrated. Although a concentration of 15 ppm (0.0015%) of MI was considered safe

for the consumer with respect to induction of contact allergy for rinse-off cosmetic products, no information was available for these products with respect to elicitation of contact allergy (SCCS, 2013).

Repeated Dose Toxicity

Repeated dose toxicity – Oral

Based on the available data, MI is not considered to cause serious damage to health from repeated oral exposure.

No treatment related effects were observed in rats (Crl:CD®BR strain) exposed to MI (up to 1000 ppm, equivalent to 65.7 and 93.5 mg/kg bw/day in males and females, respectively) in drinking water for 3 months. Dogs fed with diets prepared with MI for three months had a NOAEL of 1500 ppm (41 mg/kg bw/day) (CIR, 2010; US EPA, 1998).

Repeated dose toxicity – Dermal

No data were available for MI. Based on the available toxicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and MI, CAS No. 55965-84-9), in which there was no evidence of toxicity; MI is not considered to cause serious damage to health from repeated exposure.

A formulation containing the analogue chemical (2.55:1 ratio) was applied once daily for 91 days to the intact skin of Sprague Dawley (SD) rats by semi-occlusive dressing at doses of 0, 0.75, 3.75, or 18.75 mg/kg bw/day. Treatment-related skin reactions at all doses included slight to moderate erythema and desquamation, slight oedema and atonia, and eschar formation. Microscopic findings revealed treatment-related lesions such as inflammation, parakeratosis, and acanthosis at the treated sites. The LOAEL and NOAEL identified for local effects in this study, were = 0.104 and < 0.104 mg/kg bw/day (SCCS, 2009).

Repeated dose toxicity – Inhalation

No data were available for MI. Based on the available inhalation toxicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone, CAS No. 55965-84-9), in which there was no evidence of inhalation toxicity, MI is not considered to cause serious damage to health from repeated exposure through this route.

In a study conducted in accordance with OECD TG 413, Charles River (Crl:CD®(SD)BR) rats were exposed to an aerosol product containing 14% of the analogue chemical for 13 weeks (0, 0.34, 1.15, or 2.64 mg/m³, at 6 hours/day, 5 days/week). At the top dose, effects included decreased bodyweight gain and signs consistent with sensory irritation such as chromorhinorrhoea, rhinorrhoea, eye squint, bradypnoea, and dyspnoea. Slight to moderate eosinophilic droplets in the anterior mucosa of the nasal turbinates and slight rhinitis in the lining of the nasal cavity were also reported at the top dose. At the mid-dose, slight incidence of rhinitis was observed. The study authors noted that eosinophilic droplets in the nasal turbinates and rhinitis were possibly reversible responses to upper respiratory tract inflammation. The lowest-observed-adverse-effect-concentration (LOAEC) and no-observed-adverse-effect-concentration (NOAEC) for this study were 2.64 and 1.15 mg/m³, respectively (SCCS, 2009; US EPA, 1998).

Genotoxicity

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, MI is not considered to be genotoxic.

MI was not mutagenic in Ames tests in *Salmonella typhimurium*, with or without metabolic activation (CIR, 2010; SCCNFP, 2003). MI (0.5-40 µg/mL) was also negative in an *in vitro* chromosome aberration study using the Chinese hamster ovary (CHO) cells, both with and without metabolic activation. In another study using CHO cells, chromosomal aberrations (at 3.75 µg/mL without S-9 activation (28% aberrant cells) and at 7.50 µg/mL with S-9 activation (34% aberrant cells) were seen accompanied by significant cytotoxicity (29-48% reductions).

MI was reported to be negative in an *in vivo* mouse micronucleus assay (CIR, 2010; SCCNFP, 2003).

Carcinogenicity

No data are available for MI. Based on the weight of evidence from the available carcinogenicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and MI, CAS No. 55965-84-9), in which there was no evidence of carcinogenicity; MI is not likely to be a carcinogen.

In a two-year drinking water study on rats (CRL:CD BR) exposed to the analogue chemical, no treatment related neoplasms were observed up to the highest dose tested, 300 ppm (equivalent to 17.2 mg/kg bw/day). Hyperplasia of the forestomach was seen at mid and top doses. This was attributed to the corrosive nature of MI (CIR, 2010).

Reproductive and developmental toxicity

MI does not show specific reproductive or developmental toxicity.

In a two-generation reprotoxicity study, no treatment-related effects were noted in rats (Crl:CD IGS BR strain) exposed to MI (up to 86 mg/kg bw/day in males and 115 mg/kg bw/day in females) through drinking water (CIR, 2010; US EPA, 1998).

Two teratogenicity studies showed no treatment-related effect in rats (Crl:CD(SD) IGS BR strain) and rabbits (New Zealand White) exposed to MI at concentrations up to 40 and 30 mg/kg bw/day respectively. Based on the results, the maternal NOAELs were 20 (rats) and 10 (rabbits) mg/kg bw/day and developmental NOAELs were 40 (rats) and 30 (rabbits) mg/kg bw/day (CIR, 2010; US EPA, 1998).

Neurotoxicity

An acute *in vitro* neurotoxicity study of MI using cultures of embryonic rat (SD) cortical neurons and glia observed widespread neuronal cell death within 24 hours in the cortical cultures exposed to 100 and 300 µM (highest concentration tested) concentrations. Gliotoxicity was low. Another 14-hour *in vitro* neurotoxicity study of MI concluded that prolonged exposures to MI and related isothiazolones may damage developing nervous systems (based on cell death observed in cultures treated with 3 µM concentration of MI along with changes in signalling complexes normally found in developing neurons) (CIR, 2010). However, no evidence of neurotoxicity was observed *in vivo* in the repeat dose or reproductive and developmental animal studies.

Pre-meeting public submissions

Four (4) public submissions were received, two (2) in support and two (2) opposed.

Main points in support:

- Both submissions did not oppose the proposed amendment. However, it was requested that the decision be deferred until the EU restriction is finalised and the legislation is European law.
- One submission noted that clarification is required for the ongoing requirement of Appendix F warning, as the proposed concentration cut-off is considered safe, therefore deeming the warning unnecessary.
- Both submissions requested a realistic implementation date of 24-30 months.

Main points opposed:

- Australian cosmetic market is relatively small compared to major trading partners. Therefore, making regulatory decisions ahead of the EU could have a major impact across the industry.
- The EU decision is currently not known.

- Both submissions proposed for the committee and delegate to defer making the decision until the EU restriction has been finalised to allow alignment of both the concentration exemption level and the implementation timing of decision.
- One submission requested that any scheduling decision to include an adequate transition period of 12-24 months to allow for the reformulation of products.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that the Schedule 6 entry for methylisothiazolinone due to be implemented on 1 October 2017 stands, but that from **1 June 2018** the exemption cut-off of 0.01 per cent for rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application be amended to 0.0015 per cent as follows:

Schedule 6 – Amend Entry

METHYLISOTHIAZOLINONE **except:**

- a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing ~~0.01~~ **0.0015** per cent or less of methylisothiazolinone; or
- b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone.

The committee also recommended an implementation date of **1 June 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- While preservatives are required in cosmetic and topical therapeutic products, MI has been found to be unsafe as a stand-alone preservative based on human data.
- MI is an effective biocide and preservative, is widely used in products intended for skin contact, but is a well-documented cause of contact allergy. Risk management through scheduling is therefore necessary to mitigate risk whilst allowing limited continued use.
- The incidence of skin sensitisation in human populations from MI use has been unacceptable. The acute toxicity parameters for MI are consistent with Schedule 6 factors. In particular the *in vitro*/animal study and human case reports and epidemiological evidence indicates that MI is a strong skin sensitiser.
- A low level exemption cut-off will limit MI use in cosmetics and therapeutic goods intended for rinse off skin application and minimises risk of induction of contact allergy.
- The proposed schedule entry will result in equivalent outcome to recently announced amended EU cosmetic regulation.

- There is a disparity between elicitation concentration seen by dermatologists test and induction seen in products.¹¹

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is that the Schedule 6 entry for methylisothiazolinone due to be implemented on 1 October 2017 stands. However, from 1 June 2018 the exemption cut-off of 0.01 per cent for rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application be amended to 0.0015 per cent. The proposed Schedule entry is as follows:

Schedule 6 – Amend Entry

METHYLISOTHIAZOLINONE **except:**

- a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.0015 per cent or less of methylisothiazolinone; or
- b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone.

The proposed implementation date is **1 June 2018**. A later implementation date allows for industry alignment.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

- While preservatives are required in cosmetic and topical therapeutic products, MI has been found to be unsafe as a stand-alone preservative based on human data.
- MI is an effective biocide and preservative, is widely used in products intended for skin contact, but is a well-documented cause of contact allergy. Risk management through scheduling is therefore necessary to mitigate risk whilst allowing limited continued use.

¹¹ Rodrigues-Barata, AR and Conde-Salazar, L (2014) 'Methylisothiazolinone and methylchloroisothiazolinone: new insights', *European Medical Journal*, 101-105; Urwin, E *et al.* (2017) 'Methylisothiazolinone: the epidemic is declining – but not gone', *Contact Dermatitis*, 76, 296-321; Amsler, E *et al.* (2017) 'Airborne allergic contact dermatitis caused by isothiazolinones in water-based paints: a retrospective study of 44 cases', *Contact Dermatitis*, 1-8; Craig, S *et al.*, (2017) 'Patch test clinic experience of potential cross-reactivity of isothiazolinones', *Contact Dermatitis*, 76, 296-321.

- The incidence of skin sensitisation in human populations from MI use has been unacceptable. The acute toxicity parameters for MI are consistent with Schedule 6 factors. In particular the *in vitro*/animal study and human case reports and epidemiological evidence indicates that MI is a strong skin sensitiser.
- A low level exemption cut-off will limit MI use in cosmetics and therapeutic goods intended for rinse off skin application and minimises risk of induction of contact allergy.
- The proposed schedule entry will result in equivalent outcome to recently announced amended EU cosmetic regulation.
- There is a disparity between elicitation concentration seen by dermatologists test and induction seen in products.¹¹
- The EU adopted the SCCS 4th opinion position on 6 July 2017, and requires all products in the EU market to be compliant by 27 April 2018.

2.7. Epidermal growth factor

An application was submitted to amend the Schedule 7 entry for epidermal growth factor (EGF) to exempt topical cosmetic preparations containing low concentrations of transgenic plant EGF.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 7 – Amend Entry

EPIDERMAL GROWTH FACTOR ~~except in preparations for therapeutic use:~~

- a) in preparations for human therapeutic use; or
- b) in topical cosmetic preparations containing 0.0002% or less of transgenic, plant-made epidermal growth factor.

This is a re-scheduling proposal for epidermal growth factor (EGF) that was considered by the joint ACCS-ACMS at the November 2016 meeting. The advice at that time was that the current Schedule 7 not be amended.

In support of the application, the applicant has provided additional information and consideration of an alternative proposal to move the parent entry for EGF to Schedule 4. The applicant suggests that this would align EGF to a consistent scheduling classification with other growth factors. The applicant contends this would enable cosmetic use at very low concentrations to be exempt from scheduling.

The initial reasons for the request provided to the committee in November 2016 were:

- The wording of the current Schedule 7 entry for EGF captures any use of EGF other than for human therapeutic use. This is despite the original scheduling submission relating to injectable u-hEGF (urinary human EGF).
- Since the addition of EGF into the Poisons Standard after the November 1996 advisory committee meeting, there have been significant technological developments in cosmetic product innovation, such as the development of recombinant chemicals in plants for cosmetic use. These substances are commonly used topically in very low concentrations in cosmetic products, having acceptable safety profiles and meeting international regulatory requirements for cosmetic use.
- By amending the Schedule 7 entry, the applicant proposes that this would allow supply of their cosmetic products to Australian consumers within the provisions of Australian consumer protection laws. Therefore, the product will be able to compete with similar cosmetic products available to purchase online via overseas websites.

- The original 1996 National Drugs and Poisons Scheduling Committee (NDPSC) decision on EGF considered a veterinary application for injectable EGF. The consequent Schedule 7 entry was valid for veterinary use, and the Schedule 7 entry only exempts EGF for human therapeutic use. The decision by the NDPSC to include EGF in both Schedule 7 and Appendix J indicates that the committee's scheduling decision was focussed on veterinary use of the substance. This was further demonstrated by the Appendix J entry, confining its use to authorised or licensed persons.

New information provided by the applicant on the toxicity and safety of the substance:

A) Risks and Benefits associated with the use of a substance

The absence of any cosmetic regulatory controls by any regulatory agency of EGF, other growth factors or cytokines in cosmetic products internationally, confirms that there has been no hazard to public safety associated with this substance when used in cosmetic products, i.e. topical use at low concentrations. This supports unrestricted public availability for this usage pattern, which is significantly different to the hazard associated with systemic application of EGF in veterinary use, which prompted the original Schedule 7 entry.

B) Purposes for which a substance is to be used and the extend of use of that substance

No new information was provided.

C) Toxicity and safety of the substance

Cosmetic ingredients are subject to a different set of criteria for safety assessment compared to medicinal substances due to their vastly different intended uses and dosages. There are limited specific studies available with endpoints to assess the toxicity and safety of cosmetic products. To address the concerns expressed by the ACCS-ACMS meeting #14, it is necessary to cross refer to studies undertaken with EGF in the context of its therapeutic function in wound healing. The intended scheduling exemption is for very low concentrations of topical use of EGF in cosmetic products, and the usage profile of EGF for cosmetic purposes is very different to that used in the context of wound healing studies.

EGF has been used since 1989 to accelerate healing of open human skin wounds, such as chronic ulcers and burns, without observed increased incidence of serious adverse effects.

A 2014 publication provides a systemic review and meta-analysis of 12 randomised clinical trials, in which growth factors were used in therapeutic dosages for treatment of burns. Of these 12 studies, 4 used EGF as the treatment. 476 patients were enrolled in the EGF studies, of which 240 patients used EGF and standard wound care, whilst 236 were in the control group and used standard wound care alone. The concentration of EGF used in these studies ranged from 80,000 pg/cm² to 1200000 pg/cm². The results showed a dose dependent acceleration in wound healing.¹²

No allergic, toxicity or systemic adverse reactions were reported from these studies. The concentrations of EGF used in these studies in injured skin, enabling systemic absorption, has been calculated by the applicant to be 800 times greater than the EGF concentrations proposed for exemption from scheduling for cosmetic use on intact skin.

These results are consistent with the safety profile reported in the review published by Berlanga-Acosta (International Wound Journal, Vol 6, No 5. 2009) presented in the original submission to ACCS-ACMS.

Further to this clinical experience, the applicant's supply of EGF and the company quality managements system confirms that there have been no serious undesirable effects, or undesirable effects reported. Only limited numbers of minor or mild reported effects including mild irritation, itching, and small pimples have been reported, all of which are classified as minor or mild.

¹²Zhang, Y *et al.*, (2016), Growth factor therapy in patients with partial-thickness burns: a systemic review and meta-analysis *International Wound Journal*, 13(3):356-66.

New information provided by the applicant related to the Hebermin clinical study.¹³

New information provided by the applicant related to the Heberprot-P clinical study.¹⁴

D) Dosage, formulation, labelling, packaging and presentation of a substance

The ACCS-ACMS meeting #14 expressed concern about the therapeutic intent of cosmetic products containing very low concentrations of EGF. This was one of the reasons for retaining the current scheduling of EGF in Schedule 7.

The intended purpose of the plant-made EGF proposed for exemption from scheduling is as a skin conditioning cosmetic ingredient in formulated topical cosmetic products, at concentrations of 0.0002% or less. Cosmetic products containing this ingredient for this intended purpose are able to be purchased without restriction by consumers in the EU, USA, Canada, Japan, South Africa, China and South America.

Cosmetic products are prohibited from making any representations for therapeutic use in labelling, packaging or advertising. Concerns of therapeutic intent are adequately and appropriately controlled through the legislative provisions of the Australian Consumer Law, as set out in Schedule 2 of the [Competition and Consumer Act 2010](#).

E) Potential for misuse/abuse

No new information was provided.

F) Any other matter that may be relevant to the scheduling of a substance

A review by Zhang *et al.*, includes clinical studies using other growth factors.¹² There are no scheduling controls that apply to cosmetic products supplied in Australia that use other growth factors. For example:

- Product 1: has been subject to published reviews that identify a mixture of growth factors, cytokines, and soluble matrix proteins secreted by cultured neonatal human dermal fibroblasts during production of extracellular matrix in an oil-free gel formulation.¹⁵
- Product 2: see attached screen shot from Australian website¹⁶
- Product 3: one of many new cosmetic serums available in Australia that use the secretions of the snail *Cryptomphalus aspersa* (SCA), which contains a mixture of growth factors and peptides for the improvement of facial wrinkles.¹⁷

It is understood that this is because the parent schedule entry for the growth factors present in these other products are in Schedule 4, and the low concentrations present in cosmetic preparations enable the products to use the exemption from scheduling that apply to very low concentrations (Ref Poisons Standard Part 1 Interpretations 2 (j)) but does not include:

¹³The HEBERMIN epidermal growth factor studies were conducted in burns patients, where skin integrity is damaged, and these studies did not demonstrate systemic absorption (Hebermin Clinical results). The study results state "*the detected EGF corresponded to the endogenous human EGF, and there was very little or no protein absorption as a result of the topical application of the EGF as a cream.*" These results are important since the little penetrability revealed suggests that the molecule is captured by the receptors in the cutaneous epithelium cells, and by the dermis fibroblasts, which contributes to the safety of the product by reducing the possibility of adverse systemic or long term effects.

¹⁴ A further study on parenteral Heberprot-P injection for treating advanced diabetic foot ulcers demonstrated a dose-effect relationship for adverse effects. There were reported adverse effects of mild to moderate pain and burning at administration site as being the most frequently reported effect. Pain reported was mild to moderate in intensity and was not associated with treatment. (J.Berlanga *MEDDDIC review*, Jan 2013, 15(1) (Heberprot-P A novel product for treating advanced diabetic foot ulcer *MEDDDIC Review* Jan 2013)

¹⁵ Mehta *et al.*, (2008), Reduction in facial photodamage by a topical growth factor product. *Journal of Drugs in Dermatology*, 7(9):864-71.

¹⁶ Environ Intensive Colostrum Gel- Au website

¹⁷ Fabi *et al.*, (2013), The effects of filtrate of the secretion of the *Cryptomphalus aspersa* on photoaged skin. *Journal of Drugs in Dermatology*, 12(4):453-7.

‘any other substance included in Schedules 1 to 6, at a concentration not exceeding 10 mg per litre or 10 mg per kilogram, unless that substance is also included in Schedule 7 or 8.’

Alternatively, consideration is requested for moving the parent entry for EGF to Schedule 4. This would align EGF to a consistent scheduling classification with other growth factors. This would enable cosmetic use at very low concentrations to be exempt from scheduling.

Current scheduling status and relevant scheduling history

Epidermal growth factor is currently listed in Schedule 7 of the Poisons Standard as follows:

Schedule 7

EPIDERMAL GROWTH FACTOR **except** in preparations for human therapeutic use.

It is also included under the entry EPIDERMAL GROWTH FACTOR in Appendix J, Part 2 with the following statements:

Appendix J – Part 2

EPIDERMAL GROWTH FACTOR

Standard Statement: 1 (Not to be available **except** to authorised or licensed persons).

In November 1996, the National Drugs and Poisons Schedule Committee (NDPSC) considered an application for a recombinant epidermal growth factor for use in sheep. It was listed in the Poisons Standard in Schedule 7 and Appendix J, Condition 1.

In June 2008, the NDPSC considered a minor editorial amendment to the Schedule 7 entry of epidermal growth factor, changing the entry from “other than for” to “**except** for” in reference to “preparations for human therapeutic use”.

In November 2016, the Joint Advisory Committee on Chemicals and Medicines Scheduling (ACCS-ACMS meeting #14) considered a proposal to amend the wording of the Schedule 7 entry for EGF to exempt topical cosmetic preparations containing low concentrations of transgenic plant-made epidermal growth factor from the scope of the Schedule 7 entry. The committee recommended that the current scheduling of epidermal growth factor in Schedule 7 remained appropriate, and the scheduling delegate concurred. The scheduling delegate’s final decision can be found on the TGA website at [Scheduling delegate's final decisions, March 2017 - 2.4 Epidermal Growth Factor](#).

Australian regulatory information

According to the [TGA Ingredient Database](#), EGF is available for use as an:

- Active and excipient ingredient in biologicals and prescription medicines.

EGF is used in one PI formulation and it is present in one product on the ARTG at 15% v/v. The concentration of EGF in the PI is unknown.

Epidermal growth factor is not listed in [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#).

International regulations

There is limited information on the clinical use of EGF internationally. However, EGF has been used experimentally to treat diabetic foot ulcers¹⁸ and mucositis in patients undergoing radiotherapy.¹⁹ A

¹⁸ Berlanga *et al.*, 2013 [Heberprot-P: a novel product for treating advanced diabetic foot ulcer](#), *MEDICC Rev.* Jan;15(1):11-5.

¹⁹ Wu *et al.*, 2009 [Therapeutic effect of recombinant human epidermal growth factor \(RhEGF\) on mucositis in patients undergoing radiotherapy, with or without chemotherapy, for head and neck cancer: a double-blind placebo-controlled prospective phase 2 multi-institutional clinical trial](#), *Cancer*. Aug 15;115(16):3699-708. doi: 10.1002/cncr.24414

collation of published papers (through Pubmed and Bioline International) related to the clinical use of EGF was published in 2009.²⁰

There are no cosmetic regulatory controls of EGF, or other growth factors or cytokines in cosmetic products internationally. Cosmetic products containing EGF at concentrations of 0.0002% or less are able to be purchased without restriction by consumers in the EU, USA, Canada, Japan, South Africa, China and South America.

EGF is unclassified in NZ, the EU and the USA.

Canada

EGF is listed on the Health Canada website as being a '[Substances in Cosmetics and Personal Care Products Regulated Under the Food and Drugs Act \(F&DA\) That Were In Commerce between January 1, 1987 and September 13, 2001.](#)' EGF is classified as a medicinal ingredient in Canada according to an April 2017 document titled, '[Guidance Document on Classification of Veterinary Drugs and Animals Feeds.](#)'

Substance summary

Human EGF is a short 53 amino acid polypeptide. It is secreted by cells and acts as a mitogen, stimulating cellular proliferation, differentiation and survival primarily through the epidermal growth factor receptor (EGFR).

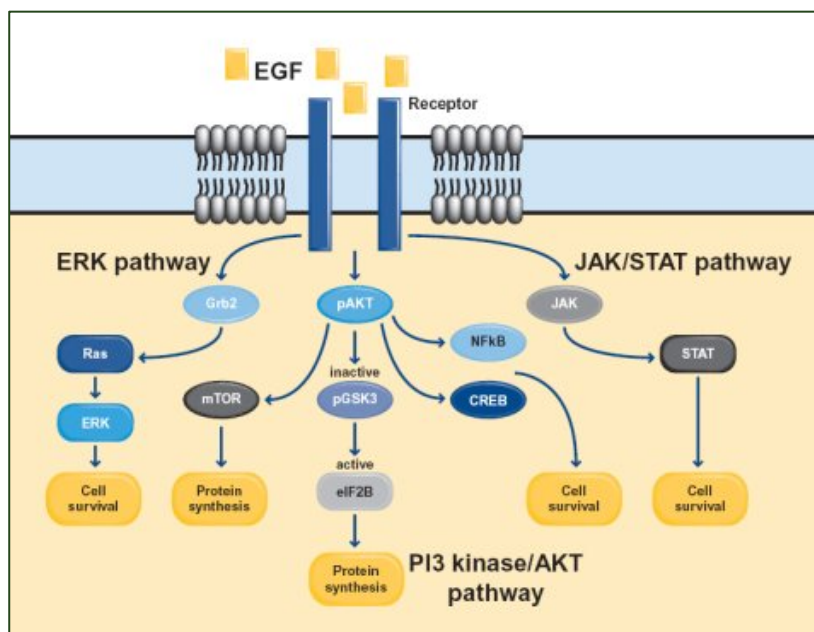


Figure 2.7.1: EGF stimulation cell signal pathway diagram

Barley sh-Oligopeptide-1(CAS 1807528-51-3) is a plant produced peptide expressed from an *in vitro* synthesised gene with a barley (*Hordeum Vulgare*) codon optimization.

Barley sh-Oligopeptide-1 is a single chain recombinant human-like growth factor, produced by the barley plant (*Hordeum Vulgare*) after insertion of a copy of a human gene into the barley DNA.

Barley sh-Oligopeptide-1 contains 53 amino acids (aa) and an *N*-terminal 6 aa histidine tag for a total length of 59 aa and has a predicted molecular mass of 7 kDa. The recombinant protein migrates with an apparent molecular mass of 9.5 kDa in SDS-PAGE. The starting gene that is inserted into the barley DNA is synthesised *in vitro* to be identical to the sequence of the human gene that codes the Epidermal

²⁰ Berlanga-Acosta *et al.*, 2009 [Epidermal growth factor in clinical practice – a review of its biological actions, clinical indications and safety implications](#), IWJ, 6(5):331-346.

Growth Factor (rhEGF; NP_001954.2). The synthesised gene is later modified with both (1) codon optimization to adjust the synthesised DNA sequence to the natural barley genomic codon frequency and (2) with histidine-based oligopeptide as His-tag for purification.

The applicant claims that by using barley as a production host, bypassing the use of bacterial or animal cell systems, the peptide is animal-free and endotoxin-free. Testing by a third party research service organization (Charles River Laboratories, France) confirms that barley produced proteins typically contain more than 200 times lower levels of endotoxins than are allowed in most other commercially available product.

Pre-meeting public submissions

Two (2) submissions were received, one (1) in support and one (1) opposed.

Main points in support:

- The submission supports the consideration of the ingredient to align Australian regulatory controls with comparable overseas jurisdictions.
- The submission also notes that they are unaware of any specific safety concerns in Australia or overseas for this substance when used in cosmetics at very low concentrations.

Main points opposed:

- EGF is a common name for human single chain recombinant human peptides derived from various sources and these ingredients are not commonly used in cosmetics in the USA.
- The submission notes that the proposed concentration of 0.0002% does not harmonise with current known practices for cosmetics, as the current international limit is 0.001% for some cosmetic uses.
- The submission recommends that the Joint ACCS-ACMS committee allow for current usage of these ingredients for topical preparations and restrict its availability to only authorised or licensed persons.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that new Appendix G entry and index cross reference for epidermal growth factor be created in the Poisons Standard as follows:

Appendix G – New Entry

EPIDERMAL GROWTH FACTOR

Column 1 – Poison: EPIDERMAL GROWTH FACTOR

Column 2 – Concentration (quantity per litre or kilogram): 10 micrograms

Index – Amend Entry

EPIDERMAL GROWTH FACTOR

cross reference: SH-OLIGOPEPTIDE-1, RH-OLIGOPEPTIDE-1

Schedule 7

Appendix G

Appendix J, Part 2

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be

used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- The safety data indicates a low level of risk associated with the use of EGF.
- The absence of regulatory controls internationally on EGF or other growth factors and cytokines, in cosmetic products by any regulatory agency confirms there has not been any hazard to public safety when this substance is used in cosmetic products (e.g. topical use at low concentrations).
- Although EGF meets international standards for cosmetics, its benefits are unknown.
- The proposal is for the use of EGF as a skin conditioning cosmetic ingredient in topical cosmetic products, at concentrations of 0.0001% or less. Likely to be used in cosmetics only as an anti-ageing cosmetic.
- There is no evidence of allergic, toxicity or systemic adverse events in human studies with doses significantly higher than the proposed cut off and when used on wounds with broken skin. Dermal penetration is limited. No toxicity noted in studies where EGF has been used on burns to assist in wound healing.
- There are no maximum limits imposed on concentrations of EGF by any international cosmetic regulatory jurisdictions. Packaged as cosmetic for topical use only.
- Amending the scheduling will align with overseas jurisdictions and provide consistency with cosmetics available overseas.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create new Appendix G entry and index cross reference for epidermal growth factor in the Poisons Standard. The proposed Schedule entry is as follows:

Appendix G – New Entry

Column 1 – Poison: EPIDERMAL GROWTH FACTOR

Column 2 – Concentration (quantity per litre or kilogram): 10 micrograms

Index – Amend Entry

EPIDERMAL GROWTH FACTOR

cross reference: SH-OLIGOPEPTIDE-1, RH-OLIGOPEPTIDE-1

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

(a) the risks and benefits of the use of a substance:

- The safety data indicates a low level of risk associated with the use of EGF.
- The absence of regulatory controls internationally on EGF or other growth factors and cytokines, in cosmetic products by any regulatory agency confirms there has not been any hazard to public safety when this substance is used in cosmetic products (e.g. topical use at low concentrations).
- Although EGF meets international standards for cosmetics, its benefits are unknown.

(b) the purposes for which a substance is to be used and the extent of use of a substance:

- The proposal is for the use of EGF as a skin conditioning cosmetic ingredient in topical cosmetic products, at concentrations of 0.0001% or less. Likely to be used in cosmetics only as an anti-ageing cosmetic.

(c) the toxicity of a substance:

- There is no evidence of allergic, toxicity or systemic adverse events in human studies with doses significantly higher than the proposed cut off and when used on wounds with broken skin. Dermal penetration is limited. No toxicity noted in studies where EGF has been used on burns to assist in wound healing.

(d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Packaged as cosmetic for topical use only.
- There are no maximum limits imposed on concentrations of EGF by any international cosmetic regulatory jurisdictions.

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

- Amending the scheduling will align with overseas jurisdictions and provide consistency with cosmetics available overseas.

2.8. Chloroacetamide

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new entry for chloroacetamide in Schedule 6 of the Poisons Standard, with no exemption cut-off.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – New Entry

CHLOROACETAMIDE.

The applicant's reasons for the request are:

- Chloroacetamide is a sensitiser with human data demonstrating that allergic reactions can be elicited at concentrations lower than 0.3% (use conditions in cosmetics products);
- Allergy prevalence rates up to 3% have been reported in Australia. These allergy prevalence rates are higher than those reported in a number of European countries;
- Chloroacetamide may be harmful to male fertility following repeated exposure. The SCCS (2011) calculated a margin of safety (MoS) of 20 (a MoS of at least 100 indicates that a cosmetic ingredient is considered safe for use);
- Chloroacetamide is reported to be used in cosmetic products in Australia;
- Chloroacetamide is prohibited or restricted for cosmetic use overseas. The European Commission is currently considering prohibiting chloroacetamide;
- The EU SCCS and US CIR have concluded that chloroacetamide is unsafe for use as a cosmetic ingredient (when used under current use conditions of 0.3%); and
- The [NICNAS IMAP report for acetamide, 2-chloro-](#) is publicly available on the NICNAS website.

Current scheduling status and relevant scheduling history

Chloroacetamide is not currently scheduled and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

N,N-diallyl-2,2-dichloroacetamide

A related molecule, *N,N*-diallyl-2,2-dichloroacetamide is in Schedule 5 of the Poisons Standard as follows:

Schedule 5

N,N-DIALLYLDICHLOROACETAMIDE **except** in preparations containing 10 per cent or less of *N,N*-diallyldichloroacetamide.

N,N-diallyldichloroacetamide (Eradicane) was first considered for scheduling in August 1978 by the Poisons Schedule (Standing) Committee (PSC). The compound is known as a 'crop protection agent' in that it allows higher concentrations of EPTC than normal to be used without damage, in controlled weeds in maize crops. The applicant sought exemption from scheduling. However, due to the limited toxicity data consideration of the application was deferred pending receipt of full 90-day studies. The secretariat was asked to clarify the impurities in the product formulation.

In August 1979 the PSC considered reports of 13-week studies in rats and dogs and agreed that based on the data presented, a Schedule 5 entry would be appropriate.

In November 1979 the PSC agreed to a proposal to exempt from scheduling, preparations containing 10% or less of *N,N*-diallyldichloroacetamide (LD₅₀ 1710 mg/kg).

Australian regulatory information

Chloroacetamide is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as follows:

Table 2.8.1: Permissible ingredients and requirements applying to chloroacetamide when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
1300	CHLOROACETAMIDE	E	Only for use in topical medicines for dermal application.

According to the [TGA Ingredient Database](#), chloroacetamide is available for use as an:

- Active ingredient in biologicals and prescription medicines; and
- Excipient in biologicals, devices, export only, listed medicines, over the counter and prescription medicines.

Chloroacetamide is not currently used in any proprietary ingredient formulations.

Chloroacetamide is not in any products currently registered with the Australian Pesticides and Veterinary Medicines Authority (APVMA).

International regulations

European Union (EU)

Currently, chloroacetamide is authorised as a preservative in cosmetics products in entry 41 of Annex V to Regulation (EC) No 1223/2009, at a concentration up to 0.3% w/w in ready for use preparations. However, in 2015, there was a consultation process on a proposal to remove entry 41 from Annex V, and to add chloroacetamide to the list of substances prohibited in cosmetic products of Annex II to Regulation (EC) No 1223/2009 (European Commission, 2015). A decision had not been finalised at the time of the preparation of this assessment report.

The Scientific Committee on Consumer Safety (SCCS) opinion conclusion states ‘On the basis of the data available, the SCCS comes to the conclusion that 2-chloroacetamide is not safe for consumers when used under the current use conditions of 0.3% in cosmetic products. Human data demonstrate that allergic reactions can be elicited at concentrations lower than 0.3% (use conditions in cosmetics products).

USA

In 1991, the United States CIR concluded that chloroacetamide is unsafe for use as a cosmetic ingredient (CIR, 1991). The CIR conclusion states ‘Based on the data included in this report and the reconfirmation that Chloroacetamide is a potential human sensitiser at use concentrations, it is concluded that Chloroacetamide is unsafe for use as a cosmetic ingredient’.

New Zealand

Chloroacetamide is listed in the New Zealand Cosmetic Products Group Standard – Schedule 7: Preservatives cosmetic products may contain with restrictions.

ASEAN

Chloroacetamide is listed on the Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex VI – Part 1 – List of preservatives allowed for use in cosmetic products:

- Maximum authorised concentration 0.3%;

- Conditions of use and warnings which must be printed on the label 'Contains chloroacetamide'.

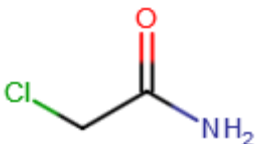
Canada

Chloroacetamide is included on the Health Canada List of prohibited ingredients (The Cosmetic Ingredient 'Hotlist'). Chloroacetamide is also subject to Significant New Activity (SNAc) provisions in Canada (Government of Canada).

Substance summary

Chloroacetamide is used as a herbicide and a preservative in cosmetics, domestic and therapeutic products.

Table 2.8.2: Chemical information for chloroacetamide

Property	Chloroacetamide
Chemical structure	
Molecular formula	C ₂ H ₄ ClNO
Molecular weight	93.5 g/mol
CAS name	Acetamide, 2-chloro-
CAS number	79-07-2
IUPAC and/or common and/or other names	2-Chloroacetamide (IUPAC); Chloroacetamide (INCI).

The following information was extracted from the [Human Health Tier II Assessment report for Acetamide, 2-chloro-](#), publicly available from the NICNAS website.

Table 2.8.3: Acute toxicity end-points for chloroacetamide

Toxicity	Species	Chloroacetamide	SPF (2015) Classification
Acute oral toxicity, LD ₅₀ (mg/kg bw)	Rat	70 – 370	Schedule 6
	Mouse	150 – 155	
	Rabbit	122	
Acute dermal toxicity, LD ₅₀ (mg/kg bw)	Rat	>2000	Schedule 5
Acute inhalational toxicity, LC ₅₀ (mg/m ³ /4h)	No data available	N/A	N/A
Skin irritation	Rabbit	Slight	Schedule 5

Toxicity	Species	Chloroacetamide	SPF (2015) Classification
Eye irritation	Rabbit	Moderate	Schedule 5
Skin sensitisation (GMPT/patch test)	Guinea pig	Positive	-
	Human	Positive	

Acute toxicity

Chloroacetamide is classified as 'Toxic if swallowed'. The available data support this classification (see above and IMAP report for more information).

Irritation

Chloroacetamide is reported to slightly irritate skin in animal studies. The effects were not sufficient to warrant hazard classification for skin sensitisation. Chloroacetamide is moderately irritating to eyes in animal studies warranting hazard classification.

Sensitisation

Chloroacetamide is classified as hazardous for sensitisation. The positive results reported in guinea pig maximisation tests (GPMT) and observations of sensitisation in humans support this classification.

In a study conducted according to OECD TG 406, Dunkin-Hartley guinea pigs were given chloroacetamide at induction doses of between 0.003 - 0.3% applied intra-dermally, followed by topical induction by applications of either between 0.3 - 30% or 0.5 - 50%. The challenge and rechallenge concentrations of 30 and 5%, respectively, of chloroacetamide in an aqueous polyethylene glycol (PEG) vehicle were topically applied to the clipped and shaved skin of the animals. Challenge concentrations of 30% caused irritation responses; thus, results at 5% were considered more robust. Positive reactions were seen for all induction doses for both challenge and re-challenge groups.

Numerous reports are available, which demonstrate that chloroacetamide can elicit contact allergies in humans.

In a 10 year retrospective study (2001–2010) of Australian patch testing data, 139 positive reactions (3%) were reported out of 4576 patients tested at 0.2% chloroacetamide in petrolatum. In another Australian study, examining patch test data for chloroacetamide tested at a concentration of 0.2% in petrolatum from 1993–2006, the rate of chloroacetamide allergy was reported as 2.1%. These allergy prevalence rates are higher than those reported in a number of European countries.

A significant number of international studies have identified chloroacetamide as a cause of contact allergy in both patch test volunteers and patients with suspected contact dermatitis.

Repeat-dose toxicity

Effects on the male reproductive system were the most sensitive effects observed in repeated dose toxicity studies (See Reproductive and Developmental Toxicity below).

Genotoxicity

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, chloroacetamide is not considered to be genotoxic routes.

Carcinogenicity

No data were available.

Reproduction and developmental toxicity

Severe testicular effects were observed in repeat dose studies. These appear to be associated with effects on male fertility. While limited data are available, there is no evidence that chloroacetamide causes specific developmental toxicity in the absence of maternal toxicity.

In a 90-day oral toxicity study conducted according to OECD TG 408 (see IMAP report for details), relevant histopathological changes in males at the highest dose (50 mg/kg bw/day) were depression and/or cessation of spermatogenesis and moderate proliferation of Leydig cells and other interstitial cells in the testes. Epididymal size was reduced, with marked absence of mature and immature sperms with only loose connective tissue present. These effects were reversible within the recovery period.

In other 90-day studies similar dose-dependent reproductive effects at the same doses (12.5 and 50 mg/kg bw/day) were reported. These include decreased testes weights in males and impaired spermatogenesis. Overall a NOAEL of 10 mg/kg bw/day was established for the testes effects.

In a dominant lethal test described previously (see IMAP report for details), the number of resorptions, the mutagenicity index and the number of viable fetuses remained unchanged throughout the entire study. A reduction in the fertility index, number of implantations and fetuses were observed during the first 3 weeks of exposure. However, after week 4, effects were no longer observed. These effects indicate toxic effects on male fertility during the first 3 weeks.

In a combined developmental and reproductive toxicity study, doses were selected based on preliminary study findings of reduction in maternal organ weight as well as maternal and offspring body weight changes at the highest dose of 60 mg/kg bw/day.

Pregnant Wistar rats were dosed in 2 series:

- 0, 3, 12 or 48 mg/kg bw/day, daily during gestation day (GD) 7 through GD 17 to determine offspring effects; and
- 0 or 24 mg/kg bw/day, daily during GD 14 to postnatal day (PD) 2 to determine effects on the reproductive systems of offspring.

In the first series, effects reported at the highest dose in offspring include: increased number of unossified sternebrae and forelimb phalanges as well as reduced body weight of viable fetuses. These effects were reported in the presence of maternal toxicity including; reduced body weight gain and organ weight (thyroid and gravid uteri).

In the second series, maternally toxic effects included reduced body weight gain and food consumption during late gestation. Offspring generation effects were limited to lower body weight in the highest dose group. No differences in the reproductive organs of offspring were noted. A NOAEL of 3 mg/kg bw/day was determined based on body weight reduction of dams (based on body weight reductions) and pups (based on ossified sternebrae and the number of ossified forelimb phalanges).

In further developmental toxicity studies in rats, with administrations by the subcutaneous or intraperitoneal routes, doses ranged between 20–2000 mg/kg bw/day. All studies included a single dose or two doses on consecutive days. Doses above 50 mg/kg bw/day were embryotoxic, with pup mortality being reported at 50%. No malformations were reported.

Observation in humans

Numerous reports are available, which demonstrate that chloroacetamide can elicit contact allergies in humans (see sensitisation above).

Public exposure

Chloroacetamide is used as a preservative up to concentrations of < 1%.

Allergy prevalence rates for chloroacetamide are higher in Australia than those reported in a number of European countries.

Chloroacetamide has been identified as being used in cosmetic products in Australia. In Australia chloroacetamide is reported to be used in a popular brand of sorbolene lotion that is marketed for use in sensitive skin. Medical practitioners in Australia commonly recommend sorbolene products to patients with eczema.

Chloroacetamide has reported potential domestic use as a preservative in detergents, paints, glues and emulsions. It is used in concentrations of less than 1% and most often 0.2 – 0.5%. Available North American databases do not give evidence for use of chloroacetamide in consumer products, indicating chloroacetamide is not likely to be widely available for domestic use.

Chloroacetamide has reported use overseas as a preservative in cosmetic and domestic products up to 1%.

Pre-meeting public submissions

Two (2) public submissions were received and both were in support.

Main points in support:

- No exemption cut-off for cosmetic use in line with the US CIR and the EU SCCS opinion.
- An appropriate exemption cut-off should be considered for domestic products, given the lower level of direct exposure, and hence a lower risk of sensitisation associated with the use of these products.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that new Schedule 6 and Appendices E and F entries be created for chloroacetamide as follows:

Schedule 6 – New Entry

CHLOROACETAMIDE

- a) in preparations for cosmetic use; or
- b) in preparations for topical therapeutic use; or
- c) in other preparations containing more than 0.3 per cent of chloroacetamide.

Appendix E, Part 1 – New Entry

CHLOROACETAMIDE

Standard Statement: **A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)).**

Appendix F, Part 1– New Entry

CHLOROACETAMIDE

Warning Statement: **28 (Repeated exposure may cause sensitisation).**

Safety Direction: **4 (Avoid contact with the skin).**

The committee also recommended an implementation date of **1 June 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; and (c) the toxicity of a substance.

The reasons for the advice were:

- There is a significant risk of skin sensitisation when chloroacetamide is applied to the skin. This offset the benefits of chloroacetamide as a preservative. Chloroacetamide is toxic if swallowed.
- Internationally, chloroacetamide is used as an herbicide and a preservative in cosmetics, domestic and therapeutic products.
- In Australia, chloroacetamide has been identified as being used in cosmetic products. Herbicide use has not been identified on PubCRIS (APVMA database). Chloroacetamide has reported potential domestic use as a preservative in detergents, paints, glues and emulsions.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create new Schedule 6 with Appendices E and F entries for chloroacetamide in the Poisons Standard. The proposed Schedule entry is as follows:

Schedule 6 – New Entry

CHLOROACETAMIDE

- a) in preparations for cosmetic use; or
- b) in preparations for topical therapeutic use; or
- c) in other preparations containing more than 0.3 per cent of chloroacetamide.

Appendix E, Part 1 – New Entry

CHLOROACETAMIDE

Standard Statement: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)).

Appendix F, Part 1– New Entry

CHLOROACETAMIDE

Warning Statement: 28 (Repeated exposure may cause sensitisation).

Safety Direction: 4 (Avoid contact with the skin).

The proposed implementation date is **1 June 2018**. A later implementation date allows for industry alignment.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are:

- There is a significant risk of skin sensitisation when chloroacetamide is applied to the skin. This offset the benefits of chloroacetamide as a preservative. Chloroacetamide is toxic if swallowed.
- Internationally, chloroacetamide is used as an herbicide and a preservative in cosmetics, domestic and therapeutic products.
- In Australia, chloroacetamide has been identified as being used in cosmetic products. Herbicide use has not been identified on PubCRIS (APVMA database). Chloroacetamide has reported potential domestic use as a preservative in detergents, paints, glues and emulsions.

2.9. Benzyl salicylate

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new Schedule 6 entry for benzyl salicylate.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – New Entry

BENZYL SALICYLATE in cosmetic and domestic products except:

- a) in leave-on preparations containing 0.001 per cent or less of benzyl salicylate when labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals; or

- b) in rinse-off products containing 0.01 per cent or less of benzyl salicylate when labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

Appendix E, Part 2 – New Entry

BENZYL SALICYLATE

Standard Statement: **E1 (If in eyes wash out immediately with water).**

Appendix F, Part 3 – New Entry

BENZYL SALICYLATE

Warning Statement: **28 ((Over) (Repeated) exposure may cause sensitisation).**

The applicant's reasons for the request are:

- Benzyl salicylate is a skin sensitiser;
- Benzyl salicylate is an eye irritant;

- Benzyl salicylate is reported to be used in cosmetic and domestic products overseas, in particular, as a fragrance, solvent and UV light absorber at concentrations up to 7%. In the absence of specific Australian information, this is taken as being representative of its use in Australia;
- There are overseas restrictions for the use of benzyl salicylate in cosmetics; and
- Skin sensitisation from use of benzyl salicylate in cosmetic products can only be mitigated by implementation of concentration limits.

Current scheduling status and relevant scheduling history

Benzyl salicylate is not currently scheduled. Therefore, a scheduling history is not available.

A derivative of benzyl salicylate, salicylic acid, is in Schedule 3 of the [Poisons Standard](#) as follows:

Schedule 3

SALICYCLIC ACID in preparations for dermal use **except** in preparations containing 40 per cent or less of salicylic acid.

Australian regulatory information

Benzyl salicylate is the AAN (reference Merck Index).

Benzyl salicylate is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as follows:

Table 2.9.1: Permissible ingredients and requirements applying to benzyl salicylate when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
791	BENZYL SALICYLATE	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.

Benzyl salicylate is an excipient in 331 listed and registered products (both oral and topical) on the ARTG.

According to the [TGA Ingredient Database](#), benzyl salicylate is available for use as an:

- Active Ingredient in: Biologicals, Prescription Medicines; and
- Excipient Ingredient in: Biologicals, Devices, Listed Medicines, Prescription Medicines.

International regulations

Benzyl salicylate is in the EU Cosmetic Regulation EC No. 1223/2009, Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down. It states that:

'This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.'

Substance summary

Benzyl salicylate is a salicylic acid benzyl ester occurring naturally in a variety of plant extracts. It is a clear, colourless to pale yellow oil with a balsamic clean herbal oily sweet scent. Benzyl salicylate is commonly used as a flavour and fragrance agent and as a UV absorber.²¹

Table 2.9.2: Chemical information for benzyl salicylate

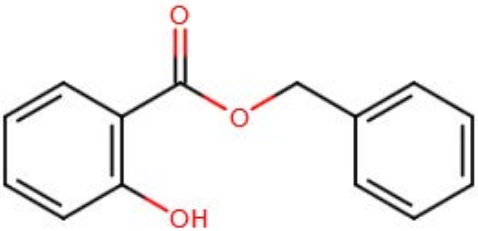
Property	Benzyl salicylate
Chemical structure	
Molecular formula	C ₁₄ H ₁₂ O ₃
Molecular weight	228.2 g/mol
CAS name	Benzoic acid, 2-hydroxy-, phenylmethyl ester
CAS Number	118-58-1
IUPAC and/or common and/or other names	Benzyl salicylate (INCI and AAN); Salicylic acid, benzyl ester; benzyl 2-hydroxybenzoate (IUPAC); Phenylmethyl 2-hydroxybenzoate.

Table 2.9.3: Acute toxicity end-points for benzyl salicylate

Toxicity	Species	Benzyl salicylate	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rats ²²	2227	Schedule 5
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rabbits ²³	14150	N/A
Acute inhalational toxicity LC ₅₀	N/A	No data	N/A

²¹ <http://www.thegoodscentscompany.com/data/rw1001791.html>

²² Strain not specified

²³ Strain not specified

Toxicity		Species	Benzyl salicylate	SPF (2015) Classification
(mg/m ³ /4h)				
Skin irritation		New Zealand White Rabbits Dunkin Hartley Guinea pigs	Slightly irritating Slight erythema	Schedule 5
Eye irritation		Rabbit ²⁴	Irritating	Schedule 6
Skin sensitisation	Local lymph node assay, LLNA	Mice ²⁵	Sensitising (EC3 1.5-2.9%)	Schedule 6
	Guinea pig maximisation test, GPMT	Dunkin Hartley Guinea pig	Sensitising	

Acute toxicity

Based on the available data, benzyl salicylate has low acute oral and dermal toxicity. No data are available for acute inhalation toxicity.

Skin irritation

Based on the available data in animals and humans (see Observation in humans section), benzyl salicylate is slightly irritating to skin:

- In two studies in female New Zealand White rabbits, slight erythema and slight oedema was reported in one study, and well defined erythema and very slight to slight oedema was reported in another study when benzyl salicylate was semi-occlusively applied to the shaved flanks.

Slight irritation was observed in Dunkin Hartley guinea pigs after benzyl salicylate was dermally administered (non-occlusively) for 24 or 48 h at 10% (1/5 animals) and 30% (5/5 animals).

Eye irritation

Based on the available data in animals, benzyl salicylate is considered to be an eye irritant:

- In an *in vivo* study (Draize method) conducted in albino rabbits (n = 3), 0.1 mL of benzyl salicylate at a 10% concentration in alcohol was instilled into the right eye and animals were observed for 10 days. Mild conjunctival irritation was observed in all rabbits and corneal opacity in one rabbit. All effects were reversed within 7 days. The mean scores reported for iritis (0/4), conjunctival redness (1.89/4), chemosis (1.22/4) and corneal opacity (0.33/4) were below the cut-off for classification. However, individual average (24, 48 and 72 h) scores for 2 rabbits for conjunctival redness were 2/4, which is sufficient for classification by GHS criteria (but not by Approved Criteria). Considering the effects observed at this concentration, benzyl salicylate is expected to be irritating to the eyes if exposed at higher or neat concentrations.

Sensitisation

Based on the available data in mice, benzyl salicylate is considered to be a skin sensitizer.

²⁴ Strain not specified

²⁵ Strain not specified

LLNA

- Mice were topically administered 25 µL of benzyl salicylate at 10% in 4:1 acetone/olive oil to the ear lobe for three days. The estimated concentration required to produce a three-fold increase in lymphocyte proliferation (EC3) was reported to be 1.5%.
- The EC3 value was determined to be 2.9% in mice after treatment with benzyl salicylate at 2.5, 5, 10, 25 or 50% in 1:3 ethanol:diethyl phthalate.

GPMT

- Hartley guinea pigs were intra-dermally and topically induced with benzyl salicylate at 10% and 50%, respectively and challenged at 5, 10 or 20%. Positive reactions were observed at the 20% challenge (2/20) and there were some 'questionable' reactions at other concentrations (3/20 at 5%, 5/20 at 10% and 4/20 at 20%).
- Hartley albino guinea pigs were intra-dermally and topically induced at 10 and 30%, respectively. After three weeks, the animals were challenged twice at 0.003, 0.01 or 0.03%. No reactions were observed after the first challenge. After the second challenge, positive reactions were reported at 0.03% after 24 h, and at all concentrations after 48 h and 72 h.
- Female albino Dunkin Hartley guinea pigs were intra-dermally induced with benzyl salicylate at 10%. Following a seven day rest period, benzyl salicylate at 10% in acetone was topically applied to the shoulder region for 48 h. Two weeks later, challenge doses of benzyl salicylate at 5, 10 or 20% in acetone were applied to the shaved flanks of each animal and observations made at 24, 48 and 72 h. Positive reactions were observed at all challenge concentrations.
- Sensitisation was not reported in outbred Himalayan white-spotted guinea pigs when benzyl salicylate was used at 5% for intradermal induction, 25% in petrolatum for topical induction and <0.1% in petrolatum for the topical challenge.
- Similarly, no positive reactions were reported in a Magnusson–Kligman GPMT after benzyl salicylate was intra-dermally applied at 1% in ethanol and dermally at 100%; no further study details are available.

Repeat-dose toxicity

No data are available for benzyl salicylate. However, based on data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS No. 69-72-7), benzyl salicylate is not expected to cause serious health effects from repeated oral or inhalation exposure.

Genotoxicity

Limited data are available for benzyl salicylate. However, based on data for the metabolite benzyl alcohol (CAS No. 100-51-6), benzyl salicylate is not considered to be genotoxic.

Carcinogenicity

No data are available for benzyl salicylate. However, based on the data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS No. 69-72-7), benzyl salicylate is not considered to be carcinogenic.

Reproduction and developmental toxicity

No data are available for benzyl salicylate. However, based on data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS 69-72-7), benzyl salicylate is not considered to cause developmental toxicity. Any developmental effects for the metabolites were only observed secondary to maternal toxicity.

Other effects

The oestrogenic activity of benzyl salicylate has been assessed *in vitro*, using MCF7 human breast cancer cells. Benzyl salicylate was used in a competitive binding assay to the cytosolic oestrogen receptor (ER) of MCF7 cells; a competitive binding assay to human recombinant ER α and ER β ; a gene expression assay using the stably transfected ERE-CAT reporter gene in MCF7 cells; and a cell proliferation assay. Benzyl salicylate mimicked oestrogenic responses in all assays. In the competitive binding assays, 3H-oestradiol was partially displaced by benzyl salicylate (when used at 3×10^6 molar excess) from cytosolic ER of MCF7 cells and from human recombinant ER α and ER β . In the gene expression assay, benzyl salicylate increased the expression of the oestrogen-responsive reporter gene (ERE-CAT) and the endogenous oestrogen-responsive pS2 gene when cells were exposed at concentrations of 0.05–0.5 mM. In the cell proliferation assay, benzyl salicylate increased proliferation of oestrogen-dependent cells over a seven day period; proliferation was inhibited by an anti-oestrogen drug (fulvestrant). However, it was reported that benzyl salicylate was less potent (requiring 1 mM versus 0.1 μ M) and took 2.5-fold longer duration (35 days versus 14 days) to achieve a similar magnitude of proliferation as endogenous 17 β -oestradiol.

Further conclusions on the endocrine disruption potential of benzyl salicylate cannot be made. This is an area of concern given the lack of data available for reproductive and developmental toxicity, and due to structural similarity of benzyl salicylate to monobenzyl phthalate (CAS No. 2528-16-7) (unscheduled), which is known to have anti-androgenic activity and the potential to impair fertility and cause teratogenic effects.

Observation in humans

Irritation

In several skin irritation studies in humans, benzyl salicylate at 15–100% was applied to the skin via an occluded patch for 4–48 h. One study reported irritation in 2/22 subjects exposed to benzyl salicylate at 30%.

Skin sensitisation

The International Fragrance Association (IFRA) reported a No Expected Sensitisation Induction Level (NESIL) of 17 700 μ g/cm² based on a human maximisation test and therefore classified benzyl salicylate as a weak sensitiser.

Reports from the Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP), 1999 and the Scientific Committee on Consumer Safety (SCCS), 2011 lists benzyl salicylate as an allergen.

In human patch test studies, results for sensitisation were varied:

- In five maximisation tests using human volunteers (n = 22–25/study, males and females), benzyl salicylate was administered at 20–30% in petrolatum. Reactions were observed in two studies, affecting 2/25 and 1/25 subjects at 20%. No positive reactions were reported at 30%.
- In a study that was conducted to determine the optimal patch testing concentration of benzyl salicylate, humans (n = 212) were dermally exposed to benzyl salicylate at 5% in petrolatum. Positive reactions were reported in 12/212 subjects.
- In three human repeated insult patch tests (HRIPT) conducted on volunteers (n = 35, 52 or 101; males and females), benzyl salicylate was administered at 5–15% in various vehicles (diethyl phthalate:ethanol (3:1) or dimethyl phthalate or alcohol SD39) and observations were made up to 144 h after the final challenge exposure. Positive reactions were not observed in any study.
- In a human patch test (HPT), 30 volunteers were dermally exposed to 0.2 mL of benzyl salicylate via application to the skin of the upper outer arm for 4 h and observed for 72 h. No reactions were reported.

Public exposure

Benzyl salicylate has been identified to be used in cosmetic (perfumes and fragrances; personal care products; and as an ultraviolet radiation absorber) and domestic products (polishes and waxes; softeners; surface treatments; air care products; and washing and cleaning products) overseas at concentrations up to 7%. This use pattern is taken to be representative of its use in Australia.

Due to the use patterns of benzyl salicylate, direct dermal exposure is expected.

Pre-meeting public submissions

Three (3) public submissions were received and all three opposed proposal.

Main points opposed:

- An Appendix B entry as has been previously considered for other flavour/fragrance ingredients used in cosmetic and household hygiene products with low acute toxicity and low public exposure.
- The EU only requires the inclusion of benzyl salicylate in the ingredients list if the concentration in the finished product is $\geq 0.001\%$ in leave-on products, and $\geq 0.01\%$ in rinse-off products.
- IFRA standards already exist for benzyl salicylate and therefore scheduling is not required. An Appendix B listing should be considered for benzyl salicylate. If scheduling is to proceed, any scheduling decisions should align with IFRA standards.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that a new Schedule 6 entry and Appendix E and F entries be created for benzyl salicylate:

Schedule 6 – New Entry

BENZYL SALICYLATE except:

- a) in preparations intended for therapeutic use; or
- b) in domestic preparations:
 - i) intended for skin contact containing 15 per cent or less of benzyl salicylate when included in the list of ingredients; or
 - ii) not intended for direct skin contact when included in the list of ingredients; or
- c) in leave-on cosmetic and personal care preparations:
 - i) containing 0.001 per cent or less of benzyl salicylate; or
 - ii) when included in the list of ingredients; or
- d) in rinse-off cosmetic and personal care preparations:
 - i) containing 0.01 per cent or less of benzyl salicylate; or
 - ii) when included in the list of ingredients.

Appendix E, Part 2 – New Entry

BENZYL SALICYLATE

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

BENZYL SALICYLATE

Warning Statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

Safety Direction: 4 (Avoid contact with skin).

The committee also recommended an implementation date of **1 June 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice were:

- Benzyl salicylate is a fragrance excipient used in many medicinal, cosmetic and personal care products. It is included as an excipient in 331 products listed on the ARTG. It is used in cosmetics and domestic products.
- The EU Cosmetic Regulation states “This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.”
- The IFRA Standard restricts use to maximum of 12.8% depending on the product use (i.e. those with skin contact). Worldwide use is widespread in cosmetic and domestic products up to 7% concentrations.
- The risks at concentrations currently used appear low.
- The toxicity profile for benzyl salicylate shows evidence of skin sensitisation in animals and humans, it is reported to slightly irritate the skin in animals but human studies show inconsistent reports and it is reported as an eye irritant at 10% concentrations in mice. It is a known contact allergen in humans. The toxicity profile meets the SPF requirements of a Schedule 6 item.

Delegate’s considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate’s interim decision

The delegate’s interim decision is that new Schedule 6 and Appendix E/F entries be created for benzyl salicylate. The proposed Schedule entry is as follows:

Schedule 6 – New Entry

BENZYL SALICYLATE **except:**

- a) in preparations intended for therapeutic use; or
- b) in domestic preparations:
 - i) intended for skin contact containing 15 per cent or less of benzyl salicylate when declared on the label; or
 - ii) not intended for direct skin contact when declared on the label; or
- c) in leave-on cosmetic and personal care preparations:
 - i) containing 0.001 per cent or less of benzyl salicylate; or
 - ii) when declared on the label; or
- d) in rinse-off cosmetic and personal care preparations:
 - i) containing 0.01 per cent or less of benzyl salicylate; or
 - ii) when declared on the label.

Appendix E, Part 2 – New Entry

BENZYL SALICYLATE

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

BENZYL SALICYLATE

Warning Statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

Safety Direction: 4 (Avoid contact with skin).

The proposed implementation date is **1 June 2018**. While it is noted that the earliest implementation date for decisions is 1 February 2018, the delegate considers that a 1 June 2018 implementation date is more appropriate as benzyl salicylate is already in the marketplace and allows sufficient time for industry to make necessary adjustments. The proposed scheduling amendment is not expected to have a significant enough impact to warrant a longer implementation following the final decision.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are:

- The delegate acknowledges the committee's advice.
- Benzyl salicylate is a fragrance excipient used in many medicinal, cosmetic and personal care products. It is included as an excipient in 331 products listed on the ARTG. It is used in cosmetics and domestic products.
- The EU Cosmetic Regulation states "This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to

in Article 19(1)g when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.”

- The IFRA Standard restricts use to maximum of 12.8% depending on the product use (i.e. those with skin contact). Worldwide use is widespread in cosmetic and domestic products up to 7% concentrations.
- The risks at concentrations currently used appear low.
- The toxicity profile for benzyl salicylate shows evidence of skin sensitisation in animals and humans, it is reported to slightly irritate the skin in animals but human studies show inconsistent reports and it is reported as an eye irritant at 10% concentrations in mice. It is a known contact allergen in humans. The toxicity profile meets the SPF requirements of a Schedule 6 item.

2.10. Cinnamaldehyde

Referred scheduling proposal

An application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new Schedule 6 entry for cinnamaldehyde for use in cosmetics and domestic preparations with appropriate warning labels and exemption cut-off concentrations in line with international standards.

Scheduling application

This was a general application. The applicant’s proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – New Entry

CINNAMALDEHYDE **except** in preparations for dermal use containing 0.01/0.05 per cent or less of cinnamaldehyde.

Appendix E – New Entry

CINNAMALDEHYDE

Standard Statement: **E1 (If in eyes wash out immediately with water).**

Appendix F – New Entry

CINNAMALDEHYDE

Warning Statements: **28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes).**

Safety Direction: **4 (Avoid contact with skin).**

The applicant’s reasons for the request are:

- Cinnamaldehyde is an established contact allergen in humans;
- Cinnamaldehyde is a potential strong skin sensitiser, based on a local lymph node assay (LLNA)-derived EC3 (estimated concentration to produce a three-fold increase in lymphocyte proliferation) value of 0.2%;
- The existing overseas restrictions (New Zealand, EU) on the use of cinnamaldehyde in cosmetic products, where the presence of cinnamaldehyde must be indicated in the list of ingredients when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products;
- The most recent SCCS opinion on cinnamaldehyde recommends a concentration limit of 0.01% for safe use of cinnamaldehyde as a fragrance in cosmetic products; and

- The current IFRA guidelines restrict use of cinnamaldehyde to concentrations of 0.02% in lip care and deodorant/anti-perspirant products, 0.04% in intimate wipes, 0.4% in mouthwashes and 0.05% in all other personal care products including fragrances.

Current scheduling status and relevant scheduling history

Cinnamaldehyde is not currently scheduled and has not previously been considered for scheduling. Therefore, a scheduling history is not available.

In July 2016, the ACCS recommended that structurally similar substances, hexyl and amyl cinnamaldehyde, be listed in Appendix B, PART 3 – ‘Substances considered not to require control by scheduling’, due to their low toxicity. The implementation date is 1 February 2017. Please see Final Decision.

Australian regulatory information

Cinnamaldehyde, as well as alpha-methyl cinnamaldehyde, alpha-hexylcinnamaldehyde and alpha-amyl cinnamaldehyde are listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as follows:

Table 2.10.1: Permissible ingredients and requirements applying to cinnamaldehyde, alpha-methyl cinnamaldehyde, alpha-hexylcinnamaldehyde and alpha-amyl cinnamaldehyde when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
453	ALPHA-AMYL CINNAMALDEHYDE	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.
459	ALPHA-HEXYLCINNAMALDEHYDE	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
468	ALPHA-METHYL CINNAMALDEHYDE	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.
1340	CINNAMALDEHYDE	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.

Cinnamaldehyde is included as an excipient in 215 formulations at present on the ARTG, including listed and registered medicines, both OTC and prescription-only. These products range from disinfectants, hand hygiene formulations, sunscreens, nicotine gum, children's pain relief and cold preparations, toothpaste, vitamins and mineral supplements and probiotics.

International regulations

Use of cinnamaldehyde in cosmetics in the European Union (EU) is subject to the restrictions described in EU Cosmetics Regulation 344/2013 (as an amendment to the listing under Annex III of Regulation 1223/2009). The presence of the substance must be indicated in the list of ingredients when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

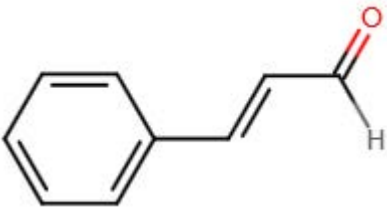
Use of cinnamaldehyde in cosmetics and domestic articles in several other countries is also restricted in accordance with the following listings:

- European Commission (EC) Toy Safety Directive 2009/48/EC: Allergenic fragrances toys shall not contain; and
- The New Zealand Cosmetic Products Group Standard: Schedule 5-Components cosmetic products must not contain except subject to the restrictions and conditions laid down. The presence of the substance must be indicated in the list of ingredients when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

Substance summary

Cinnamaldehyde is an organic compound which occurs naturally as predominately the trans (E) isomer, it gives cinnamon its flavour and odour. This pale yellow, viscous liquid occurs in the bark of cinnamon trees and other species of the genus *Cinnamomum*. The essential oil of cinnamon bark is approximately 50% cinnamaldehyde.²⁶

Table 2.10.2: Chemical information for cinnamaldehyde

Property	Cinnamaldehyde
Chemical structure	
Molecular formula	C ₉ H ₈ O
Molecular weight	132.2 g/mol
CAS name	2-Propenal, 3-phenyl-
CAS number	104-55-2
IUPAC and/or common and/or other names	(2E)-3-phenylprop-2-enal (IUPAC); Cinnamal; cinnamic aldehyde.

The following information was extracted from the [NICNAS New Chemical assessment report for cinnamaldehyde](#), publicly available on the NICNAS website. Further information can also be found in the publicly available [SCCS \(2012\) Opinion on fragrance allergens in cosmetic products](#).

Table 2.10.3: Acute toxicity end-points for cinnamaldehyde

Toxicity	Species	Cinnamaldehyde	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	>2000	Schedule 5
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rat	620–1260	Schedule 6
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	N/A	No data	-
Skin irritation	Rabbit	Severe skin irritation (undiluted)	Schedule 6
	Rabbit	Mild skin irritation (3-5% solution)	

²⁶ Singh, G., et al., (2007). "A comparison of chemical, antioxidant and antimicrobial studies of cinnamon leaf and bark volatile oils, oleoresins and their constituents". *Food and Chemical Toxicology*. **45** (9): 1650–1661

Toxicity		Species	Cinnamaldehyde	SPF (2015) Classification
		Rabbit	No irritation (1% solution)	
Eye irritation		Rabbit	Mild to severe eye irritation (0.125-1%)	Schedule 6
		Rabbit	Severe chemosis and discharge at 1.25%	
Skin sensitisation	LLNA	Mouse	Moderate to strong skin sensitiser (EC3 0.2-3.1%)	Schedule 6
	GPMT	Guinea pig	Positive reactions in 90-100% of animals tested at 0.75%. Sensitisation effects seen as low as 0.1%.	

Acute toxicity

Cinnamaldehyde has low acute oral toxicity, but moderate acute dermal toxicity based on results from animal tests (Table 2.10.3).

Irritation

The available data from animal and human studies indicate that cinnamaldehyde is irritating to the skin, eyes and respiratory system, warranting hazard classification:

- Cinnamaldehyde produced severe irritation in rabbits when applied undiluted, mild irritation in mice and guinea pigs at concentrations of 3–5%, and it was non-irritating to rabbits at 1%. The US EPA considers cinnamaldehyde a strong skin irritant in guinea pigs (no study details provided).
- In New Zealand White rabbits, cinnamaldehyde produced eye irritation when applied undiluted, and effects were not completely reversed after 7 days. In three separate experiments, concentrations of 0.125%, 1% and 1.25% cinnamaldehyde were instilled in rabbit eyes. Intense to mild conjunctival irritation was observed and, at the highest concentration (1.25%), severe chemosis and considerable discharge were observed. The effects were reversible after a week at all concentrations except the highest.
- Respiratory irritation was assessed in CF-1 female mice by recording their respiratory rate following exposure to nebulised cinnamaldehyde for 1 minute, either through nose-only exposure or via a tracheal cannula. Marked respiratory depression with nose-only exposure was observed. The ED25 (dose providing a 25% reduction in respiratory rate) was calculated to be 241 µg/L. No significant effects were observed when inhalation was via the tracheal cannula.

Sensitisation

Based on the available animal and human data, cinnamaldehyde is considered to be a moderate to strong contact skin sensitiser:

- In a study equivalent to OECD Test Guideline (TG) 429, cinnamaldehyde was reported to be positive for skin sensitisation in an *in vivo* mouse LLNA. The mice were administered 0, 0.1, 0.3, 1.0, 3.0 or 10.0% (w/v) of cinnamaldehyde in ethanol/diethyl phthalate (ratio of 3:1). Stimulation indices (SI) were not reported. However, the EC3 was determined to be 0.2%. A similar study with cinnamaldehyde, at doses of 0, 0.5, 1.0, 2.5, 5 and 10% in acetone/olive oil (ratio of 4:1), reported positive results for skin sensitisation with SI of 1, 1.4, 0.9, 1.9, 7.1 and 15.8 respectively. An EC3 of 3.1% was calculated.

- Cinnamaldehyde has also been reported as sensitising at almost all concentrations (0.1–20%) studied in various guinea pig sensitisation tests. A recent review of cinnamaldehyde by the Danish EPA reported skin sensitisation effects in 90–100% of animals tested at a concentration of 0.75% in three separate guinea pig maximisation tests (GPMTs). Strong sensitisation effects were also reported with 3% cinnamaldehyde, although further study details were not provided. In a modified Draize test, an injection challenge concentration of 0.25% cinnamaldehyde with a 20% topical application challenge dose resulted in sensitisation effects after the challenge was repeated a week later. In addition, concentrations of 0.1–1.0% cinnamaldehyde in acetone have resulted in skin sensitisation effects at all doses in a Buehler delayed hypersensitivity test.
- A 3-day application of 10% cinnamaldehyde on the ear dorsum in mice resulted in a high differentiation index (DI) of 8.7, according to OECD standards. The DI is defined as a ratio of maximum response percentages in lymph node activation and skin inflammation, where a DI >1 indicates an allergic reaction pattern.

Repeat-dose toxicity

Based on the available information, cinnamaldehyde is not considered to cause serious damage to health through repeated oral exposure. Systemic toxicity has not been demonstrated via the dermal route. No information was available for repeated dose toxicity by inhalation route.

Genotoxicity

Based on the weight of evidence from the available, well-conducted, *in vitro* and *in vivo* genotoxicity studies, cinnamaldehyde is not considered to be genotoxic.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of cinnamaldehyde. Based on the available genotoxicity data, mechanistic information and history of human oral exposure, cinnamaldehyde is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available information, cinnamaldehyde is not expected to be a reproductive or developmental toxin.

Observation in humans

Irritation

Cinnamaldehyde has been shown to cause skin irritation in humans in a number of reports. Cinnamaldehyde produced irritation in 10/63 volunteers at 3% in diethyl phthalate/ethanol (ratio of 3:1). Severe skin irritation was observed in 5/5 volunteers treated with 8% cinnamaldehyde in petrolatum. In another study, doses of 40 and 48 mg of cinnamaldehyde in petrolatum (concentrations not reported) were applied under occlusive conditions to human skin for 48 hours. Cinnamaldehyde was concluded to be severely irritating to human skin. A review carried out by the Research Institute for Fragrance Materials (RIFM) Expert Panel reported that cinnamaldehyde produced no skin irritation effects in 171 volunteers at concentrations of 0.125–1.25% in a variety of vehicles.

In a limited data eye irritation study, a solution of 8% cinnamaldehyde was instilled in human eyes. Cinnamaldehyde produced slight irritant effects. It was noted that the cornea was not affected. However, no further details were described.

Cinnamaldehyde induced coughing in all ten human subjects following inhalation of nebulised chemical (dose levels from 125–800 mM), with a distinct dose-response relationship observed—the response being the number of coughs recorded after exposure to cinnamaldehyde. Cinnamaldehyde was found to be a specific agonist of the TRPA-1 receptor, and induced cough due to chemaesthesia of the airways.

Sensitisation

Cinnamaldehyde is a well-recognised and frequently reported consumer contact allergen. It is one of eight components of the diagnostic test, the fragrance mix, used by dermatologists to determine if a patient has allergies to common chemicals used in fragrances. It is an established contact allergen in humans according to the Scientific Committee on Consumer Safety (2012), and accounts for 5–36% of the reactions to the fragrance mix.

A number of human repeat insult patch tests (HRIPTs) have been undertaken to determine the skin sensitisation potential of cinnamaldehyde in healthy volunteers, as well as groups of subjects suspected of skin allergies to fragrances. Although fewer cases of sensitisation were found when the concentration of cinnamaldehyde was less than 1%, positive allergic responses have been reported in cases where the administered concentration of cinnamaldehyde was as low as 0.2%. Skin irritation effects were generally predominant at concentrations above 3% cinnamaldehyde, and often impeded the interpretation of results from the patch testing.

Many cases of skin sensitisation have occurred following occupational and consumer exposure to cinnamaldehyde. Workers in spice manufacturing plants, hairdressing salons and bakeries have reported cases of contact dermatitis that were traced back to cinnamaldehyde. In addition, exposure of consumers to toothpaste, cosmetics and perfumes containing cinnamaldehyde as a fragrance ingredient have resulted in a number of case studies identifying cinnamaldehyde as an agent responsible for the allergic reactions.

Public exposure

Cinnamaldehyde is a very widely used and easily available fragrance ingredient. Considering the range of domestic, cosmetic and personal care products that may contain cinnamaldehyde, the main route of public (non-food) exposure is expected to be dermal. There is also possible ocular and inhalation exposure from products applied as aerosols. At the applied concentrations, the irritant effects of cinnamaldehyde are unlikely to present a risk. However, there are recorded cases of human skin sensitisation attributed to fragrance use.

The risk of skin sensitisation could be mitigated by implementing concentration limits and restricting uses to limit dermal exposure. The restrictions on the use of cinnamaldehyde in cosmetic products in New Zealand and the European Union are considered appropriate to mitigate the risk.

Pre-meeting public submissions

Three (3) public submissions were received and all three opposed the proposal.

Main points opposed:

- An Appendix B entry as has been previously considered for other flavour/fragrance ingredients used in cosmetic and household hygiene products with low acute toxicity and low public exposure.
- The EU only requires the inclusion of cinnamaldehyde in the ingredients list, on the label of products, if the concentration in the finished product is $\geq 0.001\%$ in leave-on products, and $\geq 0.01\%$ in rinse-off products.
- IFRA standards already exist for cinnamaldehyde and therefore scheduling is not required. cinnamaldehyde should be considered to be included in Appendix B.
- Cinnamaldehyde does not require scheduling due to the derivatives amyl and hexyl cinnamaldehyde being included in Appendix B in September 2016.
- If there are any decisions to schedule cinnamaldehyde, then these should align with IFRA standards.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that a new Schedule 6 entry be created for cinnamaldehyde as follows:

Schedule 6 – New Entry

CINNAMALDEHYDE *except*:

- a) in preparations intended for therapeutic use; or
- b) in domestic preparations not intended for direct skin contact containing 0.4 per cent or less of cinnamaldehyde when included in the list of ingredients; or
- c) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of cinnamaldehyde; or
- d) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of cinnamaldehyde.

The committee also recommended an implementation date of **1 June 2018**.

The committee also recommended other actions by the delegate as follows:

- The derivatives definition be reviewed to provide greater transparency for industry as part of the SPF review.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- Cinnamaldehyde is a known human allergen and there is evidence of potentially strong sensitisation potential.
- Cinnamaldehyde is a naturally occurring fragrance and flavour substance used internationally in a wide range of products including in food, therapeutic goods, cosmetics and consumer products. There is therefore a potential for significant impact from any scheduling decision.
- Cinnamaldehyde is listed in the US FDA GRAS list.
- Risk and benefit profile of cinnamaldehyde is very similar to another scheduled substance, citral.
- The toxicity profile of cinnamaldehyde show that it is a skin and eye irritant, has acute dermal toxicity, is a strong skin sensitiser and is a respiratory irritant at high concentrations.
- There is a potential for significant impact from any scheduling decision due to the wide range of uses and potentially large numbers of products affected.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989

- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for cinnamaldehyde. The proposed Schedule entry is as follows:

Schedule 6 - New Entry

CINNAMALDEHYDE **except:**

- a) in preparations intended for therapeutic use; or
- b) in domestic preparations not intended for direct skin contact containing 0.4 per cent or less of cinnamaldehyde when declared on the label; or
- c) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of cinnamaldehyde; or
- d) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of cinnamaldehyde.

The proposed implementation date is **1 June 2018**. While it is noted that the earliest implementation date for decisions is 1 February 2018, the delegate considers that a 1 June 2018 implementation date is more appropriate as cinnamaldehyde is already in the marketplace and allows sufficient time for industry to make necessary adjustments. The proposed scheduling amendment is not expected to have a significant enough impact to warrant a longer implementation following the final decision.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

- The delegate acknowledges the committee's advice.
- Cinnamaldehyde is a known human allergen and there is evidence of potentially strong sensitisation potential.
- Cinnamaldehyde is a naturally occurring fragrance and flavour substance used internationally in a wide range of products including in food, therapeutic goods, cosmetics and consumer products. There is therefore a potential for significant impact from any scheduling decision.
- Cinnamaldehyde is listed in the US FDA GRAS list.
- Risk and benefit profile of cinnamaldehyde is very similar to another scheduled substance, citral.
- The toxicity profile of cinnamaldehyde show that it is a skin and eye irritant, has acute dermal toxicity, is a strong skin sensitiser and is a respiratory irritant at high concentrations.
- There is a potential for significant impact from any scheduling decision due to the wide range of uses and potentially large numbers of products affected.

2.11. Anise alcohol

Referred scheduling proposal

An application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new Schedule 6 entry for anise alcohol for use in cosmetic and domestic products with appropriate concentration exemption cut-offs in alignment with international regulations.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – New Entry

ANISE ALCOHOL in cosmetic and domestic products *except*:

- a) in leave-on preparations containing 0.001 per cent or less of anise alcohol when labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals; or

- b) in wash-off preparations containing 0.01 per cent or less of anise alcohol when labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

Appendix E – New Entry

ANISE ALCOHOL

Standard Statement: **E1 (If in eyes wash out immediately with water).**

Appendix F – New Entry

ANISE ALCOHOL

Warning Statement: **28 ((Over) (Repeated) exposure may cause sensitisation).**

The applicant's reasons for the request are:

- Anise alcohol is a skin sensitiser;
- Anise alcohol has moderate acute oral toxicity;
- Anise alcohol is expected to be an eye irritant;
- There is reported to be widespread use of anise alcohol in cosmetic and domestic products overseas at concentrations up to 2.5%; this is assumed to be representative of its use in Australia;
- There are overseas restrictions for use of anise alcohol (the International Fragrance Association (IFRA) standard, 2015; and
- As a sensitiser, when applied directly to skin in cosmetic and domestic products, the risk can only be mitigated by concentration limits and warning statements.

Current scheduling status and relevant scheduling history

Anise alcohol is not currently listed in the Poisons Standard and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Benzyl alcohol (read across in eye irritation study) is not currently scheduled. However, similar substances, anise oil and star anise oil, are currently scheduled.

Australian regulatory information

Anise alcohol is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as follows:

Table 2.11.1: Permissible ingredients and requirements applying anise alcohol when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
593	ANISE ALCOHOL	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.

Anise alcohol is included as an excipient in 98 formulations on the ARTG, including listed and registered medicines. These products include topical and oral preparations such as sunscreen, children preparations for cold and pain relief, anti-nausea preparations, anti-depressants and oral probiotics. The listed products are therapeutic goods that are not evaluated prior to being released for sale.

International regulations

EU

Anise alcohol is listed in the EU Cosmetic Regulation EC No. 1223/2009, Annex III: List of substances which cosmetic products must not contain except subject to the restrictions laid down. Anise alcohol may be used in cosmetics and personal care products, but must be specified in the list of ingredients referred to in article 19(1)g in 0.001% leave-on and 0.01% in rinse-off products.

Additionally, IFRA has restricted the use of Anise alcohol in finished products at concentrations of 0.04–2.5% depending on the product category.

USA

Anise alcohol (listed as anisyl alcohol) is a food additive in the USA.

Canada

Anise alcohol is a flavour enhancer and fragrance ingredient in Canada.

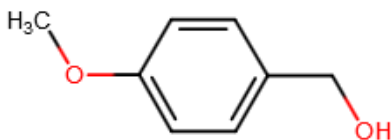
New Zealand

Anise alcohol is not regulated in New Zealand.

Substance summary

Anise alcohol is a colourless to slightly yellow liquid having a pleasant floral odour.

Table 2.11.2: Chemical information for anise alcohol

Property	Anise alcohol
Chemical structure	
Molecular formula	C ₈ H ₁₀ O ₂
Molecular weight	138.7 g/mol
CAS name	Benzenemethanol, 4-methoxy- (CAS)
CAS number	105-13-5
IUPAC and/or common and/or other names	Anise alcohol (INCI and AAN); Anisyl alcohol; 4-methoxybenzyl alcohol; anisic alcohol; <i>p</i> -methoxybenzyl alcohol.

The following information has been extracted from the [NICNAS IMAP Human Health Tier II assessment report for anise alcohol](#), publicly available on the NICNAS website.

(strain/species not specified)

Table 2.11.3: Acute toxicity end-points for anise alcohol

Toxicity	Species	Anise alcohol	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat (strain/species not specified)	1200–1340	Schedule 6
	Mice (strain/species not specified)	1600–1784	
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rabbits (strain/species not specified)	>2500 <5000	Schedule 5
	Mice (strain/species not specified)	>10 000	
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h) (Predicted, QSAR studies)	Rat (strain/species not specified)	1019	Schedule 6

Toxicity	Species	Anise alcohol	SPF (2015) Classification
	Mice (strain/species not specified)	1070	
Skin irritation	Rat (strain/species not specified), Mice and Rabbits	Moderate irritation (erythema and oedema)	Schedule 5
Eye irritation (Read across, benzyl alcohol)	New Zealand White rabbit	Expected to be irritating	Schedule 5
Skin sensitisation	CBA/Ca mice [LLNA]	Sensitising (EC3 5.9%)	Schedule 6
	Guinea pig (strain/species not specified), Hartley; Epicutaneous test, Draize method	Not sensitising	N/A

Acute toxicity

Anise alcohol has moderate acute oral toxicity based on results from animal tests. Anise alcohol has low acute dermal toxicity in rabbits and mice. Acute inhalation toxicity is predicted to be moderate.

Irritation

Based on animal studies, anise alcohol is reported to moderately irritate the skin.

- Anise alcohol (0.5 mL) was applied to albino rats (n=12, 6 with normal and 6 with abraded skin) under occlusive conditions for 24 h. Rats were monitored for 72 h. Moderate irritation including erythema and slight oedema were observed.
- In two studies conducted in mice (n=10) and rabbits (n=4), anise alcohol was administered at doses of 1250, 2500 or 5000 mg/kg bw. Moderate irritation (primary irritation score=4) was observed including moderate erythema and oedema.
- No data are available for anise alcohol for eye irritation. Based on the available data for an analogue chemical (benzyl alcohol, CAS No. 100-51-6) with similar physicochemical properties, anise alcohol is expected to be an eye irritant.
- Irritation was reported after application of the analogue chemical, benzyl alcohol, to the eyes of New Zealand White rabbits. The irritation scores were 1–2 for corneal opacity, 0.3–1 for iritis, 2–2.7 for conjunctivitis and 0.7–2.2 for chemosis.

Sensitisation

Based on the weight of evidence from the available animal and human (see Observation in humans below) studies, anise alcohol is considered to be a skin sensitizer.

- In a murine LLNA compliant with the principles of good laboratory practice (GLP), anise alcohol was diluted using 1:3 ethanol:diethyl phthalate and 25 µL was applied to the dorsal surface of each ear of CBA/Ca mice (n = 4 females/dose) at doses of 2.5, 5, 10, 25 and 50% w/v for three consecutive days. The EC3 (estimated concentration that elicits a three-fold increase in lymphocyte proliferation) value was found to be 5.9%, confirming anise alcohol as a skin sensitizer.

However, positive skin reactions were not reported in several studies conducted in guinea pigs, where:

- animals were subjected to anise alcohol at 1, 3, 10, 30 or 100% in water, acetone or petrolatum for induction and challenged with anise alcohol at 5% in the same vehicle;
- animals were subjected to a modified Draize test, using anise alcohol in petrolatum at 0.625% for induction and 10% for challenge; and
- neat anise alcohol was intra-dermally injected into the animals for the induction phase, and following a two week rest period, the animals were subjected to a modified Draize test, involving an injection of 0.25% and topical exposure of 10% to anise alcohol.

Repeat-dose toxicity

No data are available for repeated oral and inhalation exposure.

Based on the limited information available, anise alcohol is not considered to cause serious damage to health from repeated dermal exposure.

Genotoxicity

Based on the limited data available, anise alcohol is not considered to be genotoxic.

Carcinogenicity

Based on the available data in mice, anise alcohol is not expected to be carcinogenic.

Reproduction and developmental toxicity

No data are available.

Observation in humans

Irritation

Irritation was observed in a closed patch study in 11/465 (2.3%) of human subjects after application of anise alcohol (under occlusion to the forearm) at 0.05–5% in a cream base solution.

In an irritation screening study, anise alcohol did not produce skin reactions at 5% in petrolatum when applied under occlusion to the skin of human subjects (n = 7) for 48 h.

Skin sensitisation

The IFRA reported a No Expected Sensitisation Induction Level (NESIL) of 1500 µg/cm² based on a human maximisation test and, therefore, classified anise alcohol as a weak sensitiser.

Reports from the Scientific Committee on Consumer Safety (SCCS), 2012, list anise alcohol as an allergen.

Positive reactions were reported in the following human studies:

- A study conducted on 20 perfume allergic patients: anise alcohol at 5% in petrolatum gave a positive reaction in 5/20 of the subjects;
- Diagnostic patch studies on dermatological patients:
 - skin reactions in 4/20 patients who are sensitive to perfume treated with anise alcohol at 5% in petrolatum;
 - skin reactions in 1/2004 patients with dermatitis treated with anise alcohol at 1% in petrolatum; and

- skin reactions in 3/167 patients sensitive to fragrance allergens and suspected of contact dermatitis treated with anise alcohol at 5% in petrolatum.

No skin reactions were reported in the following human studies:

- A maximisation study: 25 subjects were pre-treated for 24 h with 5% aqueous sodium lauryl sulfate (SLS). Following a 10-14 day rest period, subjects were applied with anise alcohol (3450 µg/cm², 5%) in petrolatum occlusively to the forearm/back region for five 48h periods and monitored for a further 48 h;
- Diagnostic patch studies on dermatological patients:
 - 320 patients with eczema suspected of a contact allergy to fragrances or cosmetics were treated with anise alcohol at 5%; and
 - 115 patients with contact dermatitis were treated with anise alcohol at 5% in petrolatum.

Public exposure

Considering the range of domestic, cosmetic, therapeutic and personal care products that may contain anise alcohol, the main route of public exposure is expected to be through the skin, and inhalation from products applied as aerosols, and potential oral exposure from lip and oral hygiene products. Dermal application of products containing anise alcohol at high concentrations may give rise to allergic responses.

Pre-meeting public submissions

Three (3) public submissions were received and all three opposed the proposal.

Main points opposed:

- An Appendix B entry should be considered as has been previously for other flavour/fragrance ingredients used in cosmetic and household hygiene products with low acute toxicity and low public exposure.
- Based on IFRA standards, there are restrictions on concentration depending on use pattern of the product due to the concern that anise alcohol has skin sensitisation potential. Due to IFRA standards already existing for anise alcohol, scheduling is not required.
- The EU only requires the inclusion of anise alcohol in the ingredients list if the concentration in the finished product is ≥0.001% in leave-on products, and ≥0.01% in rinse-off products.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that a new Schedule 6 entry and Appendix E and F entries be created for anise alcohol as follows:

Schedule 6 – New Entry

ANISE ALCOHOL except:

- a) in preparations intended for therapeutic use; or
- b) in domestic preparations [not intended for direct skin contact] containing 5 per cent or less of anise alcohol when included in the list of ingredients; or
- c) in leave-on cosmetic and personal care preparations containing 2.5 per cent or less of anise alcohol when included in the list of ingredients and labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height; or

- d) in rinse-off cosmetic and personal care preparations containing 5 per cent or less of anise alcohol when included in the list of ingredients and labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height; or

- e) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of anise alcohol; or
- f) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of anise alcohol.

Appendix E, Part 2 – New Entry

ANISE ALCOHOL

Standard Statement: **A** (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)).

Appendix F, Part 3 – New Entry

ANISE ALCOHOL

Warning Statement: **28 ((Over) (Repeated) exposure may cause sensitisation).**

Safety Direction: **4 (Avoid contact with skin).**

The committee also recommended an implementation date of **1 February 2018** if no label change would be required by scheduling.

The committee also recommended an implementation date of **1 June 2018** to allow a 12 month phase in of the new label requirements.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice were:

- Anise alcohol is a flavour and fragrance excipient used in many medicinal, cosmetic and personal care products: 98 products on ARTG include anise alcohol as an excipient. The risks of the substance at the currently used concentrations appear low.
- It is listed as a Fragrance or Flavour Excipient (under Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017).
- The EU Cosmetic Regulation states 'This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.'
- The IRFA Standard restricts use to maximum of 2.5% depending on the product use (i.e. those with skin contact). Anise alcohol is currently specified within the Permissible Ingredients List and the

requirements that apply to these ingredients when contained in a medicine are that the flavour is no more than 5% and the fragrance is no more than 1%.

- In Australia, there are domestic products that contain up to 5% of anise alcohol available. Worldwide use is widespread in cosmetic and domestic products and is at concentrations of up to 2.5.
- The risks of anise alcohol include systemic risks through oral exposure, local risks of eye irritation and skin sensitisation and inhalational risk (which is a predicted risk). It is also a known allergen listed on the List of Established Contact Allergens, (whilst low importance category however identified as a known fragrance allergen (SCCNFP 1999)).
- The toxicity of anise alcohol includes a moderate acute oral toxicity (based on animal studies) and possible skin sensitisation (it is listed by SCCS).

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create new Schedule 6 and Appendix E/F entries for anise alcohol. The proposed Schedule entry is as follows:

Schedule 6 – New Entry

ANISE ALCOHOL **except:**

- a) in preparations intended for therapeutic use; or
- b) in domestic preparations not intended for direct skin contact containing 5 per cent or less of anise alcohol when declared on the label; or
- c) in leave-on cosmetic and personal care preparations containing more than 0.001 and up to 2.5 per cent of anise alcohol when declared on the label and labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height; or

- d) in rinse-off cosmetic and personal care preparations containing more than 0.01 and up to 5 per cent or less of anise alcohol when declared on the label and labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height; or

- e) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of anise alcohol; or
- f) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of anise alcohol.

Appendix E, Part 2 – New Entry

ANISE ALCOHOL

Standard Statement: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)).

Appendix F, Part 3 – New Entry

ANISE ALCOHOL

Warning Statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

Safety Direction: 4 (Avoid contact with skin).

The proposed implementation date is **1 February 2019**, to allow at least a 12 month phase for industry if label changes are required.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are:

- The delegate acknowledges the committee's advice.
- Anise alcohol is a flavour and fragrance excipient used in many medicinal, cosmetic and personal care products: 98 products on ARTG include anise alcohol as an excipient. The risks of the substance at the currently used concentrations appear low.
- It is listed as a Fragrance or Flavour Excipient (under Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017).
- The EU Cosmetic Regulation states:

'This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.'

- The IRFA Standard restricts use to maximum of 2.5% depending on the product use (i.e. those with skin contact). Anise alcohol is currently specified within the Permissible Ingredients List and the requirements that apply to these ingredients when contained in a medicine are that the flavour is no more than 5% and the fragrance is no more than 1%.
- In Australia, there are domestic products that contain up to 5% of anise alcohol available. Worldwide use is widespread in cosmetic and domestic products and is at concentrations of up to 2.5.
- The risks of anise alcohol include systemic risks through oral exposure, local risks of eye irritation and skin sensitisation and inhalational risk (which is a predicted risk). It is also a known allergen listed on the List of Established Contact Allergens, (whilst low importance category however identified as a known fragrance allergen (SCCNFP 1999)).

- The toxicity of anise alcohol includes a moderate acute oral toxicity (based on animal studies) and possible skin sensitisation (it is listed by SCCS).

2.12. Resorcinol

Referred scheduling proposal

An application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new Schedule 6 entry for resorcinol (1,3-benzenediol) to reflect its use in cosmetic and domestic products.

Scheduling application

This was a delegate-initiated application. The delegate's proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – New Entry

1,3-BENZENEDIOL for cosmetic and domestic products.

Appendix E, Part 2 – New Entry

1,3-BENZENEDIOL

Standard Statement: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

1,3-BENZENEDIOL

Warning Statement: 28 ((over) (repeated) exposure may cause sensitisation).

The reasons for the proposal are:

- Resorcinol is used in permanent hair dye preparations in Australia (NICNAS, 2007) and in hair lotions and shampoos overseas (refer to Import, Manufacture and Use section of IMAP Tier II report);
- Resorcinol has moderate oral toxicity and has been shown to cause skin and eye irritation as well as skin sensitisation;
- Resorcinol has existing overseas restrictions in European Union (EU) for oxidative hair colouring products at a maximum concentration of 2.5 %, with labelling requirements at lower concentrations. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, resulting in a concentration of 1.25 % when applied to hair (SCCS, 2010). Use of the chemical is also restricted in hair lotions and shampoos with a maximum authorised concentration in the finished cosmetic product of 0.5 %;
- When resorcinol is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the Poisons Standard.

Current scheduling status and relevant scheduling history

Resorcinol (1,3-benzenediol) is currently unscheduled.

In July 2016, NICNAS submitted a proposal to create a new entry for resorcinol in Schedule 6 for restriction in cosmetic and domestic products.

In January 2017, the delegate made a delegate-only final decision to enter resorcinol in Schedule 6 and Appendices E and F of the Poisons Standard as follows:

Schedule 6

RESORCINOL **except:**

- a) in hair dye preparations containing 1.25 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

- b) in hair lotions/shampoo products containing 0.5 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used on the eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

Appendix E

RESORCINOL

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).); E1 (if in eyes wash out immediately with water).

Appendix F

RESORCINOL

Warning Statement: 28 ((over) (repeated) exposure may cause sensitisation).

The implementation date of this decision was 1 February 2017.

Following the release of the final decisions on 16 January 2017, feedback from industry indicated that resorcinol is used more broadly than initially considered. On 31 January 2017, the Schedule 6 entry for resorcinol was removed from the 1 February 2017 Poisons Standard to allow further review of its broader use pattern. This final decision was implemented as [Amendment No. 1 of SUSMP 16](#). Resorcinol was subsequently referred to the March 2017 Joint ACCS-ACMS meeting.

An isomer of resorcinol, 1,2-benzenediol, is scheduled as follows:

Schedule 6

1,2-BENZENEDIOL.

Appendix E – 1,2-BENZENEDIOL (catechol)

Standard Statements: A, E1, S1

Appendix F – 1,2-BENZENEDIOL (catechol)

Warning Statements: 51, 59.

Safety Directions: 1, 4, 8.

A homologue of resorcinol, 2-methylresorcinol, was considered by the ACCS in March 2016.

Effective 1 June 2017, 2-methylresorcinol will be listed in Schedule 6 as follows:

Schedule 6 – New Entry

2-METHYLRESORCINOL except:

- a) in non-oxidative hair dye preparations containing 1.8 per cent or less of 2-methylresorcinol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING –This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

- b) in oxidative hair dye preparations containing 1.8 per cent or less of 2-methylresorcinol after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING –This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

2-METHYLRESORCINOL

Standard Statements: A, E1

Appendix F, Part 3– New Entry

2-METHYLRESORCINOL

Safety Direction: 1

Australian regulatory information

Resorcinol is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as follows:

Table 2.12.1: Permissible ingredients and requirements applying resorcinol when contained in a medicine

Column 1	Column 2 Ingredient Name	Column 3 Purpose of the ingredient in the medicine	Column 4 Specific requirements(s) applying to the ingredient in Column 2
4224	RESORCINOL	E	Permitted for use only in combination with other permitted ingredients as a flavour. If used in a flavour the total flavour concentration in a medicine must be no more than 5%.

Resorcinol has two registered OTC products and two listed export-only products on the ARTG.²⁷

Resorcinol was reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007) and in overseas hair lotions and shampoos. Currently, there are no restrictions in Australia on using this chemical in hair dyes, hair lotions and shampoos. In the absence of any regulatory controls, the characterised critical health effects (skin and eye irritation, and skin sensitisation) have the potential to pose an unreasonable risk under the identified uses. The risk could be mitigated by implementing concentration limits and labelling requirements for use in hair dyes, hair lotions and shampoos.

International regulations

The EU has restricted the use of this chemical in oxidative hair colouring products at a maximum concentration of 2.5 %. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, which corresponds to a concentration of 1.25 % when applied to hair (SCCS, 2010). Restricted use in hair lotions and shampoos was also reported to be the maximum authorised concentration in the finished cosmetic product of 0.5 %.

Resorcinol is listed on the EU Cosmetic Directive 76/768/EEC Annex III Part 1: List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down below (Galleria Chemica): (a) Hair dye substance in oxidative hair dye products for general and professional use- after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.25 % (w/w); and (b) Hair lotions and shampoos- maximum authorised concentration in the finished cosmetic product of 0.5 % (w/w).

Resorcinol is also listed on the following:

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III-Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- New Zealand Cosmetic Products Group Standard-Schedule 5-Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist'); and
- Chile list of Cosmetic Ingredients with limited use or concentration.

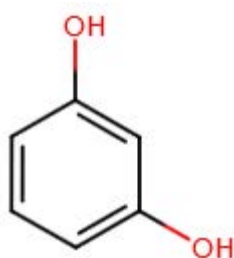
Substance summary

Resorcinol is a colourless solid with a mild odour. Resorcinol has a number of chemical (dyes, resins, plasticisers, adhesives and polymers) and medical applications (antiseptic, disinfectant, antifungal).²⁸

²⁷ <http://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg>

²⁸ Dressler, H. (1994) 'm-Aminophenol', *Resorcinol: Its Uses and Derivatives*, Springer US, pp. 125-134.

Table 2.12.2: Chemical information for resorcinol

Property	Resorcinol
Chemical structure	
Molecular formula	C ₆ H ₆ O ₂
Molecular weight	110.1 g/mol
CAS name	1,3-Benzenediol
CAS number	108-46-3
IUPAC and/or common and/or other names	Resorcinol (INCI); 1,3-dihydroxybenzene; 3-hydroxyphenol.

The following toxicology information was extracted from the [NICNAS IMAP Human Health Tier II assessment](#), publicly available on the NICNAS website. Further information can also be found in the [European Commission Scientific Committee on Consumer Safety](#) (SCCS) report.

Table 2.12.3: Acute toxicity end-points for resorcinol

Toxicity	Species	Resorcinol	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rats (Sprague Dawley)	200-980 mg/kg bw/day.	N/A
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rabbits	> 2000 mg/kg bw/day.	N/A
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rats (Harlan Wistar)	> 7800 mg/m ³ /1-hour (equivalent to 7.8 mg/L or 1732 ppm); and >2800 mg/m ³ /8-hours (equivalent to 2.8 mg/L or 622 ppm)	N/A
Skin irritation	Rabbit (albino)	Slight to severe skin irritant in diluted and semi-solid state, respectively (flaked and industrial grade).	Schedule 6
	Rabbit (New Zealand)	Not irritating to skin (2.5 % solution in	

Toxicity	Species	Resorcinol	SPF (2015) Classification
	White)	water; 98.8 % purity)	
Eye irritation	Rabbit (albino)	Severe eye irritant (see below)	Schedule 6
Skin sensitisation (Guinea Pig Maximisation Test: GPMT)	Guinea pigs (Pirbright white)	Sensitiser (relative incidence of the positive reactions in animals was > 30 %) (99.9 % purity)	Schedule 6
Skin sensitisation (mouse local lymph node assay: LLNA)	Mice (CBA/Ca)	Moderate sensitiser with EC = 1.4 and 6.3% (unspecified purity)	

Acute toxicity

The acute toxicity end-points of resorcinol are summarised in Table 2.12.3.

Skin irritation

Based on the weight of evidence, the chemical is considered to be slightly to severely irritating to skin when administered diluted in an aqueous solution or in semi-solid state (flaked or industrial grade):

- In a non-guideline (Federal Hazardous Substance Labelling Act (FHSLA)) skin irritation study, 0.5 g of the chemical (flaked grade) in saline was applied to the clipped belly skin (abraded and intact) of albino rabbits (six males) for 24 hours under occlusive patches. Observations were made at 24 and 72 hours post-treatment, and animals were kept under observation for a maximum of two weeks. Treatment-related effects were moderate irritation on intact skin and necrosis on abraded skin. Effects were more pronounced at 72 hours post-treatment. In the two week recovery period, necrotic areas were still encrusted or scarred. The primary dermal irritation index (PDII) was reported to be 4.4;
- In similar non-guideline (FHSLA) studies, a 24-hour occluded application of the chemical (flaked and industrial grade) at 0.5 g to the bellies of male albino rabbits produced moderate irritation on intact skin and necrosis on abraded sites. The chemical (industrial grade) was reported to cause slight to severe irritation of the intact areas, and from severe irritation to necrosis of the abraded areas, 24 hours after exposure. In the 2-week post-recovery period, necrotic areas were still encrusted or scarred. The primary dermal irritation index (PDII) for the chemical was reported to be 4.4 (flaked grade) and 5.4 (industrial grade); and
- In a study conducted according to the OECD Test Guideline 404 (acute dermal irritation/corrosion), 0.5 mL of the chemical (2.5 % aqueous solution) (98.8 % purity) was applied to the clipped back skin of New Zealand White rabbits (three males/group) for four hours under semi-occlusive patches. Observations were made at one, 24, 48 and 72 hours post-treatment. No adverse cutaneous reactions were reported at this low concentration.

Eye irritation

Data from one study using the chemical (flaked and industrial grade diluted in an aqueous solution and semi-solid state, respectively) indicated that the chemical should be considered a severe eye irritant:

- In a non-guideline (FHSLA) study, 0.1 g of the chemical (flaked and industrial grade) was instilled into the eyes of albino rabbits (6 males). Treatment-related effects upon administration included inflamed conjunctivae, opaque corneas and visible discomfort in animals. At 24 hours post-exposure, observations included severe conjunctivitis, iritis, corneal opacity occluding most of the iris and corneal ulcerations. Irreversible effects on the eyes were reported and by day 14, all treated eyes had kerataconus (thinning of and irregularly shaped cornea) and pannus (abnormal layer of fibrovascular tissue or granulation tissue over the cornea) formation. Total mean eye irritation Draize scores were reported to be 105/110 at 24, 48 and 72 hours and the chemical was considered to be a severe eye irritant;
- The chemical was mildly irritating in six albino rats administered 0.1 g of the chemical (dry powder). Reported mean irritation scores were 56.3, 45.0 and 39.9 out of 110 over the observation period at 24, 48 and 72 hours, respectively. No further study details were available; and
- In a study conducted according to OECD TG 405 (acute eye irritation/corrosion), 0.1 mL of the chemical (2.5 % solution in water (98.8 % purity)) was instilled into the eyes (conjunctival sacs) of New Zealand White rabbits (three males) and left for 72 hours. Mean scores of zero were reported for chemosis, iris lesions and corneal opacity over 24, 48 and 72 hours. For redness of the conjunctivae, a mean score of 0.1 was reported.

Skin sensitisation

Based on the available animal and human data, the chemical is considered to be a moderate to strong contact skin sensitizer and is recommended for classification:

- In a GPMT conducted in accordance with OECD TG 406, Pirbright white guinea pigs (treatment group 10 animals, control group 5 animals and accompanying group 20 animals used for range finding) were administered 2 % (w/v) solution of the chemical (99.9 % purity as white flakes in sodium chloride) by intradermal injection followed by occlusive, epicutaneous application of 25 % the chemical. At the challenge exposure using 25 % of the chemical (occlusive epicutaneous application), very slight to distinct erythema was observed on the skin of 2-3 animals at 24 and 48 hours observation periods. At the second challenge and compared to the control group, very slight to distinct erythema was reported in 7/10 guinea pigs at 24 hours and on 5/10 guinea pigs at 48 hours and minor swelling was also observed in one animal at 24 hours after patch removal. The relative incidence of the positive reactions in animals was over the threshold value of 30 % and the chemical was considered to be a skin sensitizer;
- In a study conducted in accordance with OECD TG 429, positive skin sensitisation was reported in LLNA studies in two independent experiments. A positive control of *a*-hexylcinnamaldehyde (HCA), a moderate sensitizer, at the concentration of 25 % (v/v) in DMF was used. In the first experiment (range finding), female CBA/J mice (four animals/dose including negative and positive controls) were administered 25 µL of the chemical (in vehicle dimethylformamide at 2.5, 5, 10, 25 or 50 %) applied to the dorsal surface of each ear, once daily for three consecutive days. Stimulation indices (SI) of 3.83, 4.14, 3.97, 3.51 and 3.30 were reported, respectively. Positive lymphoproliferative responses (SI > 3) were reported at all concentrations, but no clear dose-response relationship was observed. In the second experiment, mice (four/dose) were administered daily applications of 0.1, 0.5, 1, 5 or 25 % chemical (w/v). Treatment resulted in stimulation indices of 1.58, 2.87, 1.97, 3.51 and 5.74, respectively. A dose-related increase in SI was seen and the threshold positive value of three was exceeded. The effective concentration at which a three-fold increase in SI was achieved (EC3) was reported to be 1.4 % and the chemical was considered to be a moderate skin sensitizer; and
- The chemical (purity unspecified) was not reported to be sensitising according to two non-guideline skin sensitisation (LLNA) studies in mice (concentrations of up to 2.5 % and 25 % w/v were tested, respectively). No further study details were available and the reliability of both studies was questioned due to outdated study methods (OECD, 2008). However, the chemical was reported to be a sensitizer in mice in a LLNA study (OECD TG 429). A group of CBA/Ca female mice

(four/dose) were treated at daily concentrations of 0, 1, 5, 10, 25 and 50 % (w/v) of the chemical (purity unspecified) in acetone/olive oil (ratio of 4:1). SIs of 1.0, 0.7, 2.2, 5.2, 8.4 or 10.4 were measured respectively, and an EC value of 6.3 % was determined (REACH; OECD, 2008).

Repeat-dose toxicity

Based on the weight-of-evidence, the chemical is not considered to cause serious damage to health from repeated oral exposure.

No information was available for repeated dose toxicity by the dermal route.

There is insufficient evidence to evaluate repeated dose inhalation toxicity.

Genotoxicity

Based on the weight-of-evidence from the available *in vitro* and *in vivo* genotoxicity studies, the chemical is not considered to be genotoxic.

Carcinogenicity

Based on the available data, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available data, the chemical is not considered to be a reproductive or developmental toxin.

Observation in humans

Human patch-testing using the chemical elicited allergic skin reactions in 0.7–0.8 % of 1694 dermatitis patients. In further case histories of 34 dermatitis patients, the chemical was reported to cause reactions after epicutaneous testing.

No dermatitis of the hands was reported for 42 workers from a tyre factory after an epicutaneous test with the chemical.

In human patch tests with the chemical (2 % in petrolatum), four out of 302 hairdressers suffering from contact dermatitis reported a positive reaction. No further details were available. In another case, one patient who developed contact dermatitis after application of paint to the skin was patch tested with the chemical (5 % in petrolatum) and showed a positive result after 48 hours. In a third case, three female patients suffering from acne and contact dermatitis gave a positive patch test for the chemical (2 % in petrolatum) after 48 and 72 hours.

Pre-meeting public submissions

Two (2) pre-meeting submissions were received. One had no objections to the proposed scheduling for resorcinol. The main points of the submission were:

- Resorcinol is permitted internationally in over the counter (OTC) and consumer products (such as hair dyes). The scheduling of resorcinol in Australia should reflect international regulations.
- Resorcinol is used in topical therapeutic goods, scheduling should not capture this use pattern.
- Scheduling of resorcinol should reflect recent decisions made on similar substances used in hair dyes, such as 2-methylresorcinol.
- An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified. There is no evidence to suggest immediate action is required for the risk management of this substance.
- One submission requested a specific exemption for OTC products.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that a new Schedule 6 entry and Appendix E and F entries be created for resorcinol as follows:

Schedule 6 – New Entry

- a) in preparations for human therapeutic use; or
- b) in oxidative hair dye preparations containing 1.25 per cent or less of resorcinol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

- c) in oxidative eyelash and eyebrow dye preparations containing 1.25 per cent or less of resorcinol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height; or

- d) in hair lotions/shampoo products containing 0.5 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

RESORCINOL

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.)

Appendix F, Part 3 – New Entry

RESORCINOL

Warning Statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes)

Safety Directions: 1 (Avoid contact with eyes), 3 (Wear eye protections when mixing or using), 4 (Avoid contact with skin)

Index – New Entry

RESORCINOL

cross reference: 1,3-benzenediol

Schedule 6

The committee also recommended an implementation date of **1 June 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice were:

- Resorcinol is used as a reaction-modifying agent in hair dyes and dyes applied to eyebrows and eyelashes, as well as in hair lotions and shampoos. It is used in permanent oxidative hair dyes that are mixed prior to use. Use settings are both in-salon as well as packed and labelled products used by consumers. Resorcinol also has other domestic and industrial uses, such as use in adhesives and curing agents.
- The toxicity profile of resorcinol is primarily skin irritation, eye irritation, and moderate skin sensitisation. Resorcinol shows low oral and inhalation toxicity and it is not genotoxic or carcinogenic; there is no reproductive or developmental toxicity. The toxicological profile fits with the Schedule 6 criteria of the SPF.
- The proposed entry, including concentration cut-offs, allows consistency with international controls in the EU and ASEAN.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for resorcinol with accompanying Appendix E and F entries. The proposed Schedule entry is as follows:

Schedule 6 – New Entry

RESORCINOL **except:**

- a) in preparations for human therapeutic use; or

- b) in oxidative hair dye preparations containing 1.25 per cent or less of resorcinol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

- c) in oxidative eyelash and eyebrow dye preparations containing 1.25 per cent or less of resorcinol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height; or

- d) in hair lotions/shampoo products containing 0.5 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

RESORCINOL

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.).

Appendix F, Part 3 – New Entry

RESORCINOL

Warning Statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

Safety Directions: 1 (Avoid contact with eyes), 3 (Wear eye protections when mixing or using), 4 (Avoid contact with skin).

Index – New Entry

RESORCINOL

cross reference: 1,3-benzenediol

Schedule 6

Appendix E, Part 2

Appendix F, Part 3

The proposed implementation date is **1 February 2019** to allow at least a 12 month phase for industry if label changes are required.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are:

- The delegate acknowledges the committee's advice.
- Resorcinol is used as a reaction-modifying agent in hair dyes and dyes applied to eyebrows and eyelashes, as well as in hair lotions and shampoos. It is used in permanent oxidative hair dyes that are mixed prior to use. Use settings are both in-salon as well as packed and labelled products used by consumers. Resorcinol also has other domestic and industrial uses, such as use in adhesives and curing agents.
- The toxicity profile of resorcinol is primarily skin irritation, eye irritation, and moderate skin sensitisation. Resorcinol shows low oral and inhalation toxicity and it is not genotoxic or carcinogenic; there is no reproductive or developmental toxicity. The toxicological profile fits with the Schedule 6 criteria of the SPF.
- The proposed entry, including concentration cut-offs, allows consistency with international controls in the EU and ASEAN.

2.13. Trans-anethole

Referred scheduling proposal

An application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new entry for trans-anethole in Schedule 6 to include use in cosmetic and domestic products with an exemption concentration cut-off.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are:

Schedule 6 – New Entry

TRANS-ANETHOLE in cosmetic and domestic products **except** in preparations containing 10 per cent or less of trans-anethole.

Appendix E, Part 2 – New Entry

TRANS-ANETHOLE

Standard Statement: **E1 (If in eyes wash out immediately with water).**

Appendix F, Part 3 – New Entry

TRANS-ANETHOLE

Warning Statement: **28 ((Over) (Repeated) exposure may cause sensitisation).**

The applicant's reasons for the request are:

- Trans-anethole is a skin sensitiser;
- Trans-anethole is reported to be used in cosmetic and domestic products overseas, particularly as a fragrance ingredient at concentrations up to 10%. In the absence of specific Australian information, this is taken as being representative of its use in Australia; and

- Internationally, there is a recommendation for use of trans-anethole at concentrations up to 10%. However, the available data does not preclude skin sensitisation occurring following exposure to concentrations below 10% (Scientific Committee on Consumer Safety (SCCS), 2012).

Current scheduling status and relevant scheduling history

Trans-anethole is not specifically scheduled and has not been previously considered for scheduling.

Australian regulatory information

Trans-anethole is listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#) as an excipient.

Trans-anethole is as an ingredient in 249 products on the ARTG, including disinfectants, sunscreens, dental hygiene preparations, cold and cough relief products, anti-depressants, nicotine chewing gum products and gastric reflux relief preparations.

International regulations

New Zealand

Anethole is unclassified in New Zealand.

Canada

A number of over the counter (OTC) products containing anethole have been cancelled post market in Canada. There are no approved products containing anethole currently available in Canada.

USA

Anethole has a “Generally Recognised as Safe” status in the USA.²⁹

EU

Anethole is in the [European Chemicals Agency \(ECHA\) Annex III inventory requiring REACH \(Registration, Evaluation, Authorisation and Restriction of Chemicals\) Registration](#).

Substance summary

Trans-anethole is a component of a number of essential oils, such as anise, fennel, anise myrtle, guarana, camphor and star anise. Trans-anethole is also present in absinthe, magnolia blossoms and liquorice and is closely related to estragole, present in tarragon and basil.

Trans-anethole is a precursor for paramethoxyamphetamine (PMA).

Anethole is used broadly in multiple sectors due to its presence in essential oils, some of which have already been scheduled. It contributes a large component of the odour and flavour of the substances listed in Table 2.13.1 below.

Table 2.13.1: Anethole-containing essential oils, herbs and plants

Anethole-containing substance	Plant genus/family	Schedule	% of Anethole
Anise	<i>Pimpinella anisum</i> /Apiaceae	Part 2, Section Two Containers	79-95% ^{30, 31}

²⁹ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrcfr/cfrsearch.cfm?fr=582.60>

³⁰ Neşet Arslan, B *et al.*, (2004) *Turk. J. Agric. For.*, 28, 173-177.

³¹ Zheljazkov, V.D.J *et al.*, (2013) *HORTSCIENCE*, 48 (11), 1393-1396.

Anethole-containing substance	Plant genus/family	Schedule	% of Anethole
(seed) oil		<p>Name of the Poison: Anise oil when included in Schedule 5.</p> <p>Nominal capacity: 200 millilitres or less</p> <p>Schedule 5</p> <p>ANISE OIL except:</p> <ul style="list-style-type: none"> a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 50 mL or less fitted with a restricted flow insert and compliant with the requirements of the Required Advisory Statements for Medicine Labels; b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 50 mL or less fitted with a restricted flow insert, and labelled with the warning: KEEP OUT OF REACH OF CHILDREN; or c) in preparations containing 50 per cent or less of anise oil. <p>Appendix E, Part 2 – ANISE OIL</p> <p>Standard Statement: A, G3.</p>	
Fennel oil	<i>Foeniculum vulgare</i> /Apiaceae	<p>Not currently scheduled.</p> <p>Considered for scheduling at November 2016 meeting of the Joint Advisory Committee on Chemicals and Medicines Scheduling.</p>	82-88% ^{32,33,34,35}
Star anise	<i>Illicium verum</i> /Illiciaceae	<p>Schedule 5</p> <p>STAR ANISE OIL except:</p> <ul style="list-style-type: none"> a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 50 mL or less fitted with a restricted flow insert and compliant with the 	77-92% ^{36,37}

³² Senatore, F *et al.*, (2013) *Fitoterapia*, 90, 214-219.

³³ Dadalioglylu, I and Evrendilek G.A. (2004) *J. Agric. Food Chem.* 52, 8255-8260.

³⁴ Dio, W *et al.*, (2014) *Food Control*, 35 (1), 109-116.

³⁵ Piccaglia, R and Marotti, M (1993) *Flavour and Fragrance Journal*, 8, 115-122.

³⁶ Gholivand, M. B., *et al.*, (2009) *Analytical Letters*; 42 (10), 1382-1397.

³⁷ Wong, Y.C., *et al.*, (2014) *Oriental Journal of Chemistry*, 30 (3), 1159-1171.

Anethole-containing substance	Plant genus/family	Schedule	% of Anethole
		<p>requirements of the Required Advisory Statements for Medicine Labels;</p> <p>b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 50 mL or less fitted with a restricted flow insert, and labelled with the warning:</p> <p>KEEP OUT OF REACH OF CHILDREN; or</p> <p>c) in preparations containing 50 per cent or less of star anise oil.</p>	
Anise myrtle oil	<i>Syzygium anisatum</i> /Myrtaceae	Not scheduled.	90% ^{38, 39}
Liquorice ⁴⁰	<i>Glycyrrhiza glabra</i> /Fabaceae	<p>Appendix B, Part 3</p> <p>LIQUORICE, DEGLYCYRRHISINISED.</p> <p>Date of entry: May 2009</p> <p>Reason for Entry – a, low toxicity</p> <p>Area of Use – 7.1, general, any use</p>	Not found
Dill	<i>Anethum graveolens</i> /Apiaceae	Not scheduled.	11% ⁴¹
Magnolia blossoms ⁴²	<i>Magnolia salicifolia</i> /Magnoliaceae	Not scheduled.	6.0% ⁴³
Coriander	<i>Coriandrum sativum</i> /Apiaceae	Not scheduled.	Trace ⁴⁴
Cicely	<i>Myrrhis odorata</i> / Apiaceae	Not scheduled.	85% ⁴⁵
Sweet cicely	<i>Osmorhiza longistylis</i> /Apiaceae	Not scheduled	95% ⁴⁵

³⁸ Blewitt, M and Southwell, I.A. (2000) *J. Ess. Oil Res.*, 12 (4), 445-454.

³⁹ Sultanbawa, Y (2016) 'Chapter 23 Anise Myrtle (*Syzygium anisatum*) Oils' in *Essential Oils in Food Preservation, Flavor and Safety*, Elsevier Inc.

⁴⁰ Fenwick, GR (1990) *Food Chemistry*, 38, 119-143.

⁴¹ Singh, G *et al.*, (2005) *J. Food Sci.*, 70(4).

⁴² Kelm *et al.*, (2008) *International Journal of Pharmacognosy*, 35(2), 84-90.

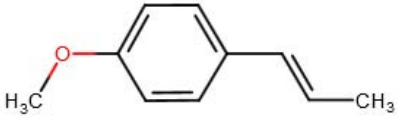
⁴³ Fujita, S-I and Fujita, Y (1975) *Chem. Pharm. Bull.*, 23(10), 2443-2445.

⁴⁴ Baratta, MT *et al.*, (2011) *J. Ess. Oil Res.*, 10, 618-627. M208-M215.

⁴⁵ Surana, S.J. *et al.*, (2006) *Natural Product Radiance*, 5(4), 270-278.

Anethole-containing substance	Plant genus/family	Schedule	% of Anethole
Marigold pepper	<i>Piper marginatum</i> / <i>Piperaceae</i>	Not scheduled.	80% ⁴⁵

Table 2.13.2: Chemical information for trans-anethole

Property	Trans-anethole
Chemical structure	
Molecular formula	C ₁₀ H ₁₂ O
Molecule weight	148.2 g/mol
CAS name	Benzene, 1-methoxy-4-(1-propenyl)-, (E)-
CAS number	4180-23-8
IUPAC and/or common and/or other names	Trans-anethole (INCI); 1-Methoxy-4-[(1E)-prop-1-en-1-yl]benzene (IUPAC); (E)-1-p-methoxyphenylpropene; anethole (AAN); Anisole; anise camphor; p-propenyl-, (E)-; p-propenylanisole; isoestragole.

The following information was extracted from the [NICNAS IMAP Human Health Tier II assessment report for trans-anethole](#), publicly available on the NICNAS website.

Table 2.13.3: Acute toxicity end-points for trans-anethole

Toxicity	Species	Trans-anethole	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Osborne-Mendel Rats	2090-3200	Schedule 5
	CD-1 Mice	1820-5000	
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rabbits (strain not specified)	>4900	Schedule 5
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rats (strain not specified)	>5100	N/A

Toxicity		Species	Trans-anethole	SPF (2015) Classification
Skin irritation		New Zealand White Rabbits	Not irritating (slight erythema)	N/A
Eye irritation		New Zealand White Rabbits	Not irritating	N/A
Skin sensitisation	Local lymph node assay, LLNA	CBA Mice	Sensitising (EC3 <25%)	Schedule 6
	Guinea pig maximisation test, GPMT	Guinea pig (strain not specified)	Sensitising	

Acute toxicity

Trans-anethole has low acute toxicity based on results from animal tests following oral, dermal and inhalation exposure.

Irritation

Trans-anethole is not considered to be a skin or eye irritant:

- slight erythema (fully resolved after 8 h) was observed after trans-anethole was semi-occlusively applied to clipped, intact dorsal skin of New Zealand White rabbits for 4 h; and
- no signs of pain or irritation were observed after neat trans-anethole was instilled into the eyes of New Zealand White rabbits.

Sensitisation

Trans-anethole is considered to be a skin sensitiser based on the positive results seen in a mouse LLNA and GPMT:

- In a mouse LLNA conducted according to OECD TG 442B, female CBA mice (n = 4 animals/dose) were exposed to trans-anethole at 25, 50, or 100% in acetone/olive oil (4:1 v/v). The stimulation indices (SI) calculated were 3.49, 3.53 and 3.85 for the low, mid and high doses, respectively, indicating that trans-anethole was positive for skin sensitisation.
- In a GPMT conducted according to the OECD TG 406, 10 guinea pigs were induced with trans-anethole at 2% (intradermal) and 50% (topical). Trans-anethole at 10% was administered as a challenge dose and 10/10 animals tested positive for skin sensitisation. Each guinea pig was then challenged weekly, at a non-irritating concentration and 10/10 guinea pigs tested positive for skin sensitisation.

Repeat-dose toxicity

Based on the available data, repeated oral exposure to trans-anethole is not considered to cause serious damage to health. No data are available for repeated dermal and inhalation toxicity.

Genotoxicity

Based on the negative results from several *in vitro* and *in vivo* studies, trans-anethole is not considered to be genotoxic.

Carcinogenicity

Based on the data available, trans-anethole is not considered to be carcinogenic.

Reproduction and developmental toxicity

Trans-anethole does not show any signs of reproductive or developmental toxicity. Any developmental effects seen were secondary to maternal toxicity.

Public exposure

Trans-anethole has been identified to be used in cosmetic (perfumes and fragrances) and domestic products (polishes and waxes; softeners; soaps and cleaning products; and air care products) overseas at concentrations up to 10%. This use pattern is taken to be representative of its use in Australia [see Australian regulatory information].

Due to the use patterns of trans-anethole, direct dermal exposure is expected.

Pre-meeting public submissions

Two (2) public submissions were received and both opposed the proposal.

Main points opposed:

- An Appendix B entry has been previously considered for other flavour/fragrance ingredients used in cosmetic and household hygiene products with low acute toxicity and low public exposure.
- Due to the similarity of this substance with other scheduled items, regulatory control must be consistent with other related existing schedule entries and across all current uses of the substance (both therapeutic and cosmetic/domestic).

The public submissions will be made available on the [TGA website](#).

Summary of ACCS-ACMS advice to the delegate

The committee recommended that further consideration of exemption cut-offs applied to associated essential oils, such as star anise, anise oil and fennel oil, for the purposes of scheduling consistency before any advice can be provided on this application.

The committee recommended that no scheduling is required at this stage, pending further advice to ensure consistency in any scheduling decision.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- Anethole is a large and natural component of essential oils, used as a fragrance and flavour ingredient. It is found in 249 products on ARTG and these products have a wide range of uses. Anethole is also used in an unknown amount of cosmetic and household hygiene/domestic products, such as perfumes, fragrances, polishes, waxes, soaps, cleaning products, air care products and food flavourings. These products are used orally, topically and domestically with greatly varied packaging/labelling.
- The benefits of anethole were not presented for both medicinal and domestic use. However, its presence in a number of essential oils and wide range of products means the substance should continue to be available and accessible. Anethole is typically found in products that are designed to be applied topically and consumed up to 10%.

- The potential for misuse or abuse is low. However, there is a risk that anethole can be synthesised to create a recreational drug, paramethoxyamphetamine (PMA), that has been known to cause death in users.
- Anethole has skin sensitising potential (EC3 <25%) and has low acute oral toxicity (LD₅₀ >~2g/kg). The severity of skin sensitisation does not appear to be well established. There is no evidence of human poisoning presented.
- A new Schedule 6 entry for anethole will require a review of all scheduled essential oils of which trans-anethole is a major component of as they are currently either Schedule 5 or unscheduled (fennel oil).

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS-ACMS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to defer a decision on trans-anethole and refer the application back to the applicant for further consideration of an exemption cut-off to ensure consistency in any scheduling decision.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

- The delegate acknowledges the committee's advice.
- Anethole is a large and natural component of essential oils, used as a fragrance and flavour ingredient. It is found in 249 products on ARTG and these products have a wide range of uses. Anethole is also used in an unknown amount of cosmetic and household hygiene/domestic products, such as perfumes, fragrances, polishes, waxes, soaps, cleaning products, air care products and food flavourings. These products are used orally, topically and domestically with greatly varied packaging/labelling.
- The benefits of anethole were not presented for both medicinal and domestic use, however its presence in a number of essential oils and wide range of products means the substance should continue to be available and accessible. Anethole is typically found in products that are designed to be applied topically and consumed up to 10%.
- The potential for misuse or abuse is low. However, there is a risk that anethole can be synthesised to create a recreational drug, paramethoxyamphetamine (PMA), that has been known to cause death in users.

- Anethole has skin sensitising potential (EC3 <25%) and has low acute oral toxicity (LD₅₀ >~2g/kg). The severity of skin sensitisation does not appear to be well established. There is no evidence of human poisoning presented.
- A new Schedule 6 entry for anethole will require a review of all scheduled essential oils of which trans-anethole is a major component of as they are currently either Schedule 5 or unscheduled (fennel oil).
- The delegate has decided to defer the interim decision for trans-anethole to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.

3. Advisory Committee on Chemicals Scheduling (ACCS #20)

Summary of delegate's interim decisions

Substance	Interim Decision
Isofetamid	Appendix B – New Entry ISOFETAMID Reason for Entry – a, low toxicity Area of Use – 1.3, fungicide The proposed implementation date is 1 February 2018 .
Pydiflumetofen	Appendix B – New Entry PYDIFLUMETOFEN Reason for Entry – a, low toxicity Area of Use – 1.3, fungicide The proposed implementation date is 1 February 2018 .
<i>Duddingtonia flagrans</i>	Appendix B – New Entry DUDDINGTONIA FLAGRANS, STRAIN IAH 1297 Reason for Entry – a, low toxicity Area of Use – 2.7, anthelmintic The proposed implementation date is 1 February 2018 .
Lambda-cyhalothrin	Schedule 6 – Amend Entry LAMBDA-CYHALOTHRIN: <ol style="list-style-type: none"> in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or in emulsifiable granule formulations containing 25 per cent or less

Substance	Interim Decision
	<p>lambda-cyhalothrin; or</p> <p>c) in other preparations containing 1.6 per cent or less of lambda-cyhalothrin</p> <p>except when included in Schedule 5.</p> <p>The proposed implementation date is 1 February 2018.</p>
<i>Bacillus amyloliquefaciens</i>	<p>Appendix B – New Entry</p> <p>BACILLUS AMYLOLIQUEFACIENS STRAIN QST 713.</p> <p>Reason for Entry – a, low toxicity</p> <p>Area of Use – 1.3, fungicide</p> <p>Index – New Entry</p> <p>BACILLUS AMYLOLIQUEFACIENS STRAIN QST 713 cross reference: BACILLUS SUBTILIS STRAIN QST 713</p> <p>The proposed implementation date is 1 February 2018.</p>
Butyl benzyl phthalate	<p>Schedule 10 – New Entry</p> <p>BUTYL BENZYL PHTHALATE.</p> <p>The proposed implementation date is 1 February 2018.</p>
Basic Red 76	<p>Schedule 7 – Amend Entry</p> <p>AZO DYES that are derivatives by diazotisation of any of the following substances:</p> <p><i>p</i>-aminoazobenzene (CAS No. 60-09-3)</p> <p><i>o</i>-aminoazotoluene (CAS No. 97-56-3)</p> <p><i>o</i>-anisidine (CAS No. 90-04-0)</p> <p><i>p</i>-chloroaniline (CAS No. 106-47-8)</p> <p>4-chloro-<i>o</i>-toluidine (CAS No. 95-69-2)</p> <p>6-methoxy-<i>m</i>-toluidine (<i>p</i>-cresidine) (CAS No. 120-71-8)</p> <p>2-naphthylamine (CAS No. 91-59-8)</p> <p>5-nitro-<i>o</i>-toluidine (CAS No. 99-55-8)</p> <p>2,4-toluenediamine (CAS No. 95-80-7)</p> <p><i>o</i>-toluidine (CAS No. 95-53-4)</p> <p>2,4,5-trimethylaniline (CAS No. 137-17-7)</p> <p>except for BASIC RED 76 (CAS No. 68391-30-0) when included in Schedule 6.</p> <p>Schedule 6 – New Entry</p> <p>BASIC RED 76 (CAS No. 68391-30-0) in non-oxidative hair dye preparations</p>

Substance	Interim Decision
	<p>and eyebrow/eyelash colouring products containing 2 per cent or less of BASIC RED 76 and 0.001 per cent or less of free <i>o</i>-anisidine.</p> <p>Appendix E, Part 2 – New Entry</p> <p>BASIC RED 76</p> <p>Standard Statement: A (Poisons Advice hotline)</p> <p>Appendix F, Part 3 – New Entry</p> <p>BASIC RED 76</p> <p>Warning Statement: 5 (Wear protective gloves when mixing or using).</p> <p>Index – New Entry</p> <p>BASIC RED 76 (CAS No. 68391-30-0) cross reference: [7-HYDROXY-8-[(2- METHOXYPHENYL)AZO]-2-NAPHTHYL]TRIMETHYLAMMONIUM CHLORIDE (CAS No. 68391-30-0)</p> <p>Schedule 7 Schedule 6</p> <p>The proposed implementation date is 1 February 2018.</p>

3.1. Isofetamid

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new entry for isofetamid in Schedule 5 of the Poisons Standard, with no exemptions.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 5 – New Entry

ISOFETAMID.

The applicant's reasons for the request are:

- No product has been proposed for registration in this current application. However, isofetamid is a broad-spectrum fungicide whose mode of action involves the inhibition of succinate dehydrogenase in complex II of fungal respiration. Therefore, it is anticipated that isofetamid could be used to control diseases caused by Botrytis, Monilia, and Sclerotinia (and Rhizoctonia) fungi in a range of crops;
- It is noted that isofetamid is a carboxamide fungicide and several carboxamide fungicides are currently listed in Appendix B of the poisons Standard (substances considered not to require control by scheduling), such as carboxin and boscalid. While recently (February 2012), the carboxamide fungicide fluxapyroxad with the same mode of action as isofetamid was listed in Schedule 5 of the Poisons Standard with no cut-off or exemptions, with the concern being slight skin irritation in rabbits;

- Based on the observed slight eye irritation in rabbits, isofetamid meets the Scheduling Policy Framework (2015) criteria for scheduling it to Schedule 5 of the Poisons Standard with no cut-off or exemptions;
- The toxicokinetic profile established in oral gavage doses in rats indicated that absorption of isofetamid was essentially complete at the low and high dose; i.e. >93%. Isofetamid was widely distributed to tissues with the highest concentrations being in the liver and kidneys. There was no evidence of accumulation in tissues following repeat oral dosing. Isofetamid is extensively metabolised, and the major routes of metabolism were O-dealkylation, hydroxylation and subsequent glucuronidation. Excretion was rapid with the majority of the administered dose eliminated in the urine (11% in males and 48% in females) and bile (85 – 88%) within 48 hours after administration. The difference between sex types with regard to the extent of excretion via urine and faeces was shown to be due to a quantitative difference rather than the presence of unique metabolites in bile or urine;
- The observed systemic toxicity does not warrant scheduling. Additionally, there was no evidence that isofetamid was neurotoxic or immunotoxic. Therefore, isofetamid does not warrant scheduling for these endpoints;
- There was no evidence that isofetamid was carcinogenic in mice and rats, and isofetamid was tested for genotoxicity in an adequate range of *in vitro* and *in vivo* assays and was negative. Therefore, isofetamid does not warrant scheduling for these endpoints;
- In a study of developmental toxicity in rats, maternal (liver) toxicity was seen at the top (limit) dose of 1000 mg/kg bw/d. While rare major abnormalities to the heart and major vessels were seen in one and two fetuses (2 litters) at the mid and high dose respectively, the findings were seen at the same incidence in studies from the laboratories historical database with the exception of incomplete caudal vena cava with persistent cardinal vein. However, the singular occurrence of this finding at the mid- and high-dose was considered likely incidental to treatment. For minor visceral abnormalities, a low incidence of brain haemorrhage and left-sided umbilical artery was seen, that were stated by the study author to be within normal limits and of low biological significance and not adverse. However, no historical control data was provided, though obtained data on the background incidence of left-sided umbilical artery in rat fetuses in four other testing laboratories indicated they were likely incidental to treatment. No data on the background incidence of brain haemorrhages in rat fetuses was obtained and, therefore, this finding at the limit dose cannot be completely discounted. However, brain haemorrhages are not a structural abnormality per se, this non-statistical finding was seen (at a lower incidence) in concurrent controls, and was seen at a dose level producing maternal toxicity. Therefore, while this finding was considered potentially treatment-related, it was not considered to fully demonstrate an increased sensitivity of the embryo/foetus to isofetamid. While it is considered that the observance of a dose-related increase in ossification leading to fewer fetuses showing incomplete ossification/unossified is unlikely to be toxicologically significant; and
- In a study of developmental toxicity in rabbits, marked maternal toxicity (that included a bodyweight loss over GD 6-9) was seen at the top (limit) dose of 1000 mg/kg bw/d, and skeletal malformations were seen in 1, 1, and 4 fetuses (4 litters) at 0, 300 and 1000 mg/kg bw/d, respectively. At the limit dose specific malformations were only seen in a single animal with the exception of fused sternbrae in 2 fetuses, and neither the incidence of individual or total malformations were statistically significant. Therefore, it is considered that the observed low incidences of skeletal malformations were likely incidental to treatment, and an increased sensitivity of the embryo/foetus to isofetamid has not been demonstrated. It was concluded that isofetamid was not teratogenic in rats and rabbits. Therefore, isofetamid does not warrant scheduling for this endpoint.

Current scheduling status and relevant scheduling history

Isofetamid is not currently scheduled and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Isofetamid is a carboxamide fungicide; several carboxamide fungicides (such as carboxin and boscalid) are currently listed in Appendix B of the Poisons Standard (substances considered not to require control by scheduling).

Boscalid

In June 2003, the National Drugs and Poisons Scheduling Committee (NDPSC) decided to include boscalid (first generation carboxamide) in Appendix B because of its low acute toxicity potential, i.e. low oral, dermal and inhalation toxicity and it was not a skin irritant in rabbits or a skin sensitiser in guinea pigs, but was a slight eye irritant in rabbits. The NDPSC therefore agreed to exempt boscalid from the requirements of scheduling.

Carboxin

In July 1987, the Drugs and Poisons Scheduling Committee (DPSC) decided to include carboxin in Appendix B on the basis of low acute oral, dermal and inhalation toxicity; and an absence of reproductive effects.

Fluxapyroxad

In February 2012, the carboxamide fungicide fluxapyroxad, with the same mode of action as isofetamid, was listed in Schedule 5 with no cut-off or exemptions, with the concern being slight skin irritation in rabbits.

Australian regulatory information

Isofetamid is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#), and is not an excipient or active in any products on the ARTG.

Isofetamid is not listed on the National Industrial Chemicals Notification and Assessment Scheme's (NICNAS) Australian Inventory of Chemical Substances (AICS).

International regulations

USA

Isofetamid 400SC Fungicide was listed as a pesticide by EPA in the USA in July 2015 under the Federal Insecticide, Fungicide and Rodenticide Act (EPA registration number 71512-22).⁴⁶

Canada

In June 2016, Canada granted full registration for the sale and use of Technical Isofetamid Fungicide and Isofetamid 400 SC Fungicide, containing the active ingredient isofetamid, to control various *Botrytis* and *Sclerotinia* diseases on grape, lettuce (head and leaf), rapeseed, low growing berry and turfgrass on golf courses and sod farms.

EU

Isofetamid is approved for use in certain EU countries according to Regulation (EC) No 1107/2009.

Substance summary

The mode of action is inhibition of succinate dehydrogenase in complex II of the mitochondrial respiratory chain, resulting in inhibition of spore germination, germ tubes, and mycelial growth.⁴⁷

⁴⁶ [Notice of Registration for Isofetamid 71512-22](#)

Table 3.1.1: Chemical information for Isofetamid

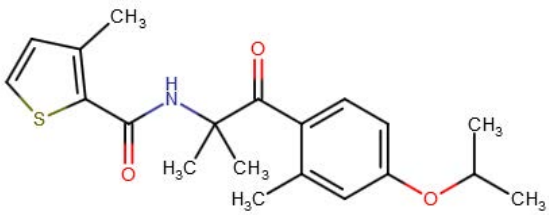
Property	Isofetamid
Chemical structure	
Molecular formula	C ₂₀ H ₂₅ NO ₃ S
Molecular weight	359.5 g/mol
CAS name	<i>N</i> -[1,1-dimethyl-2-[2-methyl-4-(1-methylethoxy)phenyl]-2-oxoethyl]-3-methyl-2-thiophenecarboxamide
CAS number	875915-78-9
IUPAC and/or common and/or other names	IKF-5411; <i>N</i> -[1,1-dimethyl-2-(4-isopropoxy- <i>o</i> -tolyl)-2-oxoethyl]-3-methylthiophene-2-carboxamide; <i>N</i> -[1,1-dimethyl-2-[2-methyl-4-(1-methylethoxy)phenyl]-2-oxoethyl]-3-methyl-2-thiophenecarboxamide.

Table 3.1.2: Acute toxicity end-points for Isofetamid

Toxicity	Species	Isofetamid	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	>2000	Schedule 5
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rat	>2000	Schedule 5
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rat	>4820	Schedule 5
Skin irritation	Rabbit	Not irritant	Appendix B
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation (LLNA)	Mouse (LLNA)	Not a sensitiser	Schedule 5

Acute toxicity

Based on the available oral, dermal and inhalation data, isofetamid has low acute toxicity.

⁴⁷ Piqueras *et al.*, (2014), [Effectiveness of isofetamid, a new succinate dehydrogenase inhibitor fungicide, in the control of grapevine gray mold](#), *International Journal on Agriculture and Natural Sources*, 41 (3)

Skin irritation

Based on available data, isofetamid is not a skin irritant:

- Three female rabbits received a single (semi-occlusive) topical application of 0.5 g isofetamid moistened with 0.5 mL de-ionised water for 4 h. Observation for skin irritation was performed at 1, 24, 48 and 72 h after patch removal. Observations for signs of toxicity were made once daily. As there was no irritating response at 72 h animals were sacrificed at that time.

Eye irritation

Based on available data, isofetamid is a slight eye irritant:

- Six female rabbits were administered 0.1 g isofetamid (powder) by ocular instillation. The eyes of three rabbits were irrigated with lukewarm water after 20 seconds. Observation for ocular irritation was performed at 1, 24, 48 and 72 h after instillation. Observations for signs of toxicity were made once daily. As there was no irritating response at 72 h animals were sacrificed at that time. Redness of the conjunctivae (grade 1) was seen in all animals at 1 h, with discharge seen in 1 animal whose eyes were irrigated (grade 1) and in all animals whose eyes were not irrigated (grade 1, 2 and 3). Additionally, at 1 h chemosis of the conjunctivae was seen in all animals whose eyes were not irrigated (grade 1, 2 and 2). At 24 h, redness of the conjunctivae (grade 1) was still present in 2 animals whose eyes were not irrigated. Corneal opacity and iritis were not observed, and ocular irritation was absent in all animals at 48 h. No other treatment-related clinical signs were observed during the study. Under the study conditions described, isofetamid was a slight eye irritant.

Sensitization

Based on available data, isofetamid is not a skin sensitiser:

- Five groups of 5 female mice received topical application of 0 (vehicle control), 10, 25 or 50% isofetamid in dimethylformamide (DMF), or 25% of the positive control α -hexylcinnamaldehyde in DMF, for 3 consecutive days to both ears. Observations for signs of toxicity and local irritation were made once daily. On test day 6 of the assay, mice received ^3H -methyl thymidine by tail vein injection and were sacrificed 5 h later. Cell proliferation in the draining lymph nodes of the ears of mice from the test substance and positive control groups was then evaluated and compared to the vehicle control group. The stimulation indices for cell proliferation were 1.0, 1.1 and 1.1 at 10, 25 and 50% of the test substance, respectively. The positive control demonstrated the sensitivity of the assay. No skin irritation or treatment-related clinical signs were observed during the study. Under the study conditions described, isofetamid was not a skin sensitiser.

Repeat-dose toxicity

In short- and long-term repeat-dose dietary studies in mice, rats and dogs, the primary target organ was the liver. If an increased liver weight occurred in the absence of a corresponding increase in plasma levels of some liver derived enzymes (gamma glutamyl transpeptidase (GGPT), alkaline phosphatase (ALP)) then it was considered to be an adaptive effect. This was observed in mice. However, in rats and dogs, increased liver weights with histopathological changes were consistently seen in the presence of clinical chemistry changes, specifically increased GGPT in both species and ALP in dogs, at the LOAEL in long-term repeat-dose dietary studies in rats. Additionally, in rats thyroid follicular cell hypertrophy was observed at dose levels producing liver toxicity. A prolongation in blood clotting time/potential was seen, in the absence of treatment-related changes in other haematology parameters, secondary to disturbances in liver function.

Genotoxicity and carcinogenicity

There was no evidence that isofetamid was carcinogenic in mice and rats. Further, isofetamid was tested for genotoxicity in an adequate range of *in vitro* and *in vivo* assays and based on these studies isofetamid is not genotoxic.

Reproduction and developmental toxicity

The reproduction toxicity studies on isofetamid showed no treatment related signs of toxicological significance. Therefore isofetamid was not a reproductive toxicant in rats. Further, the submitted studies on developmental toxicity showed that isofetamid was not teratogenic in rats and rabbits.

Toxicological data on metabolites and/or degradants

GPTC, the glucoside of 4HP and a significant plant metabolite, had an oral LD₅₀ value > 2000 mg/kg bw in the rat, and was negative in a bacterial reverse mutation assay with and without S9 metabolic activation. The available toxicity data indicate that GPTC is of no greater toxicity than isofetamid.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that a new Appendix B entry for isofetamid be created as follows:

Appendix B – New Entry

ISOFETAMID

Reason for Entry – a, low toxicity

Area of Use – 1.3, fungicide

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- Isofetamid is expected to be used for agricultural purposes as a broad spectrum fungicide. The use in Australia is unknown at this time, and therefore the risks and benefits are unknown.
- The low toxicology profile of isofetamid does not appear to warrant scheduling. There is a risk of slight eye irritation, which is reduced by irrigation and is reversible within 48 hours.
- The APVMA is well placed to develop suitable warning statements, safety directions and first aid instructions for the product label of future products containing isofetamid.
- Isofetamid is similar to a number of carboxamide fungicides already listed in Appendix B.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS advice
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Appendix B entry for isofetamid. The proposed Schedule entry is as follows:

Appendix B – New Entry

ISOFETAMID

Reason for Entry – a, low toxicity

Area of Use – 1.3, fungicide

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are:

- Isofetamid is expected to be used for agricultural purposes as a broad spectrum fungicide. The use in Australia is unknown at this time, and therefore the risks and benefits are unknown.
- The low toxicology profile of isofetamid does not appear to warrant scheduling. There is a risk of slight eye irritation, which is reduced by irrigation and is reversible within 48 hours.
- The APVMA are well placed to develop suitable warning statements, safety directions and first aid instructions for the product label of future products containing isofetamid.
- Isofetamid is similar to a number of carboxamide fungicides already listed in Appendix B.

3.2. Pydiflumetofen

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new entry for pydiflumetofen in Schedule 5 of the Poisons Standard, with no exemption cut-off.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 5 – New Entry

PYDIFLUMETOFEN.

The applicant's reasons for the request are:

- Pydiflumetofen is a new broad-spectrum fungicide of the chemical group of *N*-methoxy-(phenyl-ethyl)-pyrazole-carboxamide. The active ingredient is a mixture of the R & S isomers of pydiflumetofen. The mode of action of pydiflumetofen is inhibition of respiration in phytopathogenic fungi at succinate dehydrogenase (or Electron Transport Chain Complex II) in mitochondria;
- Two product applications were submitted for the registration by the APVMA. However, one product application has now been withdrawn;

- Based on the observed slight eye irritation in rabbits, pydiflumetofen meets the Scheduling Policy Framework (2015) criteria for including it in Schedule 5 of the Poisons Standard with no cut-offs or exemptions;
- Pydiflumetofen is not a reproduction or developmental toxin, is not neurotoxic and does not present a genotoxic or carcinogenic risk to humans; and
- The product containing 20% w/v of pydiflumetofen has low acute oral toxicity in rats (LD₅₀ 2958 mg/kg bw), low acute dermal toxicity in rats (LD₅₀ >5000 mg/kg bw, no deaths or clinical signs), low acute inhalation toxicity in rats (LC₅₀ >3500 mg/m³ with 1 death at 3500 mg/m³), is not a skin irritant in rabbits or a skin sensitiser in the mouse (LLNA). The product produced slight transient eye irritation in the rabbit resolving after 1 hour and was not an irritant in an isolated chicken eye study.

Current scheduling status and relevant scheduling history

Pydiflumetofen is not currently scheduled and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Pydiflumetofen is not captured by any group entry nor is it a salt or derivative of any entry in the current (June 2017) Poisons Standard.

Scheduling and scheduling history of related compounds

[Penthiopyrad](#) was included in the Poisons Standard in Schedule 5 on 1 May 2012 following a delegate only decision.

[Fluxapyroxad](#) was included in the Poisons Standard in Schedule 5 on 1 May 2012 following referral to the ACCS.

[Sedaxane](#) was included in the Poisons Standard in Schedule 5 on 1 September 2012 following a delegate only decision.

[Penflufen](#) was included in the Poisons Standard in Schedule 5 on 1 January 2013 following referral to the ACCS.

[Bixafen](#) was included in the Poisons Standard in Schedule 5 on 1 February 2016 following a delegate only decision.

[Isopyrazam](#) was included in the Poisons Standard in Schedule 6 on 1 October 2016 following referral to the ACCS.

Australian regulatory information

Pydiflumetofen is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#), and is not an excipient or active in any products on the ARTG.

International regulations

Pydiflumetofen applications are currently pending in the EU (EC Regulation 1107/2009), Canada and Argentina.

Substance summary

Pydiflumetofen is a new broad-spectrum fungicide of the chemical group of *N*-methoxy-(phenyl-ethyl)-pyrazole-carboxamide. The active ingredient is a mixture of the R & S isomers of pydiflumetofen. The mode of action of pydiflumetofen is inhibition of respiration in phytopathogenic fungi at succinate dehydrogenase (or Electron Transport Chain Complex II) in mitochondria. An extensive data base of toxicology, metabolism and toxicokinetic studies have been provided for pydiflumetofen.

Table 3.2.1: Chemical information for Pydiflumetofen

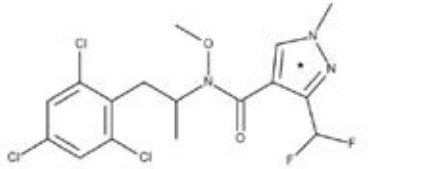
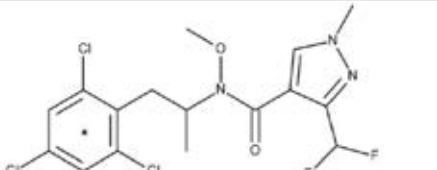
Property	Pydiflumetofen
Chemical structure and position of radiolabel for Pydiflumetofen	<p>[Pyrazole-5-¹⁴C]SYN545974 (• = Position of ¹⁴C)</p>  <p>[Phenyl-(U-¹⁴C)]-SYN545974 (• = Position of ¹⁴C)</p> 
Molecular Formula	C ₁₆ H ₁₆ Cl ₃ F ₂ N ₃ O ₂
Molecular weight	426.7 g/mol
CAS number	1228284-64-7
IUPAC and/or common and/or other names	3-(difluoromethyl)- <i>N</i> -methoxy-1-methyl- <i>N</i> -[1-methyl-2-(2,4,6-trichlorophenyl)ethyl]-1 <i>H</i> -pyrazole-4-carboxamide (CAS); 3-(difluoromethyl)- <i>N</i> -methoxy-1-methyl- <i>N</i> -[(<i>RS</i>)-1-methyl-2-(2,4,6-trichlorophenyl)ethyl]pyrazole-4-carboxamide (IUPAC)

Table 3.2.2: Acceptable Daily Intake for pydiflumetofen⁴⁸

Chemical	ADI (mg/kg bw/d)	NOAEL (mg/kg bw/d)	Date	Study
Pydiflumetofen	0.1	10	21 February 2017	1-year dietary rat study; a NOAEL of 10 mg/kg bw/d was based on reduced body weight gain, food consumption and food energy conversion efficiency at the next higher dose.

Table 3.2.3: Acute toxicity end-points for Pydiflumetofen

Toxicity	Species	Pydiflumetofen	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	>5000	Nil
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rat	>5000	Nil
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rat	>5110	Schedule 5

⁴⁸ [Acceptable Daily Intakes for Agricultural and Veterinary Chemicals](#), APVMA

Toxicity	Species	Pydiflumetofen	SPF (2015) Classification
Skin irritation	Rabbit	Not irritant	Nil
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation (LLNA)	Mouse	Not a sensitiser	Nil

Acute toxicity

Pydiflumetofen has low to very low acute oral toxicity in the rat ($LD_{50} > 5000$ mg/kg bw with no deaths and no clinical signs after 4 hours – 1 animal had a slight reduction in activity at < 4 h), has low to very low acute dermal toxicity in the rat ($LD_{50} > 5000$ mg/kg bw with no deaths but decreased activity during day 1) and low to very low acute inhalation toxicity in rats ($LC_{50} > 5110$ mg/m³ with 1 death and clinical signs of toxicity). Pydiflumetofen is neither a sensitiser in a mouse LLNA assay nor a skin irritant in rabbits but was a slight eye irritant in rabbits (Initial pain reaction, discharge conjunctival redness, all resolving by 72-hours. No corneal effects).

Eye irritation

Pydiflumetofen is a slight eye irritant in rabbits (Initial pain reaction, discharge conjunctival redness, all resolving by 72-hours. No corneal effects).

Sensitization

Pydiflumetofen is not a sensitiser in a mouse LLNA assay.

Repeat-dose toxicity

In repeat dose toxicity studies the primary target organ of toxicity was the liver with increased liver weight, associated with hepatocyte hypertrophy, generally defining the LOAEL in conjunction with reduced body weight gains. Mode of action studies demonstrated that these observations were associated with induction of microsomal enzymes in a phenobarbital like pattern.

Genotoxicity

The overall weight of evidence is that pydiflumetofen does not present a genotoxic risk to humans.

Carcinogenicity

Pydiflumetofen was not carcinogenic in a rat chronic study but did increase the incidence of hepatic carcinoma and adenoma in male mice. The mechanism of action of pydiflumetofen in the production of mouse hepatic cancers was examined in a series of studies that demonstrated a mode of action that is not relevant to humans (a phenobarbital like activation of Constitutive Androstane Receptor – CAR – with a consequent induction of Cyp450, increased cell proliferation, hepatomegaly and hepatocyte hypertrophy).

Reproduction and developmental toxicity

Pydiflumetofen was neither a reproductive toxin in rats nor a developmental toxin in rats and rabbits. The compound was tested in a battery of *in vivo* and *in vitro* genotoxicity studies. With the exception of a positive after 22 hours of exposure in the absence of S9 in a human lymphocyte clastogenicity assay, all assays were negative.

Public exposure

Both products are intended for use in agriculture and the applicant has not sought approval for home garden use, although the toxicological profile of pydiflumetofen is not inconsistent with the criteria for this use pattern. Public exposure to the product concentrate and in use dilutions is likely to be negligible other than possibly to spray drift moving into public areas. Under normal use scenarios such exposure is likely to be uncommon, short term and infrequent.

Pre-meeting submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that a new Appendix B entry for pydiflumetofen be created as follows:

Appendix B – New Entry

PYDIFLUMETOFEN

Reason for Entry – a, low toxicity

Area of Use – 1.3, fungicide

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice were:

- The risks associated with pydiflumetofen are minimal. Pydiflumetofen meets the SPF criteria for Schedule 5 for low acute inhalation toxicity and slight temporary eye irritation. However, it is unscheduled based on its low acute oral and dermal toxicity. Pydiflumetofen has no skin irritation or sensitisation demonstrated.
- Pydiflumetofen is a fungicide for agricultural use.
- The APVMA is well placed to develop suitable warning statements, safety directions and first aid instructions for the product label of future products containing pydiflumetofen.

Delegate's considerations

- The delegate considered the following regarding this proposal:
- Scheduling proposal
- ACCS advice
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Appendix B entry for pydiflumetofen. The proposed Schedule entry is as follows:

Appendix B – New Entry

PYDIFLUMETOFEN

Reason for Entry – a, low toxicity

Area of Use – 1.3, fungicide

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are:

- The risks associated with pydiflumetofen are minimal. Pydiflumetofen meets the SPF criteria for Schedule 5 for low acute inhalation toxicity and slight temporary eye irritation. However, it is unscheduled based on its low acute oral and dermal toxicity. Pydiflumetofen has no skin irritation or sensitisation demonstrated.
- Pydiflumetofen is a fungicide for agricultural use.
- The APVMA is well placed to develop suitable warning statements, safety directions and first aid instructions for the product label of future products containing pydiflumetofen.

3.3. *Duddingtonia flagrans*

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new entry for *Duddingtonia flagrans* in Schedule 5 of the Poisons Standard, with no exemption cut-off.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 5 – New Entry

DUDDINGTONIA FLAGRANS.

The applicant's reasons for the request are:

- The ubiquitous fungus, *Duddingtonia flagrans*, is present in animal faeces, soil and compost where it feeds on parasitic nematodes of grazing animals. *D. flagrans* spores, known as chlamydospores, are robust and can survive passage through the digestive tract of animals to be excreted in faeces, where they then germinate. There are at least 25 characterised isolates of *D. flagrans* in Australia. Genetic characterisation of these isolates show they fall into four major phylogenetic groups. One of these isolates, *D. flagrans* (strain IAH 1297), is the microbial constituent (active) in the current application.
- *D. flagrans* is not infective, pathogenic or acutely toxic, although the proposed product, containing a chlamydospore preparation of the fungus, was a slight eye irritant in rabbits. Large intratracheal doses of chlamydospore preparations to rats were obstructive and led to initial respiratory difficulties, as well as an associated induction of multifocal lesions and diffuse purulent pneumonia with necrosis in areas of the pulmonary tissue. However, once the spores were cleared adverse effects were resolved. It is unknown if the fungus is a skin or respiratory sensitiser. *D. flagrans* spore preparations are proteinaceous and in the absence of suitable studies its respiratory sensitisation potential or ability to induce a cell mediated immunological response cannot be ruled

out. However, appropriate personal protective equipment (i.e. dust mask) can be recommended to minimise these risks.

- Based on the observed slight eye irritation in rabbits, *D. flagrans* meets the Scheduling Policy Framework (2015) criteria for scheduling it to Schedule 5 of the Poisons Standard with no cut-off or exemptions.
- No short-term or long-term toxicology studies were submitted. Further, there are no publicly available studies with other *D. flagrans* strains or their secondary metabolites. As *D. flagrans* is a ubiquitous non-pathogenic/non-infectious fungi that does not produce secondary metabolites at a level that are a concern to human health, longer term studies of toxicity and carcinogenicity are not required and have not been provided.
- No *in vitro* or *in vivo* studies were submitted. However, the Applicant provided *in silico* Quantitative structure–activity relationship (QSAR) modelling study that predicts flagranone A, the major secondary metabolite of *D. flagrans* (strain IAH 1297), is not genotoxic and does not exceed the ‘Threshold of Toxicological Concern’.

Current scheduling status and relevant scheduling history

Duddingtonia flagrans is not currently scheduled and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Australian regulatory information

Duddingtonia flagrans is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#), and is not an excipient or active in any products on the ARTG.

International regulations

New Zealand

The EPA registered *Duddingtonia flagrans* on 3 August 2016.⁴⁹

EU

EFSA provided an opinion on the safety of *D. flagrans* when used as a feed additive for calves in 2006.⁵⁰

Substance summary

The ubiquitous fungus, *Duddingtonia flagrans*, is present in animal faeces, soil and compost where it feeds on parasitic nematodes of grazing animals. *D. flagrans* spores, known as chlamydospores, are robust and can survive passage through the digestive tract of animals to be excreted in faeces, where these then germinate. There are at least 25 characterised isolates of *D. flagrans* in Australia. Genetic characterisation of these isolates show they fall into four major phylogenetic groups. One of these isolates, *D. flagrans* (strain IAH 1297), is the microbial constituent (active) in the current application.

⁴⁹ [Environmental Protection Authority – BioWorma and Livamol with BioWorma](#)

⁵⁰ [Opinion of the Panel on additives and products or substances used in animal feed \(FEEDAP\) on the safety of the micro-organism preparation of *Duddingtonia flagrans*, for use as a feed additive for calves in accordance with Council Directive 70/524/EEC](#)

Table 3.3.1: Chemical information for *Duddingtonia flagrans*

Property	<i>Duddingtonia flagrans</i>
IUPAC and/or common and/or other names	<i>Arthrobotrys flagrans</i> (Dudd.) Sidorova, Gorlenko & Nalepina; <i>Trichothecium flagrans</i> Dudd.

Table 3.3.2: Acute toxicity end-points for *Duddingtonia flagrans*

Toxicity	Species	<i>Duddingtonia flagrans</i>	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	>5000 (1.9 x 10 ⁷ spores/kg bw)	Nil
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rat	>5000 (1.7 x 10 ⁵ spores/kg bw)	Nil
Acute inhalational toxicity ⁵¹	Rat	2.0 x 10 ⁵ cfu/kg bw	Nil
Skin irritation	Rabbit	Not irritant	Nil
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation	Not tested	Not tested	N/A

Acute toxicity

No deaths, treatment related clinical signs or abnormal histopathological findings were observed. The acute oral LD₅₀ for *D. flagrans* chlamydospores (strain IAH 1297) was greater than 5000 mg/kg bw (1.9 x 10⁷ spores/kg bw). Based on the data, *D. flagrans* has low acute toxicity. *D. flagrans* (strain IAH 1297) has very low toxicity in conventional acute toxicity tests. The organism will not be associated with animal produce and none of its metabolites exceed the Threshold of Toxicological Concern. Consequently the establishment of an Acceptable Daily Intake (ADI), or of an Acute Reference Dose (ARfD), is not required.

D. flagrans has not yet been approved for use in food producing animals internationally.

The proposed products are estimated to be of low toxicity as demonstrated by acute oral, dermal and intratracheal administration of various quantities of chlamydospores and the low toxicity of the excipient constituents.

Repeat-dose toxicity

No short-term studies of toxicity were submitted. However, the applicant made reference to three target animal safety studies performed with cattle, horses and sheep.

Cattle

D. flagrans spores (strain IAH 1297) when fed as a supplement to cattle at a minimum of 3.75 x 10⁵/kg bw/d caused no deaths, treatment related clinical signs or abnormal bodyweight

⁵¹ Single instillation of 58 mg spores/kg bw (2.0 x 10⁵ *D. flagrans* chlamydospores/kg bw in rats, no clinical signs apart from large doses causing physical blockage of airways, no signs of infectivity.

gain/loss over a 56 day period. No adverse biochemical or haematological signs were observed during the study.

Sheep

D. flagrans spores (strain IAH 1297) when fed as a supplement to sheep at a minimum of 1.5×10^5 /kg bw/d caused no deaths, treatment related clinical signs or abnormal bodyweight gain/loss over a 43 day period. No adverse biochemical or haematological signs were observed during the study.

Horses

D. flagrans spores (strain IAH 1297) when fed as a supplement to horses at a minimum of 3×10^5 /kg bw/d caused no deaths, treatment related clinical signs or abnormal bodyweight gain/loss over a 56 day period. No adverse biochemical or haematological signs were observed during the study.

Skin irritation

The proposed product (containing approximately 1.7×10^4 chlamydospores of *D. flagrans* (strain IAH 1297)) when applied to rabbit skin resulted in no clinical signs of systemic toxicity. No local dermal signs of irritation were observed in the treated animals up to 72 hours after patch removal. *D. flagrans* is not a skin irritant.

Eye irritation

The effects of the proposed product (containing approximately 1×10^3 chlamydospores of *D. flagrans* (strain IAH 1297)) were judged to be irritating, but not sufficient to classify them as severe to isolated chicken eyes. The irritating nature of the test item in the study is likely attributable to its particulate nature. They are estimated to be slight eye irritants.

Genotoxicity

No *in vitro* or *in vivo* studies were submitted. Further, there are no publicly available studies with other *D. flagrans* strains or their secondary metabolites. However, the Applicant provided *in silico* Quantitative structure–activity relationship (QSAR) modelling that predicts that flagranone A, the major secondary metabolite of *D. flagrans* (strain IAH 1297), is not genotoxic.

Carcinogenicity

No studies were submitted. Further, there are no publicly available studies with other *D. flagrans* strains or their secondary metabolites.

As *D. flagrans* is a ubiquitous non-pathogenic/non-infectious fungi that does not produce toxins or antimicrobials at a level that are a concern to human health, longer term studies of toxicity and carcinogenicity are not required and have not been provided.

Reproduction and developmental toxicity

No studies were submitted. Further, there are no publicly available studies with other *D. flagrans* strains or their secondary metabolites.

As *D. flagrans* is a ubiquitous non-infectious fungi that does not produce toxins or antimicrobials at a level that are a concern to human health, reproductive and developmental studies are not required and have not been provided.

Other studies

In silico QSAR modelling for the secondary metabolite flagranone A using Derek Nexus and Leadscope software was submitted. Flagranone A is not likely to be genotoxic, toxic to reproduction, or carcinogenic. Flagranone A is predicted not to exceed the TTC for a non-genotoxic substance.

Public exposure

Both the proposed products are planned for use with food animals (cattle, sheep and goats). Feeding animals *D. flagrans* through the use either proposed products will expose animal to large levels of the fungus. Most fungal components will undergo normal digestive processes with the chlamydospores passing through the animals largely intact. The major secondary metabolite of *D. flagrans* (strain IAH 1297), flagranone A, is unstable and is unlikely to survive digestion. As such, the likelihood that components of *D. flagrans* (strain IAH 1297) and flagranone A will accumulate in the tissues of treated animals is negligible. Therefore, public exposure to *D. flagrans* (strain IAH 1297), and its major secondary metabolite flagranone A, through consumption of treated animal products (e.g. meat and milk) is highly unlikely.

Exposure of the public (other than owners of horses) to the products as a result of use will be limited. Some public may visit farms and other areas where animals are kept but they are unlikely to be involved in feeding or handling feed containers. Therefore, public exposure is expected to be highly unlikely.

Pre-meeting submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that a new Appendix B entry for *Duddingtonia flagrans* strain IAH 1297 be created as follows:

Appendix B – New Entry

DUDDINGTONIA FLAGRANS, STRAIN IAH 1297

Reason for Entry – a, low toxicity

Area of Use – 2.7, anthelmintic

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- *Duddingtonia flagrans* strain IAH 1297 has a low risk to human health and safety. However, it is a slight eye irritant.
- A toxicological profile is only available for this specific strain. Any further applications of other strains should be considered independently.
- There is a slight risk of adverse outcomes from accidental exposure to *Duddingtonia flagrans*. However, there is no data available on children. The risk is expected to be low and appropriate packaging and labelling will minimise this risk.
- *Duddingtonia flagrans* strain IAH 1297 is proposed to be used for the prevention and treatment of nematode infestations in grazing animals. It is intended to be used as a feed supplement in animals in a farm environment.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS advice
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Appendix B entry for *Duddingtonia flagrans* strain IAH 1297. The proposed Schedule entry is as follows:

Appendix B – New Entry

DUDDINGTONIA FLAGRANS, STRAIN IAH 1297

Reason for Entry – a, low toxicity

Area of Use – 2.7, anthelmintic

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are:

- *Duddingtonia flagrans* strain IAH 1297 has a low risk to human health and safety. However, it is a slight eye irritant.
- A toxicological profile is only available for this specific strain. Any further applications of other strains should be considered independently.
- There is a slight risk of adverse outcomes from accidental exposure to *Duddingtonia flagrans*. However, there is no data available on children. The risk is expected to be low and appropriate packaging and labelling will minimise this risk.
- *Duddingtonia flagrans* strain IAH 1297 is proposed to be used for the prevention and treatment of nematode infestations in grazing animals. It is intended to be used as a feed supplement in animals in a farm environment.

3.4. Lambda-cyhalothrin

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the existing entry for lambda-cyhalothrin in Schedule 6 of the Poisons Standard to include a subclause for emulsifiable granule formulations containing 25 per cent or less lambda-cyhalothrin.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 6 – Amend Entry

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or
- b) in other preparations containing 1.6 per cent or less of lambda-cyhalothrin; or
- c) in emulsifiable granule formulations containing 25 per cent or less lambda-cyhalothrin

except when included in Schedule 5.

The applicant's reasons for the request are:

- Lambda-cyhalothrin is present in a number of registered agricultural products and its toxicity profile has been well established. It is a synthetic pyrethroid insecticide which contains only two (*1R cis Z-S* and *1S cis Z-R*) of cyhalothrin's four possible stereoisomers. Lambda-cyhalothrin insecticidal activity is believed to be through interference with sodium channels in the nervous system of insects, leading to paralysis and, eventually, death;
- The formulated proposed product is considered to have moderate oral, low dermal and low inhalation toxicity. The product was shown to cause slight skin irritancy and moderate eye irritancy in rabbits. The studies regarding skin sensitisation were inconclusive. However, considering that lambda-cyhalothrin has previously been shown to have a positive response for sensitisation, the product will be considered to be a skin sensitiser; and
- Based on the product acute toxicity, and providing that adequate warnings and safety directions recommended in the present report are displayed on the product label, the product formulation containing lambda-cyhalothrin meets the Scheduling Policy Framework (2015) criteria for scheduling it to Schedule 6 of the Poisons Standard.

Current scheduling status and relevant scheduling history

Lambda-cyhalothrin is currently listed in Schedules 7, 6 and 5 as follows:

Schedule 7

LAMBDA-CYHALOTHRIN **except** when included in Schedule 5 or 6.

Schedule 6

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or
- b) in other preparations containing 1.6 per cent or less of lambda-cyhalothrin

except when included in Schedule 5.

Schedule 5

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 1 per cent or less of lambda-cyhalothrin; or
- b) in aqueous preparations containing 2.5 per cent or less of microencapsulated lambda-cyhalothrin.

In November 1987, the Drugs and Poisons Schedule Committee (DPSC) decided to include first aid and safety directions for lambda-cyhalothrin.

In August 1990, the DPSC decided to include preparations containing 1% or less of lambda-cyhalothrin in Schedule 6 and all other preparations containing lambda-cyhalothrin in Schedule 7, based on the toxicity profile of lambda-cyhalothrin.

In November 1991, the DPSC decided to include aqueous preparations containing 1% or less of lambda-cyhalothrin in Schedule 5. The reason for this decision was that the water-based product containing 1% or less of lambda-cyhalothrin would be used by pest control operators therefore registration mechanism would be applicable.

In November 1994, the NDPSC considered toxicological data on microencapsulated suspensions containing 2.5% or less of lambda-cyhalothrin and decided to include them in Schedule 5.

In August 1999, the NDPSC decided to include microencapsulated preparations containing 25% or less of lambda-cyhalothrin in Schedule 6.

In August 2014, the ACCS decided to increase the allowed concentration in Schedule 6 from 1.5 to 1.6 per cent to ensure that the product formulation, when expressed in grams per 100 millilitre (as per Part I of the Poisons Standard), is covered by the amended entry.

Australian regulatory information

Lambda-cyhalothrin is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#), and is not an excipient or active in any products on the ARTG.

There are no adverse reports relating to lambda-cyhalothrin in the APVMA's [Adverse Experience Reporting Program annual reports](#) from 1995-2013.

Lambda-cyhalothrin was included in a residue-related [review of sheep ectoparasiticides](#) by the APVMA. However, as products containing this active were discontinued during the course of the review, no outcomes could be applied to products.

International regulations

USA

Lambda-cyhalothrin was registered with the EPA in 1989 and is registered as a biochemical/conventional chemical. It is a restricted use, broad spectrum insecticide used to control most major aphid, caterpillar and beetle pests on a wide variety of crops and for public health pests such as mosquitoes and cockroaches in non-agricultural settings.⁵²

Canada

Lambda-cyhalothrin is a registered pesticide with Health Canada.

UK

Lambda-cyhalothrin was first approved for use in the UK in 1988 (Advisory Committee on Pesticides, 1988).

EU

Lambda-cyhalothrin is currently a registered product with the European Chemicals Agency.

New Zealand

Lambda-cyhalothrin is currently a registered product.

⁵² [Lambda-Cyhalothrin and Gamma-Cyhalothrin Summary Document Registration Review: Initial Docket, December 2010, US EPA](#)

Substance summary

Lambda-cyhalothrin is a synthetic pyrethroid insecticide which contains only two (1*R cis Z*-S and 1*S cis Z*-R) of cyhalothrin's four possible stereoisomers. Lambda-cyhalothrin insecticidal activity is believed to be through interference with sodium channels in the nervous system of insects, leading to paralysis and, eventually, death.

Table 3.4.1: Chemical information for Lambda-cyhalothrin

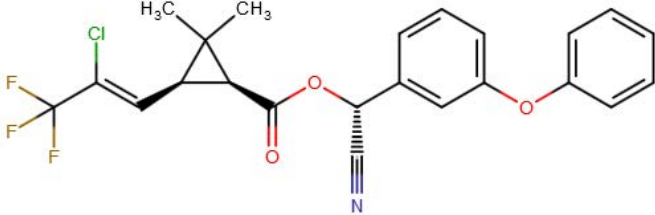
Property	Lambda-cyhalothrin
Chemical structure	
Molecular formula	C ₂₃ H ₁₉ ClF ₃ NO ₃
Molecular weight	449.9 g/mol
CAS name	(<i>R</i>)-cyano(3-phenoxyphenyl)methyl (1 <i>S</i> ,3 <i>S</i>)-rel-3-[(1 <i>Z</i>)-2-chloro-3,3,3-trifluoro-1-propen-1-yl]-2,2-dimethylcyclopropanecarboxylate
CAS number	91465-08-06
IUPAC and/or common and/or other names	3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyano(3-phenoxyphenyl)methyl cyclopropanecarboxylate (IUPAC); Cyhalothrine (other).

Table 3.4.2: Acute toxicity end-points for Lambda-cyhalothrin

Toxicity	Species	Lambda-cyhalothrin	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	310	Schedule 6
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rat	> 5000	Nil
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rat	2840	Schedule 6
Skin irritation	Rabbit	Moderate irritant	Schedule 5
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation	Guinea pig	Sensitiser	Schedule 5

Acute toxicity

The applicant provided acute toxicity studies with the formulated product in rats. Based on the APVMA's assessment of these studies, the product is considered to have moderate oral ($LD_{50} = 310 \text{ mg/kg bw}$), low dermal ($LD_{50} > 5000 \text{ mg/kg bw}$) and low inhalation toxicity ($LC_{50} 4 \text{ h} > 2840 \text{ mg/m}^3$).

Repeat-dose toxicity

In a 90-day feeding study in rats given cyhalothrin, the NOAEL was 50 ppm, equal to 2.6 mg/kg bw per day, on the basis of reduced body-weight gain and food consumption. In a 90-day feeding study in rats given lambda-cyhalothrin, the NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw per day, on the basis of reduced body-weight gain and food consumption. In a 26-week study in dogs fed capsules containing cyhalothrin and a 1-year study in dogs fed capsules containing lambda-cyhalothrin, increased incidences of liquid faeces was observed, with an overall NOAEL of 0.1 mg/kg bw per day. The increased incidences of liquid faeces were observed from the first week of treatment. Other pyrethroids produce this effect, which may be the consequence of the local gastrointestinal equivalent of paraesthesia in the skin. In the two studies in dogs, signs of systemic neurotoxicity (ataxia, tremors, and occasionally convulsions) were observed, with an overall NOAEL of 0.5 mg/kg bw per day. Signs of systemic neurotoxicity were observed from the first week and generally occurred within a few hours after treatment.

Skin irritation

There were no mortalities or clinical signs of systemic toxicity. All treated sites exhibited well-defined erythema and very slight oedema 24 h after removing the dressings, and desquamation between Day 7 and Day 10. All treated sites were free of dermal lesions on Day 10. Lambda-cyhalothrin is considered a slight skin irritant.

Eye irritation

There were no mortalities or clinical signs of systemic toxicity. All treated eyes exhibited corneal opacity, iritis, and conjunctivitis following instillation of the test item. All treated eyes were free of ocular irritation by Day 10. Lambda-cyhalothrin is considered a moderate eye irritant.

Sensitization

The studies regarding skin sensitisation were inconclusive. However, considering that lambda-cyhalothrin has previously been shown to have a positive response for sensitisation, lambda-cyhalothrin is considered a skin sensitizer.

Genotoxicity

Lambda-cyhalothrin was tested for genotoxicity in an adequate range of assays, both *in vitro* and *in vivo*. No evidence for genotoxicity was observed in any test.

Carcinogenicity

Lambda-cyhalothrin is not carcinogenic in rodents. In view of the lack of genotoxicity of lambda-cyhalothrin and the absence of carcinogenicity shown by cyhalothrin in mice and rats, the JMPR (2007) concluded that lambda-cyhalothrin is unlikely to pose a carcinogenic risk to humans.

Reproduction and developmental toxicity

In a multigenerational dietary study with cyhalothrin in rats, the NOAEL for parental toxicity was 30 ppm, equivalent to 2.0 mg/kg bw per day, on the basis of a reduction in body-weight gain. The NOAEL for offspring toxicity was 30 ppm, equivalent to 2 mg/kg bw per day, on the basis of reduced body-weight gain during lactation. The NOAEL for reproductive toxicity was 100 ppm, equivalent to 6.7 mg/kg bw per day, i.e., the highest dose tested.

The effect of oral exposure to cyhalothrin on prenatal development was investigated in rats and rabbits. In a study of developmental toxicity in rats treated by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of a reduction in body weight and loss of limb coordination. The NOAEL for foetal toxicity was 15 mg/kg bw per day, i.e., the highest dose tested.

In a study of developmental toxicity in rabbits treated by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reduced body-weight gain and food.

Neurotoxicity

In a study of acute neurotoxicity in rats given lambda-cyhalothrin by gavage, the NOAEL was 2.5 mg/kg bw per day on the basis of signs of neurotoxicity (increased breathing rate, urinary incontinence, salivation, reduced response to sound).

There were no signs of maternal or offspring toxicity observed in the developmental neurotoxicity study for lambda-cyhalothrin.

Observation in humans

In case reports in humans, no systemic effects were reported. In most cases exposure was by the dermal and inhalation routes. Predominant signs were skin paraesthesia, numbness, irritation of the skin, red eyes, coughing and sneezing.

Public exposure

The product use patterns, application methods and use rates are the same as the registered reference product which contains 250 g/L lambda-cyhalothrin in an emulsifiable concentrate microencapsulated formulation. Therefore, similar exposure is expected using either the proposed product, or the reference, provided that the same safety directions are applied while mixing/loading and using both products, which includes wearing the same PPE when opening the container and preparing spray and using the prepared spray. Therefore, new exposure estimates are not required. Post-application exposure is considered similar with the proposed product and with the reference product, provided that the same re-entry statements are displayed on both products' labels. Therefore, new post-application exposure estimates are not required.

Pre-meeting submissions

One (1) public submission was received that supported the proposal on the basis of the acute oral toxicity of lambda-cyhalothrin.

The public submission will be made available on the [TGA website](#).

Summary of ACCS advice to the delegate

The committee recommended that the Schedule 6 listing for lambda-cyhalothrin be amended as follows:

Schedule 6 – Amend Entry

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or
- b) in emulsifiable granule formulations containing 25 per cent or less lambda-cyhalothrin; or**
- c) in other preparations containing 1.6 per cent or less of lambda-cyhalothrin

except when included in Schedule 5.

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

The reasons for the advice were:

- Lambda-cyhalothrin is already used in Australia in aqueous preparations in a microencapsulated form. The product formulation change to emulsifiable granule is not expected to greatly increase the current use of lambda-cyhalothrin.
- Use of emulsifiable granules containing 25% or less of lambda-cyhalothrin, in addition to the aqueous products containing microencapsulated lambda-cyhalothrin, is expected to be mainly commercial, resulting in an increased choice of agricultural insecticides available for end users.
- There were no reported cases of adverse events involving lambda-cyhalothrin between 1995 and 2013, which suggests a low risk with the existing controls in place.
- Lambda-cyhalothrin has moderate acute oral toxicity, is a slight skin irritant, is a skin sensitiser and a moderate eye irritant. It meets the Schedule 6 criteria. There is no evidence to suggest the emulsifiable formulation has increased toxicity to the end-user.
- Lambda-cyhalothrin would be managed by APVMA registration processes and is expected to be in line with aqueous products containing microencapsulated lambda-cyhalothrin.
- The potential for abuse of lambda-cyhalothrin is low to none.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 6 listing for lambda-cyhalothrin to include emulsifiable granule formulations containing 25 per cent or less of lambda-cyhalothrin. The proposed Schedule entry is as follows:

Schedule 6 – Amend Entry

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or
- b) in emulsifiable granule formulations containing 25 per cent or less lambda-cyhalothrin; or
- c) in other preparations containing 1.6 per cent or less of lambda-cyhalothrin

except when included in Schedule 5.

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

The reasons for the interim decision are:

- Lambda-cyhalothrin is already used in Australia in aqueous preparations in a microencapsulated form. The product formulation change to emulsifiable granule is not expected to greatly increase the current use of lambda-cyhalothrin.
- Use of emulsifiable granules containing 25% or less of lambda-cyhalothrin, in addition to the aqueous products containing microencapsulated lambda-cyhalothrin, is expected to be mainly commercial, resulting in an increased choice of agricultural insecticides available for end users.
- There were no reported cases of adverse events involving lambda-cyhalothrin between 1995 and 2013, which suggests a low risk with the existing controls in place.
- Lambda-cyhalothrin has moderate acute oral toxicity, is a slight skin irritant, is a skin sensitiser and a moderate eye irritant. It meets the Schedule 6 criteria. There is no evidence to suggest the emulsifiable formulation has increased toxicity to the end-user.
- Lambda-cyhalothrin would be managed by APVMA registration processes and is expected to be in line with aqueous products containing microencapsulated lambda-cyhalothrin.
- The potential for abuse of lambda-cyhalothrin is low to none.

3.5. *Bacillus amyloliquefaciens*

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a new entry for *Bacillus amyloliquefaciens* (*B. amyloliquefaciens*) in Schedule 5 of the Poisons Standard, with no exemption cut-off.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 5 – New Entry

BACILLUS AMYLOLIQUEFACIENS.

The applicant's reasons for the request are:

- *B. amyloliquefaciens* is a ubiquitous bacterium found in water, soil, air, decomposing plant material, on fresh produce and is widely used for the production of enzymes and specialty chemicals. *B. amyloliquefaciens* is described as being antagonistic towards fungal plant pathogens via nutrient competition, site exclusion and colonisation.
- Based on the observed moderate eye irritation in rabbits, *B. amyloliquefaciens* strain QST 713 meets the Scheduling Policy Framework (2015) criteria for scheduling it to Schedule 5 of the Poisons Standard with no cut-off or exemptions.
- The acute inhalation toxicity $LC_{50} = 2150 \text{ mg/m}^3 \text{ 4 h}$ achieved for the formulated product was below the cut-off of $3000 \text{ mg/m}^3 \text{ 4 h}$. However, no mortalities were observed at the achieved aerosol exposure and at necropsy, 2/10 rats had discoloured lungs and 8/10 rats were normal. Therefore,

while the cut-off exposure of $\geq 3000 \text{ mg/m}^3$ 4 h was not achieved, the absence of mortalities and adverse clinical and macroscopic signs of toxicity at $2150 \text{ mg/m}^3/4 \text{ h}$ suggest that this criterion was likely to have been achieved if the test was performed on the active constituent at 3000 mg/m^3 4 h.

- The formulated product was found to be positive for skin sensitisation and classified as 'May cause skin sensitisation by contact.' Therefore, in the absence of a study performed on the pure microbial preparation, it was also considered to be a skin sensitiser. The extent of skin sensitisation reported was considered to approximate the descriptor of 'slight' where scores were between 'no visible change' and 'discrete or patchy erythema.'
- The potential for respiratory sensitisation has not been specifically tested. In a 4-week inhalation toxicity study, there was no clear evidence of irreversible systemic toxicity. In the statements from the applicant regarding worker exposure at two production plants, there was no indication of an increased incidence of respiratory illnesses/sensitisation reactions as a result of long-term exposure. However, limited mutagenicity, reproductive toxicity and developmental toxicity studies performed using subtilin and/or surfactin C, the major endogenous protein metabolites produced by *B. amyloliquefaciens* did not indicate any toxicity findings of concern.
- Repeat dose toxicity, carcinogenicity, genotoxicity, reproductive toxicity, developmental toxicity and neurotoxicity studies were not performed as it was a microbial preparation.

Current scheduling status and relevant scheduling history

B. amyloliquefaciens is not currently scheduled and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Australian regulatory information

B. amyloliquefaciens is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#), and is not an excipient or active in any products on the ARTG.

International regulations

USA

The US EPA: *B. amyloliquefaciens* MBI 600 (antecedent *Bacillus subtilis* MBI 600) was registered in 1998; *B. amyloliquefaciens* strain D747 was registered in 2011; and *B. amyloliquefaciens* strain PTA-4838 was registered in 2017.

UK

B. amyloliquefaciens was approved in 2016 as a pesticide.

EU

B. amyloliquefaciens is currently in the pre-registration process.

Substance summary

B. amyloliquefaciens is a ubiquitous bacterium found in water, soil, air, decomposing plant material, on fresh produce and is widely used for the production of enzymes and specialty chemicals.

Table 3.5.1: Acute toxicity end-points for *Bacillus amyloliquefaciens* strain QST 713

Toxicity	Species	<i>Bacillus amyloliquefaciens</i>	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (cfu/rat)	Rat	$>1.13 \times 10^8$	Nil

Toxicity	Species	<i>Bacillus amyloliquefaciens</i>	SPF (2015) Classification
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rat	>2000	Schedule 5
Acute inhalational toxicity LC ₅₀ (cfu/rat)	Rat	>1.2 x 10 ⁸	Nil
Skin irritation	Rabbit	Not irritant	Nil
Eye irritation	Rabbit	Moderate	Schedule 5
Skin sensitisation	Not tested	Not tested	N/A

Acute toxicity

The acute toxicity of *B. amyloliquefaciens* QST 713 was low by oral, dermal and intra-tracheal administration (LD₅₀ >1.13 x 10⁸ cfu/rat, >2000 mg/kg bw and >1.2 x 10⁸ cfu/rat respectively). *B. amyloliquefaciens*, QST 713 was a slight eye irritant but not a skin irritant. A skin sensitisation study was not performed on the microbial preparation.

Acute microbial pesticide evaluation also included an acute intravenous toxicity study for infectivity where the intravenous LD₅₀ was >9.4 x 10⁶ cfu/rat, demonstrating low systemic infectivity/pathogenicity potential (in rodents). No treatment-related mortalities occurred in any of the acute toxicity studies.

Skin irritation

There was no evidence of moderate or severe skin irritation caused by the test substance as assessed by the described methodology. Following the 4 h topical treatment period, very slight erythema was observed in 4/6 rabbits at 30-60 min, and 3/6 rabbits at 24 h after removal of the semi-occlusive dressing.

The test substance is considered a non-skin irritant due to the absence of irritation at 72 h.

While the study was not considered to be equivalent to a test guideline compliant study and sufficient to support formal classification of skin irritancy potential, the APVMA considers that the test substance would be unlikely to be a skin irritant.

Eye irritation

There was no evidence of persistent moderate or severe eye irritation caused by the test substance.

Following treatment, conjunctival redness grade 2 was present in 6/6 rabbits at 1 h and 1/6 rabbits at 24 h post dosing and persisted as grade 1 in 3/6 rabbits at 72 h. Conjunctival chemosis occurred 6/6 rabbits ranging from grade 1 to grade 3 at 1 h, and decreased to grade 1 in 1/6 rabbits at 24 h.

The test substance is considered to be a slight eye irritant due to the presence of slight irritation without corneal opacity.

While the study was not considered to be equivalent to a test guideline compliant study, the APVMA considers that the test substance would be likely to be a slight eye irritant.

Repeat-dose toxicity

Repeat dose toxicity studies were not conducted based on the absence of findings in the acute toxicology and infectivity/pathogenicity studies. This is reasonable and appropriate for a non-pathogenic biological active ingredient of this type. A 4-week inhalation study was performed in rats in which no toxicologically significant adverse effects were observed at the single dose level tested.

Supportive evidence for minimal short-term toxicity was provided by a 28-day oral toxicity of surfactin C rats (Hwang *et al.*, 2009). No clinical signs of toxicity, alterations in body weight, body weight gain and food consumption, alterations on the haematological parameters, differences in organ weights or histopathological findings were noted at 500 mg/kg bw/d. Decreased bodyweight, increased alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase, increased liver weights and hydrophic necrosis of hepatocytes were observed at higher doses.

Genotoxicity

No evidence of genotoxicity has been shown to be produced by *B. amyloliquefaciens*.

Carcinogenicity

No information was provided.

Reproduction and developmental toxicity

No evidence of reproduction or developmental toxicity has been shown to be produced by *B. amyloliquefaciens*.

Clinical observations

EFSA conducted a review update of the safety concerns for the Qualified Presumption of Safety (QPS) status of biological agents that are added intentionally to food and animal feeds including *Bacillus* species (EFSA, 2013). The observations reported and summarised in the QPS document were considered clinically relevant to the current assessment and addressed reports of claims where *B. amyloliquefaciens* was a causative agent in clinical cases. The relevant QPS review text is presented below (with minor edits). Collectively, there was no substantive new evidence that confirmed that *B. amyloliquefaciens* was the causative agent in the clinical reports and also confirmed the existing EFSA position of non-toxicogenic/non-pathogenic potential of *B. amyloliquefaciens* towards humans.

In total, 230 articles found by relevant search terms were screened. A bacteraemia related to a pacemaker wire infection was caused by *B. licheniformis* (Idelevich *et al.*, 2012). *B. amyloliquefaciens* and *B. licheniformis* were identified as the cause of a bacteraemia in a patient with an oesophageal perforation (La Jeon *et al.*, 2012). Kim *et al.*, (2012) reported a case of bacteraemia caused by *B. licheniformis* following vertebrotherapy in a patient with lung cancer. Safety concerns for food producing animals were also considered in the search because 'the body of knowledge about the organisms for which QPS is sought must be sufficient to provide adequate assurance that any potential to produce adverse effects in humans, livestock or the wider environment is understood and predictable' (EFSA, 2007). A *Bacillus* sp. was isolated from abscesses in several sheep and goats, but authors could not identify the isolates to the species level by phenotypic tests and sequence of 16s rRNA gene (Mariappan *et al.*, 2012). Gangrenous mastitis in several goats was caused by *Bacillus* spp., one of the isolates was identified *B. cereus*, but other isolates were not identified at the species level (Mavangira *et al.*, 2013). *B. amyloliquefaciens* was isolated, together with *staphylococcus*, from milk of goats with subclinical mastitis (Razi *et al.*, 2012), but without evidence that *B. amyloliquefaciens* was the cause of the mastitis.

These infections in humans were linked to specific predisposing factors and did not suggest a risk for the consumer *via* exposure through the food and feed chain. The abscesses reported in sheep were not sufficiently characterised to determine whether *Bacillus* species from the QPS list were involved. In respect to the report of mastitis in goats, the co-isolation of *S. aureus*, a well-known agent of mastitis, raised doubt regarding the role of *B. amyloliquefaciens* in the infection.

Public exposure

A review article on foodborne illness(es) caused by *Bacillus* species, including some QPS *Bacillus* species was published in 2012 (Logan, 2012). The outcomes of the review were in line with the previous QPS assessment (EFSA, 2008) concerning the rare implication of QPS *Bacillus* species in foodborne illnesses, and the likely implication of peptidolipids with toxic activities produced by the responsible strains. Two articles described some biological activities of peptidolipids with biosurfactants produced by *B. amyloliquefaciens*. A biosurfactant produced by a strain of *B. amyloliquefaciens* caused epithelium cell vacuolisation and microvilli damage in the mid-gut of an insect larvae (LC₅₀ approx. 200 ng/mg according to Ghribi *et al.*, 2012) and a *B. amyloliquefaciens* strain isolated from a Korean fermented soybean paste produced up to 48 mg surfactin per kg in the fermented food, and the surfactin inhibited growth of human breast cancer cells (IC₅₀ 10 µg/mL, Lee *et al.*, 2012).

The applicant identified a range of clinically relevant publications in which *B. amyloliquefaciens* was associated with a range of disease manifestations (Ochoa, 2015, Aoki *et al.*, 2015; Baur & Bakehe, 2014; Hong *et al.*, 2008; Inomata *et al.*, 2007; Long *et al.*, 2014; Pavic *et al.*, 2005; Stickel *et al.*, 2008). Collectively, these publications identified *B. amyloliquefaciens* as being present along with other possible co-causative agents. The case subjects (human and domestic/farm animals) often had pre-existing conditions or a reasonable likelihood of compromised immune system function. *B. amyloliquefaciens*, QST 713 was not identified as being associated with a clinical condition in the citations and no citation suggested an association between *B. amyloliquefaciens* with genotoxic, carcinogenic or reproductive toxicity potential. Broadly, the citations were consistent with the EFSA QPS review summary discussed above.

Several citations have investigated allergenic or hypersensitivity reactions in individuals who have been repeatedly exposed *B. amyloliquefaciens* and such responses have been attributed to exposure to the extracellular enzyme subtilisin (EPA 1997) and may be consistent with the slight skin sensitisation response observed for the formulated product. However, the applicant provided statements for the absence of an increased incidence in allergy/respiratory related concerns in *B. amyloliquefaciens* QST 713 manufacturing facilities (Miille, 2015; Navarro, 2015). In addition, ELISA testing of the QST 713 strain for subtilisin was reported to be negative (Manker, 2002, Chemistry and Manufacturing submission, APVMA data No. 116454) indicating that the sensitisation response in animals is towards another formulation component.

Antibiotic susceptibility testing against common human antibiotics provided supportive evidence for the absence of resistance genes in *B. amyloliquefaciens* QST 713 with the exception of bacitracin (Lehman, 2001, 2002).

Pre-meeting submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that a new Appendix B entry for *Bacillus amyloliquefaciens* strain QST 713 be created as follows:

Appendix B – New Entry

BACILLUS AMYLOLIQUEFACIENS STRAIN QST 713.

Reason for Entry – a, low toxicity

Area of Use – 1.3, fungicide

The committee recommended that a cross-reference in the Index for *Bacillus subtilis* QST 713 be created as follows:

Index – New Entry

BACILLUS AMYLOLIQUEFACIENS STRAIN QST 713
cross reference: BACILLUS SUBTILIS STRAIN QST 713

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; and (c) the toxicity of a substance.

The reasons for the advice were:

- The risks posed by *Bacillus amyloliquefaciens* strain QST 713 are very low. There may be a small risk to groups susceptible to infection.
- There are a range of benefits for preventing fungal disease in certain food crops.
- *Bacillus amyloliquefaciens* is a naturally occurring microorganism with very low infectivity, low pathogenicity and a low risk of causing skin irritancy. The risk is mitigated by personal protective equipment worn on mixing/loading and application in accord with APVMA labels.
- Worker data shows that *Bacillus amyloliquefaciens* strain QST 713 is unlikely to be a respiratory sensitiser.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS advice
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Appendix B entry for *Bacillus amyloliquefaciens* QST 713, with an index cross reference for *Bacillus subtilis* Strain QST 713. The proposed Schedule entry is as follows:

Appendix B – New Entry

BACILLUS AMYLOLIQUEFACIENS STRAIN QST 713.

Reason for Entry – a, low toxicity

Area of Use – 1.3, fungicide

Index – New Entry

BACILLUS AMYLOLIQUEFACIENS STRAIN QST 713
cross reference: BACILLUS SUBTILIS STRAIN QST 713

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are:

- The risks posed by *Bacillus amyloliquefaciens* strain QST 713 are very low. There may be a small risk to groups susceptible to infection.
- There are a range of benefits for preventing fungal disease in certain food crops.
- *Bacillus amyloliquefaciens* is a naturally occurring microorganism with very low infectivity, low pathogenicity and a low risk of causing skin irritancy. The risk is mitigated by personal protective equipment worn on mixing/loading and application in accord with APVMA labels.
- Worker data shows that *Bacillus amyloliquefaciens* strain QST 713 is unlikely to be a respiratory sensitiser.

3.6. Butyl benzyl phthalate

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new entry for butyl benzyl phthalate (BBP) in Schedule 10 of the Poisons Standard for cosmetic use, with no exemption cut-off.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 10 – New Entry

BUTYL BENZYL PHTHALATE for cosmetic use.

The applicant's reasons for the request are:

- BBP is classified as reproductive and developmental toxicant in accordance with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).
- Toxic effects related to repeated exposure to BBP include systemic toxicity (increased liver and/or kidney weight), fertility (mediated by testicular toxicity) and developmental toxicity (antiandrogenic effects, reduced birth weight, embryoletality and teratogenicity). BBP is considered to have a toxicity profile equivalent to dibutyl phthalate (DBP) – a phthalate of similar molecular weight and sharing one monoester metabolite, monobutyl phthalate. Reproductive toxicity induced by BBP might have serious long-term effects on the development and reproduction of future generations if the exposure occurs within a critical window of human development.
- The available data indicates that BBP, along with DBP and diethylhexyl phthalate (DEHP), are antiandrogens with a mode of action that involves alterations of steroidogenesis and gene expression critical for the male reproductive development. Although there are uncertainties regarding the exact mechanism by which BBP affects fertility, foetal hormonal levels, and growth and development in rodents, this is considered a plausible mode of action for phthalates that is relevant to humans if the exposure to antiandrogenic phthalates, including BBP, is high and within a critical window of human development.
- While there is no current indication of BBP being used in cosmetics in Australia, BBP may be considered as a possible substitute for other phthalates that are currently listed in Schedule 10 (e.g. DBP, DEHP), based on its properties, functions and uses. This may result in an increased exposure to BBP.
- As a result, imposing a similar regulatory measure on phthalates and classifying them as toxic to reproduction is warranted. This is due to the uncertainties of market availability, potential for substitution, the severe and irreversible (fertility-based and teratogenic) health effects and exposure levels in different population groups.

Current scheduling status and relevant scheduling history

Butyl benzyl phthalate is not currently scheduled and has not been previously considered for scheduling. Therefore a scheduling history is not available.

Related compounds dibutyl phthalate, diethylhexyl phthalate (considered in March 2011), diethylphthalate, diisobutyl phthalate, dimethylphthalate and di(methyloxyethyl) phthalate are listed in Schedule 10 of the Poisons Standard for cosmetic use or for use in leave-on skin products.

Australian regulatory information

No restrictions on the introduction (manufacture and/or import) or use of BBP were identified in Australia. BBP has the potential to be substituted for already regulated phthalates (e.g. DBP, DEHP). Given this, there is potential for widespread use of BBP in a variety of consumer products, including cosmetics.

BBP is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#), and is not an excipient or active in any products on the ARTG, although it does have the Australian Approved Name butyl benzyl phthalate.

There are no reports of adverse events related to BBP on the [Database of Adverse Events Notifications \(DAEN\)](#).

International regulations

EU

BBP is currently listed in the European Commission Cosmetic Ingredients and Substances (CosIng) Annex II (List of substances prohibited in cosmetic products) and Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [Annex XIV \(List of substances subject to authorisation\)](#).

Canada

BBP is controlled in Canada according to the Canada Consumer Products Safety Act: [Phthalates Regulations \(SOR/2016-188\)](#). These regulations restrict the usage of phthalates, including BBP, in soft vinyl children's toys and child care articles to not more than 1000 mg/kg of di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP) or benzyl butyl phthalate (BBP) when tested in accordance with a method that conforms to good laboratory practices.

USA

According to the electronic Code of Federal Regulations (e-CFR), [Title 16, Chapter II, Subchapter B, Part 1199 – Children's toys and child care articles: Phthalate-containing inaccessible component parts](#), the sale of any “children's toy or child care article” containing more than 0.1 percent of three specified phthalates (di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP)) are prohibited.

Substance summary

Table 3.6.1: Chemical information for butyl benzyl phthalate

Property	Butyl benzyl phthalate
Chemical structure	
Molecular formula	C ₁₉ H ₂₀ O ₄
Molecular weight	312.4 g/mol
CAS name	1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester
CAS number	85-68-7
IUPAC and/or common and/or other names	Butyl benzyl phthalate (INCI); Benzyl butyl benzene-1,2-dicarboxylate (IUPAC)

The following information was extracted from the PEC report for BBP and the [NICNAS Human Health Tier II Assessment for C4-6 side chain transitional phthalates](#), publicly available on the NICNAS website.

Table 3.6.2: Acute toxicity end-points for butyl benzyl phthalate

Toxicity	Species	Butyl benzyl phthalate	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	>2000 mg/kg bw	Schedule 5
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rat	>2000 mg/kg bw	Schedule 5
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	No data are available	No data are available	N/A
Skin irritation	Rabbit	Slight	Schedule 5
Eye irritation	Rabbit	Slight	Schedule 5
Skin sensitisation (GPMT)	Guinea pig	Negative	Nil

Acute toxicity

BBP has low acute oral and dermal toxicity in animals (LD₅₀ >2000 mg/kg bw).

Irritation

BBP may cause slight eye and skin irritation.

Sensitisation

BBP may be a slight skin sensitiser in humans.

Repeat-dose toxicity

BBP is not considered to cause severe systemic effects other than reproductive and developmental effects following repeated oral exposure. Limited data are available on repeated dermal and inhalational exposure.

Mutagenicity and genotoxicity

BBP was negative in *in vitro* and *in vivo* mutagenicity and genotoxicity tests.

Carcinogenicity

The International Agency for Research on Cancer (IARC, 1999) considered that on the weight of evidence the available data do not provide adequate evidence of carcinogenicity for BBP in humans.

Reproductive and developmental toxicity

In the PEC assessment for BBP (NICNAS, 2015) there is sufficient evidence in appropriate animal studies to conclude that BBP causes testicular toxicity and/or toxic effects to fertility. These effects are more prominent after perinatal exposure (i.e. F₁ generation). Testicular toxicity induced by BBP is manifested reproducibly as statistically significant reductions in testes weights, testicular and accessory sex organ atrophy, as well as dose-dependent decreases in spermatozoa concentrations. Although deleterious effects of BBP on the testes and/or fertility were sometimes observed at the higher or the same dose levels as other toxic effects, they are highly specific and not considered secondary consequences of systemic maternal toxicity.

There are also sufficient reports of BBP-induced developmental toxicity, including prenatal, neonatal and postnatal endpoints. They commonly included resorption, post-implantation loss or embryo-foetal death, foetal malformation, teratogenicity, decreased foetal weight and birth weight. For reproductive development, females seem less susceptible than males to the adverse effects of BBP. In males, there are reports of reduced foetal testosterone levels, altered neonatal anogenital distance and retained infant areolae and delayed puberty. Following puberty there were decreases in testosterone, impaired sexual differentiation, malformed reproductive organs (including hypospadias and cryptorchidism), and altered reproductive functions (including increased testicular pathology, sperm abnormality, and reduced fertility in F₁ generation).

These are clear results in appropriate animal studies. The effects have been observed in the absence of marked maternal toxicity (mainly reduced body weight gain accompanied by a decreased food consumption), or around the same dose levels as other toxic effects (mainly increased kidney and/or liver weight). The findings are not considered secondary non-specific consequences of the maternal toxic effects. On this basis, BBP is currently classified as a Reproductive Toxicant Category 1B with the hazard statements '*May damage the unborn child. Suspected of damaging fertility*'.

Observation in humans

The human data on the reproductive and developmental effects of BBP are limited. However, the available data indicate that BBP is considered to have a toxicity profile equivalent to DBP and DEHP with a mode of action that involves alterations of steroidogenesis and gene expression critical for the male reproductive development. Reproductive toxicity induced by BBP may have serious long-term

effects on the development and reproduction of future generations if the exposure occurs within a critical window of human development.

Public exposure

While there is no current indication of BBP use in cosmetics in Australia, BBP may be considered as a possible substitute for other phthalates that are currently listed in Schedule 10 (e.g. DBP, DEHP), based on its properties, functions and uses.

Pre-meeting submissions

Two (2) public submissions were received and both supported the proposal.

Main points in support:

- A Schedule 10 entry for cosmetic use is consistent with the EU Cosmetics Regulation for butyl benzyl phthalate and with other phthalates that are considered hazardous.
- There is no known use of butyl benzyl phthalate in cosmetics in Australia.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS advice to the delegate

The committee recommended that a new Schedule 10 entry for butyl benzyl phthalate be created as follows:

Schedule 10 – New Entry

BUTYL BENZYL PHTHALATE.

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- There is a potential for butyl benzyl phthalate to be used in cosmetic products. Currently, there is no evidence of butyl benzyl phthalate being used in cosmetics in Australia. However, the banning or strict limits of other similar phthalates increases the risk of substitution with butyl benzyl phthalate. Applying similar scheduling controls on butyl benzyl phthalate can manage this risk.
- Risk of reproductive and developmental toxicity makes butyl benzyl phthalate unsuitable for use in cosmetics.
- Inclusion of butyl benzyl phthalate in Schedule 10 for use in cosmetics provides consistency with the EU cosmetic regulations.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989

- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 10 entry for butyl benzyl phthalate. The proposed Schedule entry is as follows:

Schedule 10 – New Entry

BUTYL BENZYL PHTHALATE.

The proposed implementation date is **1 February 2018**. This is the earliest possible implementation date and no known products in Australia will be affected.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are:

- There is a potential for butyl benzyl phthalate to be used in cosmetic products. Currently, there is no evidence of butyl benzyl phthalate being used in cosmetics in Australia. However, the banning or strict limits of other similar phthalates increases the risk of substitution with butyl benzyl phthalate. Applying similar scheduling controls on butyl benzyl phthalate can manage this risk.
- Risk of reproductive and developmental toxicity makes butyl benzyl phthalate unsuitable for use in cosmetics.
- Inclusion of butyl benzyl phthalate in Schedule 10 for use in cosmetics provides consistency with the EU cosmetic regulations.

3.7. Basic Red 76

Referred scheduling proposal

An application was submitted to amend the Schedule 7 entry of the Poisons Standard for the azo dyes that are derivatives by diazotisation and to create a new Schedule 6 entry for azo dyes to allow the use Basic Red 76 in cosmetic non oxidative hair, eyelash and eyebrow dye products containing no more than 0.001% free *o*-anisidine.

Scheduling application

This was a general application. The applicant's proposed amendments to the [Poisons Standard](#) are:

Schedule 7 – Amend Entry

AZO DYES that are derivatives by diazotisation of any of the following substances:

p-aminoazobenzene (CAS No. 60-09-3)

o-aminoazotoluene (CAS No. 97-56-3)

o-anisidine (CAS No. 90-04-0)

p-chloroaniline (CAS No. 106-47-8)

4-chloro-*o*-toluidine (CAS No. 95-69-2)

~~6-methoxy-*m*-toluidine (*p*-cresidine) (CAS No. 120-71-8)~~

~~2-naphthylamine (CAS No. 91-59-8)~~

5-nitro-*o*-toluidine (CAS No. 99-55-8)

2,4-toluenediamine (CAS No. 95-80-7)

o-toluidine (CAS No. 95-53-4)

~~2,4,5-trimethylaniline (CAS No. 137-17-7)~~

except when included in Schedule 6

Schedule 6 – New Entry

AZO DYES that are derivatives by diazotisation when used in non-oxidative hair, eyelash and eyebrow dye products where the percentage of free *o*-anisidine as listed in Schedule 7 is no more than 0.001%.

OR

AZO DYES that are derivatives by diazotisation when used in cosmetic hair, eyelash and eyebrow dye products where the percentage of free carcinogen as listed in Schedule 7 is no more than 0.001%.

The applicant's reasons for the request are:

- A proposal to further the cascade of scheduling controls for *o*-anisidine based on risk from Schedules 10 and 7 to include a lower risk Schedule 6 entry to cover the presence of free *o*-anisidine in products at levels below 0.001% which is the cut-off included in Schedule 10.
- The non-oxidative dye Basic Red 76, (formulated in rinse-off semi-permanent or non-oxidative colourants with short skin contact times and no strong reducing agents) does not decouple to release the carcinogen of concern, *o*-anisidine, as demonstrated by lack of colour change on application.
- Although under percutaneous conditions as demonstrated by *in vitro* mutagenic studies, decoupling does occur, these same studies demonstrated without rat liver S9 activation resulted in no decoupling.
- Percutaneous adsorption of Basic Red 76 is very low at 0.47%, and absorption has to occur before decoupling can occur through metabolic processes. The contact time is short for non-oxidative hair dyes, typically 5 to 20 minutes, and the delivery base is normally a shampoo or conditioner that functionally removes dirt and debris from the hair and scalp including any excess hair dye and carcinogen.
- The Scientific Committee on Consumer Safety (SCCS) in an Opinion, SCCS/1385/10, has classified Basic Red 76, when used as a non-oxidative hair dye up to 2%, as not posing a risk for consumers. Australia is currently out of alignment with the SCCS Opinion and the rest of the world on Basic Red 76.
- Many products for New Zealand come into Australian warehouses as a combined shipment for Australia and New Zealand. If the current Poisons Standard restrictive entry continues to apply to hair dyes containing Basic Red 76 shipments for New Zealand (where Basic Red 76 is approved for use), this would be seen in Australia as being "supplied" and therefore in contravention of the Poisons Standard.
- When the scheduling of azo dyes (that are derivatives by diazotisation) was first proposed at the August 2015 meeting of the ACCS, the then delegate received a public submission concerned about the sheer number of dyes being entered as part of the group entry without due consideration for each individual dye. One dye of concern listed in the submission was Basic Red 76 (CAS 6831-30-0).

In their final decision, the then delegate suggested “*that if this dye is of importance to the Australian industry, a submission should be made to exempt this specific substance from the proposed Schedule 7 generic entry, with proposals on how it should be regulated.*”

Current scheduling status and relevant scheduling history

Basic Red 76 is not specifically scheduled in the Poisons Standard but is captured by the Schedule 7 entry for azo dyes.

Schedule 7

AZO DYES that are derivatives by diazotisation of any of the following substances:

- p*-aminoazobenzene (CAS No. 60-09-3)
- o*-aminoazotoluene (CAS No. 97-56-3)
- o*-anisidine (CAS No. 90-04-0)
- p*-chloroaniline (CAS No. 106-47-8)
- 4-chloro-*o*-toluidine (CAS No. 95-69-2)
- 6-methoxy-*m*-toluidine (*p*-cresidine) (CAS No. 120-71-8)
- 2-naphthylamine (CAS No. 91-59-8)
- 5-nitro-*o*-toluidine (CAS No. 99-55-8)
- 2,4-toluenediamine (CAS No. 95-80-7)
- o*-toluidine (CAS No. 95-53-4)
- 2,4,5-trimethylaniline (CAS No. 137-17-7).

o-Anisidine is also captured by the above Schedule 7 entry for azo dyes and on 1 February 2018 will have a specific entry in Schedule 10 as follows:

Schedule 10

o-ANISIDINE (excluding derivatives) in preparations for skin colouration (including tattoos) and dyeing of hair, eyelashes or eyebrows **except** in preparations containing 0.001% or less of *o*-anisidine.

In November 2013, the Advisory Committee on Chemicals Scheduling (ACCS) considered scheduling a number of benzidine-based azo dyes due to their potential to be metabolised by azo reductases (diazotisation) *in vivo* to benzidine (CAS No. 92-87-5), a known human carcinogen. The committee noted that although these are useful chemicals (CAS No. 94249-03-3, 3567-65-5, 12217-14-0, 54579-28-1, 1937-37-7, 2429-73-4, 2602-46-2, 2429-82-5, 16071-86-6, 3626-28-6, 4335-09-5, 573-58-0 and 3530-19-6), their access for domestic use needed to be restricted due to concerns of carcinogenicity. The committee recommended that benzidine-based azo dyes be included in Schedule 7 and the delegate concurred. A delayed implantation date of 12 months to 1 June 2014 was implemented to allow industry to recall products and to enable consumers to make informed choices about using products that contain benzidine-based azo dyes.

In November 2014, the ACCS considered scheduling benzidine-congener-based dyes and benzidine-based azo dye C.I. Acid Black 29 (CAS No. 12217-14-0) in Schedule 7 due to the potential of these substances to be metabolised to carcinogenic benzidine-congeners, similar to that for benzidine-based azo dyes. The toxicological profile of the 66 benzidine-congener-based dyes presented to the committee was based on ‘read-across’ (based on quantitative structure-activity relationships (QSAR)) from 6 of the benzidine-congener-based dyes; C.I. Direct Blue 14, C.I. Direct Blue 53, C.I. Direct Blue 1,

C.I. Acid Red 114, C.I. Direct Blue 15 and C.I. Direct Blue 218. Given that benzidine-congener-based dyes are metabolised *in vivo* to carcinogenic dichlorobenzidine (3,3'-DCB), 3,3'-dihydroxybenzidine (3,3'-DHB), 3,3'-dimethoxybenzidine (3,3'-DMOB) or 3,3'-dimethylbenzidine (3,3'-DMB), the committee recommended that benzidine-congeners should not be accessible for domestic use and to list them in Schedule 7. The delegate agreed and a new Schedule 7 entry for BENZIDINE-CONGENER (3,3'-disubstituted) azo dyes was implemented on 1 June 2015.

In August 2015, the ACCS considered scheduling various azo dyes that could release selected carcinogenic and/or genotoxic amines and/or aromatic amine precursors through reductive cleavage of the azo linkages. A Schedule 7 entry was proposed in favour of a Schedule 10 entry to allow legitimate use of these dyes in industrial settings while preventing use in the domestic market. The delegate agreed to a new Schedule 7 listing for azo dyes, which are derivatives by diazotisation (i.e., that can be reduced by azoreductases to yield 8 specific carcinogenic aromatic amines) including: *o*-anisidine (CAS No. 90-04-0), *o*-toluidine (CAS No. 95-53-4), *p*-aminoazobenzene (CAS No. 60-09-3), *o*-aminoazotoluene (CAS No. 97-56-3), 2,4-toluenediamine (CAS No. 95-80-7), 5-nitro-*o*-toluidine (CAS No. 99-55-8), *p*-chloroaniline (CAS No. 106-47-8), and 4-chloro-*o*-toluidine (CAS No. 95-69-2). This decision was implemented on 1 February 2016.

- The delegate received a public submission concerned about the sheer number of dyes being entered as part of the group entry without due consideration for each individual dye. One dye of concern listed in the submission was Basic Red 76 (CAS 6831-30-0). In their final decision, the then delegate suggested *“that if this dye is of importance to the Australian industry, a submission should be made to exempt this specific substance from the proposed Schedule 7 generic entry, with proposals on how it should be regulated.”*
- *o*-Anisidine was first included in Schedule 7 in February 2016 as part of the above azo dyes entry due to their carcinogenicity and genotoxicity. The toxicological data for *o*-anisidine provided to the committee in August 2015 were the same as those provided with this current application.

In November 2015, the ACCS considered azo dyes that could release selected carcinogenic amines (not listed on AICS). The ACCS recommended and the delegate agreed that the Schedule 7 listing for azo dyes be amended to extend the list of carcinogenic amines in order to include three extra azo dyes. An implementation date of 1 June 2016 was recommended to remove any such products from the Australian market on safety grounds. The delegate's final decision on azo dyes (not listed on AICS) was to add these to the generic Schedule 7 listing for azo dyes. The Delegate noted a public submission raised a point that some of the listed aromatic amines may be present as manufacturing impurities in the relevant azo dyes. However, the ACCS did not consider this to be a problem, since the objective is to control the parent dyes, and the resultant aromatic amines are not specifically listed as individual substances in Schedule 7. At the meeting, the delegate noted that the point of the generic listing was for purposes of not creating an entire list of individual azo dyes and to capture substances that “could be diazotised”.

In March 2016 the ACCS considered the scheduling of Disperse Yellow 3, and recommended to the delegate that the sensitisation and carcinogenic potential warrants control in cosmetic and consumer products and should not be used in hair dyes. The committee agreed it was appropriate to have both a Schedule 6 entry for general use and a Schedule 10 entry to specifically prohibit use in hair dyes and cosmetics. Members agreed that warning statements for general use to advise of the skin sensitization potential was warranted and that the name Disperse Yellow 3 be used in any Schedule entry with a cross-reference to the chemical name

4-(2-hydroxy-5-methylphenylazo)acetanilide in the index. Members agreed that the substance was not captured by the existing benzidine azo dye entries or azo dyes derived by diazotisation and therefore should be listed separately. The delegate accepted the ACCS advice to create new listings for Disperse Yellow 3 in Schedules 6 and 10, and in Appendices E and F and noted that this substance would not be captured under any existing Schedule entries for phenylenediamines or azo dyes. The decision was implemented on 1 October 2016.

In March 2016 the ACCS also considered the scheduling of chrysoidine and its salts and recommended a Schedule 6 entry, based on toxicity, rather than capturing it in the other scheduled dyes entries. Further, it was noted that there is evidence of use in the hobby industry, and this should be considered when scheduling chrysoidine. The committee noted that the Schedule 6 will preclude use of chrysoidine and its salts in cosmetics (due to the requirement for POISON labelling), but this would not prevent use of these substances in hair dye products. Given this, a Schedule 10 entry was also recommended. The Delegate accepted the ACCS recommendations to create new listings for Chrysoidine in Schedules 6 and 10, and in Appendix E. This decision was implemented on 1 October 2016.

Australian regulatory information

Basic Red 76 (CAS No. 68391-30-0) is on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

Basic Red 76 is not approved for therapeutic use in the TGA permissible ingredients repository.

Basic Red 76 is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 3 of 2017](#).

Solvent Red 23 (CAS No 85-86-9) which is also an AZO DYE covered by the Schedule 7 entry as a derivative of *p*-aminoazobenzene is a TGA approved dye under the name of Sudan III and is "Available for use as an Active Ingredient in: Biologicals, Prescription Medicines Available for use as an Excipient Ingredient in: Biologicals, Devices, Export Only, Listed Medicines, Over the Counter, Prescription Medicines (TGA Ingredient Summary 2017)." Its use is restricted to therapeutic products for topical use and has been approved and in use for at least the last 15 years.

International regulations

Basic Red 76

Table 3.7.1: Basic Red 76 – conditions of use in countries/jurisdictions

Country/Jurisdiction	Conditions
European Union	Basic Red 76 is listed in the EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down. Basic Red 76 is allowed in non-oxidative hair dye products at a maximum concentration of 2 %.
ASEAN	Annex III – allowed up to 2% in non-oxidative hair dyes
New Zealand	Schedule 4 – allowed up to 2% in non-oxidative hair dyes
USA	Approved
Canada	Approved
Japan	Approved

o-Anisidine

o-Anisidine was first included in Schedule 7 in February 2016 as part of the azo dyes entry due to their carcinogenicity and genotoxicity. In February 2018, the scheduling of *o*-anisidine will change to

Schedule 10 in preparations for skin colouration (including tattoos) and dyeing of hair, eyelashes or eyebrows except in preparations containing 0.001% or less of *o*-anisidine on 1 February 2018.

o-Anisidine is classified as a carcinogen in most countries around the world. However, different jurisdictions have set different thresholds for safe use:

EU

- REACH Regulations: Annex XVII, *o*-Anisidine cannot be used in substances and preparations placed on the market for sale to the general public in individual concentrations >0.1 % (European Parliament and Council 1999; European Parliament and Council 2006; European Parliament and Council 2008). *o*-Anisidine is also included as part of 22 aromatic amines listed in Appendix 8 which places restrictions on their presence in leather or textile articles.
- *o*-Anisidine is on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2013). In the EU, companies could have legal obligations if the chemical that they produce, supply or use is included on the candidate list whether on its own, in mixtures, or present in articles.
- Cosmetics Regulation 1223/2009 Annex II – List of substances prohibited in cosmetic products (does not cover derivatives).
- SCCS: 10 ppm in non-oxidation hair dye products (0.001%).

ASEAN

- Annex II, not permitted for use in cosmetic products (does not cover derivatives).

NZ

- HSNO Approval No. HSR004606. Hazardous Substances (Classes 6, 8, and 9 Controls) Regulations 2001 Regs 11-27 Limiting exposure to toxic substances through the setting of TELs. No ADE, PDE, TELs set at this time for this substance. Regs 46-48 Restrictions on use of substances in application areas.
- Cosmetics Group Standard (As amended 2012): Schedule 4: Components cosmetic products must not contain (does not cover derivatives).

USA California Environmental Protection Agency

- Cancer Potency: 0.14 mg/kg/day; 10-5 Risk Specific Intake: 5 µg/day.

IARC

- Non threshold carcinogen 2.

Other cosmetic Azo Dyes

The chemicals Solvent Red 24; Solvent Red 23; Solvent Red 1; CAS No. 4482-25-1; CAS No. 5413-75-2; CAS No. 5421-66-9; CAS No. 8005-78-5; CAS No. 85136-74-9; CAS No. 68425-18-3; CAS No. 118658-98-3; CAS No. 118658-99-4 are listed in the:

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II – List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard – Schedule 4: Components cosmetic products must not contain.

- Canada: Based on the information obtained from Galleria Chemica, the chemicals Solvent Red 24 (CAS Nos. 85-83-6) and Solvent Red 23 are listed in the Health Canada List of prohibited and restricted cosmetic ingredients (the cosmetic ingredient "Hotlist").
- Philippines: The chemicals Solvent Red 24; Solvent Red 23; and CAS No. 131-79-3 are listed in the Philippines Restricted Ingredients For Use In Cosmetics – List of substances which must not form part of the composition of cosmetic products.

Solvent Red 24

The chemicals Solvent Red 24; CAS No. 85136-74-9; CAS No. 108225-03-2; and CAS No. 118658-99-4 are prohibited for all uses, whereas the other chemicals are prohibited when used as a substance in hair dye products.

Solvent Red 23

The chemical Solvent Red 23 (identified as CI 26100) is listed in the:

- ASEAN Cosmetic Directive Annex IV Part 1 – List of colouring agents allowed for use in cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II – List of colourants allowed in cosmetic products; and
- New Zealand Cosmetic Products Group Standard – Schedule 6: Colouring agents cosmetic products may contain with restriction.

In the above directives, Solvent Red 23 is specified as 'not to be used in products applied to mucous membranes'; purity criteria also apply.

Azo dyes

Azo dyes are restricted by Annex XVII to REACH Regulation as follows:

- Azo dyes which, by reductive cleavage of one or more azo groups, may release one or more of the aromatic amines listed in Appendix 8, in detectable concentrations, i.e. above 30 ppm in the finished articles or in the dyed parts thereof, according to the testing methods listed in Appendix 10, shall not be used in textile and leather articles which may come into direct and prolonged contact with the human skin or oral cavity, such as:
 - clothing, bedding, towels, hairpieces, wigs, hats, nappies and other sanitary items, sleeping bags;
 - footwear, gloves, wristwatch straps, handbags, purses/wallets, briefcases, chair covers, purses worn round the neck;
 - textile or leather toys and toys which include textile or leather garments; and
 - yarn and fabrics intended for use by the final consumer.

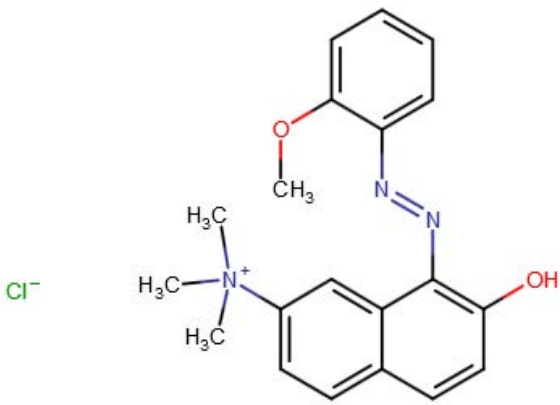
Other azo dyes

The chemicals *o*-anisidine; *o*-toluidine; *p*-aminoazobenzene; 2,4-toluenediamine; *o*-aminoazotoluene; 5-nitro-*o*-toluidine; *p*-chloroaniline; and 4-chloro-*o*-toluidine are listed in Appendix 8 of EU REACH Annex XVII.

Substance summary

Basic Red 76 is used as a dyeing aid, a photographic developer and as an intermediate in drugs and perfumes.

Table 3.7.2: Chemical information for Basic Red 76

Property	Basic Red 76
Chemical structure	
Molecular formula	C ₂₀ H ₂₂ N ₃ O ₂ .Cl
Molecular weight	371.8 g/mol
CAS name	2-Naphthalenaminium,7-hydroxy-8-[(2-methoxyphenyl)azo]-N,N,N-trimethyl-,chloride
CAS number	68391-30-0
IUPAC and/or common and/or other names	8-(2-methoxyphenylazo)-7-hydroxy-2-naphthyltrimethylammonium chloride; C.I. Basic Red 76; 7-hydroxy-8-((2-methoxyphenyl)azo)-N,N,N-trimethyl-2-naphthalenam-inium chloride; Arianor Madder Red; C.I. 12245

*Toxicity***Table 3.7.3: Acute toxicity end-points for Basic Red 76**

Toxicity	Species	Basic Red 76	SPF (2015) Classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rat	>2000	Schedule 5
Acute dermal toxicity LD ₅₀ (mg/kg bw)	No data available	No data available	N/A
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	No data available	No data available	N/A
Skin irritation	Rabbit	Non-irritating	N/A
Eye irritation	Rabbit	Slight	Schedule 5
Skin sensitisation (LLNA)	Mice	Negative	N/A

Genotoxicity

The genotoxicity of Basic Red 76 is sufficiently investigated for the three endpoints of genotoxicity: gene mutations, chromosome aberrations and aneuploidy. Basic Red 76 did not induce gene mutations neither in bacteria (Ames Test) nor in mammalian cells. While an *in vitro* micronucleus test did result in an increase in V79 cells with micronuclei, this positive finding was not confirmed in an *in vivo* micronucleus test in mice (SCCS Opinion 2011).

Table 3.7.4: Acute toxicity end-points for *o*-anisidine

Toxicity	Species	Outcome	SPF (2015) classification
Acute oral toxicity LD ₅₀ (mg/kg bw)	Rats	1505–1890	Schedule 6
Acute dermal toxicity LD ₅₀ (mg/kg bw)	Rats	>2000	Schedule 5
Acute inhalational toxicity LC ₅₀ (mg/m ³ /4h)	Rats	>3870	Schedule 5
Skin irritation	Rabbits	Slight irritant	Schedule 5
Eye irritation	Rabbits	Slight irritant	Schedule 5
Skin sensitisation	local lymph node assay (LLNA) and guinea pig maximisation test (GPMT)	Equivocal	N/A

Detailed claims against the requirements of section 52E(1) of the Therapeutic Goods Act 1989

(A) The risks and benefits of the use of a substance

Basic Red 76 does not cleave and form *o*-anisidine under the conditions of use for products containing Basic Red 76. Basic Red 76 is a non-oxidative hair dye used in semi-permanent hair colourants. These are sold worldwide. These colourants are applied to the hair, not the scalp, usually in a shampoo or conditioner base. They are left on the hair for 5 to 20 minutes and then thoroughly washed off. Poor removal will result in later colour residues being left on clothes and bedding. The application is pH 6.5. There is no hydrogen peroxide, ammonia or monoethanolamine that may be used with oxidation or permanent hair colourants that are high pH and much more reactive. These agents are not used for semi-permanent hair dyes. The azo chemical bond under normal conditions of use semi-permanent hair dye products is very stable. This is also demonstrated in *in vitro* testing where there is no *o*-anisidine present from cleavage when there is no metabolic activity. Metabolic cleavage does not occur with use of these products. In addition, the percutaneous absorption of Basic Red 76 into and through the skin is only 0.47% across 24 hours. A margin of exposure/safety calculation will show the level of risk from this absorption is very low.

Formation of aromatic amines such as *o*-anisidine by azo-cleavage is not expected in semi-permanent hair colourants and have not been found in finished products testing during storage or during application where time frames of these rinse off products are short and no loss of colour has been seen in the many applications to hair that have been applied over decades to human hair from these products.

(B) The purposes for which a substance is to be used and the extent of use of that substance

Basic Red 76 is to be used in rinse off non-oxidative hair colourants also called semi-permanent hair dyes at levels up to 2%. This use is aligned with the approved maximum expressed in the European Scientific Committee for Consumer Safety SCCS/1385/10 Opinion for Basic Red 76 and adopted into the European Regulation for Cosmetics, Annex III/267 for use in non-oxidative hair dye products with a maximum concentration of 2%.

(C) Toxicity and safety of the substance

For full summary of toxicity assessment please refer to the [SCCS Opinion on Basic Red 76](#).

(D) Dosage, formulation, labelling, packaging and presentation of a substance

Information on formulations, labelling and packaging were included in the application.

(E) Potential for misuse/abuse of the substance

All products supplied come with detailed directions for use. The application method is simple – apply to the hair in the same way as someone would shampoo or condition their hair. There is no mixing with other packs as products containing Basic Red 76 are not permanent colourant products. These product dosage form may be liquids or mousses and be supplied in bottles or tubes. Child resistant closures are not generally required for these products.

(F) Any other matter that may be relevant to the scheduling of a substance

Nil.

Pre-meeting submissions

Six (6) public submissions were received, five (5) in support and one (1) opposed.

Main points in support:

- Basic Red 76 is approved in the EU, USA, New Zealand and in all ASEAN counties.
- In the European Union, Basic Red 76 is used in non-oxidative hair dyes up to 2% and is a common colourant.
- Two submissions noted that they are unaware of any other countries besides Australia where Basic Red 76 is banned.
- Basic Red 76 is essential to providing a full range of colours for use by professional hairdressers. This substance is also used to colour shampoos and other cosmetic products.
- Australian regulations should align with the EU levels, and warning statements in line with other scheduled hair dye substances.
- The carcinogen, *o*-anisidine, is not formed during the use of this hair dye in hair colourant products as this would destroy the colour provided by Basic Red 76 and result in the unsatisfactory consistency and appearance of the colour.
- The proposal to exclude Basic Red 76 is supported along with proposed wording for the new Schedule 6 entry of Basic Red 76. The proposed entry suggests a maximum 2% in non-oxidative hair dye preparations and eyelash and eyebrow products when the packets are labelled with safety and warning statements.
- Three submissions also supported the reinstated use of colour CI 26100 (CAS No 85-86-9; synonyms Solvent Red 23, Sudan III) for general use in cosmetic products as a colourant, as this colourant has also been caught by the current Schedule 7 entry for azo dyes.

Main points opposed:

- There needs to be a comprehensive review of the impact of the Schedules 5, 6 and 7 entries for azo dyes on therapeutic goods, with the preferred outcome being that therapeutic goods should be excluded from any schedule entry for azo dyes.
- There remains confusion as to which substances are specifically captured by the Schedule 7 entry of azo dyes as the list of captured substances is not comprehensive. The impact on therapeutic goods was not included in the original scheduling decision in November 2015 and it is unclear how many products are registered and listed on the ARTG that have the potential to be affected by scheduling decisions relating to azo dyes.

The public submissions will be made available on the [TGA website](#).

Summary of ACCS advice to the delegate

The committee recommended that the Schedule 7 entry for azo dyes be amended as follows:

Schedule 7 – Amend Entry

AZO DYES that are derivatives by diazotisation of any of the following substances:

p-aminoazobenzene (CAS No. 60-09-3)
o-aminoazotoluene (CAS No. 97-56-3)
o-anisidine (CAS No. 90-04-0)
p-chloroaniline (CAS No. 106-47-8)
4-chloro-*o*-toluidine (CAS No. 95-69-2)
6-methoxy-*m*-toluidine (*p*-cresidine) (CAS No. 120-71-8)
2-naphthylamine (CAS No. 91-59-8)
5-nitro-*o*-toluidine (CAS No. 99-55-8)
2,4-toluenediamine (CAS No. 95-80-7)
o-toluidine (CAS No. 95-53-4)
2,4,5-trimethylaniline (CAS No. 137-17-7)

except for BASIC RED 76 (CAS No. 68391-30-0) when included in Schedule 6.

The committee recommended that a new Schedule 6 entry for Basic Red 76 be created as follows:

Schedule 6 – New Entry

BASIC RED 76 (CAS No. 68391-30-0) in non-oxidative hair dye preparations and eyebrow/eyelash colouring products containing 2 per cent or less of BASIC RED 76 and 0.001 per cent or less of free *o*-anisidine.

The committee recommended the following Appendix E and F entries for Basic Red 76 be created as follows:

Appendix E, Part 2 – New Entry

BASIC RED 76

Standard Statement: **A (Poisons Advice hotline)**

Appendix F, Part 3 – New Entry

BASIC RED 76

Warning Statement: 5 (Wear protective gloves when mixing or using).

The committee recommended a new index entry for Basic Red 76 be created as follows:

Index – New Entry

BASIC RED 76 (CAS No. 68391-30-0)
cross reference: [7-HYDROXY-8-[(2- METHOXYPHENYL)AZO]-2-NAPHTHYL]TRIMETHYLAMMONIUM CHLORIDE (CAS No. 68391-30-0)

Schedule 7

Schedule 6

The committee also recommended an implementation date of **1 February 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; and (c) the toxicity of a substance.

The reasons for the advice were:

- While Basic Red 76 is used by industry in hair dyes, there is a potential risk of dermal absorption of the genotoxic carcinogen, *o*-anisidine.
- Basic Red 76 has comparatively widespread use in non-oxidative hair dyes.
- Basic Red 76 has low toxicity. There is a small risk of decoupling to *o*-anisidine in non-oxidative hair/eyebrow/eyelash dyes.
- There is a potential for skin bacteria to convert Basic Red 76 to the genotoxic carcinogen, *o*-anisidine.

Delegate's considerations

The delegate considered the following regarding this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the Therapeutic Goods Act 1989
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 7 entry for azo dyes, create new entries for Basic Red 76 in Schedule 6 and Appendix E and F and to create a new index entry for Basic Red 76. The proposed Schedule entry is as follows:

Schedule 7 – Amend Entry

AZO DYES that are derivatives by diazotisation of any of the following substances:

p-aminoazobenzene (CAS No. 60-09-3)

o-aminoazotoluene (CAS No. 97-56-3)

o-anisidine (CAS No. 90-04-0)
p-chloroaniline (CAS No. 106-47-8)
4-chloro-*o*-toluidine (CAS No. 95-69-2)
6-methoxy-*m*-toluidine (*p*-cresidine) (CAS No. 120-71-8)
2-naphthylamine (CAS No. 91-59-8)
5-nitro-*o*-toluidine (CAS No. 99-55-8)
2,4-toluenediamine (CAS No. 95-80-7)
o-toluidine (CAS No. 95-53-4)
2,4,5-trimethylaniline (CAS No. 137-17-7)

except for BASIC RED 76 (CAS No. 68391-30-0) when included in Schedule 6.

Schedule 6 – New Entry

BASIC RED 76 (CAS No. 68391-30-0) in non-oxidative hair dye preparations and eyebrow/eyelash colouring products containing 2 per cent or less of BASIC RED 76 and 0.001 per cent or less of free *o*-anisidine.

Appendix E, Part 2 – New Entry

BASIC RED 76

Standard Statement: A (Poisons Advice hotline)

Appendix F, Part 3 – New Entry

BASIC RED 76

Warning Statement: 5 (Wear protective gloves when mixing or using).

Index – New Entry

BASIC RED 76 (CAS No. 68391-30-0)
cross reference: [7-HYDROXY-8-[(2- METHOXYPHENYL)AZO]-2-NAPHTHYL]TRIMETHYLAMMONIUM CHLORIDE (CAS No. 68391-30-0)

Schedule 7

Schedule 6

The proposed implementation date is **1 February 2018**, as this is the earliest possible implementation date.

The matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are:

- While Basic Red 76 is used by industry in hair dyes, there is a potential risk of dermal absorption of the genotoxic carcinogen, *o*-anisidine.
- Basic Red 76 has comparatively widespread use in non-oxidative hair dyes.
- Basic Red 76 has low toxicity. There is a small risk of decoupling to *o*-anisidine in non-oxidative hair/eyebrow/eyelash dyes.
- There is a potential for skin bacteria to convert Basic Red 76 to the genotoxic carcinogen, *o*-anisidine.