Australian Government
Department of Health
Therapeutic Goods Administration

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

15 September 2016

(ACMS, Joint ACCS-ACMS, and ACCS meetings – July 2016)

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

A delegate of the Secretary to the Department of Health hereby gives notice of delegates' interim decisions for amending the Poisons Standard (the *Standard for the Uniform Scheduling of Medicines and Poisons* - SUSMP) under subsection 42ZCZP of the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect (the implementation date) of the decision.

The delegates' interim decisions and reasons relate to:

- scheduling proposals initially referred to the July 2016 meeting of the Advisory Committee on Medicines Scheduling (ACMS#18);
- scheduling proposals initially referred to the July 2016 Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS#13); and
- scheduling proposals initially referred to the July 2016 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#17).

Pre-meeting public notices

Pre-meeting public notices inviting submissions on the scheduling proposals referred to the expert advisory committees were published on 7 April 2016 (Medicines) and 26 May 2016 (Chemicals) on the TGA website at: Public notice about scheduling.

Redacted versions of public submissions received in response to the requests 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

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 (published on 7 April 2016 and 26 May 2016 at https://www.tga.gov.au/scheduling-advisory-commitees-invitations-public-comment).

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, 29 September 2016.

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

The closing date for further submissions is 29 September 2016.

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 freecall 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

Abbreviation	Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
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

Abbreviation	Name
HCN	Health Communication Network
IMAP	Inventory Multi-tiered Assessment Prioritisation
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

Abbreviation	Name
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
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

Abbreviation	Name
SCCP	Scientific Committee on Consumer Products
SPF	Scheduling Policy Framework
STANZHA	States and Territories and New Zealand Health Authorities
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

Contents

Part A - Interim decisions on scheduling proposals referred to an advisory committee (July 2016)

1. Advisory Committee on Medicines Scheduling (ACMS#18)

Summary of delegate's interim decisions

Substance	Interim decision
Ulipristal	**Schedule 4 – Amend Entry** ULIPRISTAL **except** when included in Schedule 3. **Schedule 3 – New Entry** ULIPRISTAL for emergency post-coital contraception. Proposed implementation date: **1 February 2017**
Fexofenadine	**Schedule 4 – Amend Entry** FEXOFENADINE **except:** a) when included in Schedule 2; or b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine. **Schedule 2 – Amend Entry** FEXOFENADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: a) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and b) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine. Proposed implementation date: **1 February 2017**
2,4-Dinitrophenol	**Schedule 10 – New Entry** 2,4-DINITROPHENOL for human use.

Substance	Interim decision
	Schedule 7 – Amend Entry DINITROPHENOLS **except** when included in Schedule 4, 6 or 10. Proposed implementation date: **1 February 2017**
N,N-Dimethyltryptamine	The current scheduling remains appropriate for *N,N*-dimethyltryptamine.
Piper methysticum (kava)	The current scheduling remains appropriate for piper methysticum (kava).

1.1 Ulipristal

Referred scheduling proposal

An application was submitted to reschedule ulipristal and create a new Schedule 3 entry for ulipristal for emergency post-coital contraception.

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

Schedule 4 –Amend entry

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

Schedule 3 – New Entry

ULIPRISTAL for emergency post-coital contraception.

The applicant's reasons for the request are:

- The applicant believes the substance meets the criteria for inclusion in Schedule 3, on the same basis as the current scheduling of levonorgestrel;
- The risk of pregnancy is highest when ovulation is due to happen in the first day or two after unprotected sexual intercourse (UPSI) or contraceptive failure (Brache 2013, Glasier 2010). However, the timing of ovulation is difficult to predict. Ovulation can occur as early as the 8th day and as late as the 60th day of the menstrual cycle (Wilcox 2000);
- For both levonorgestrel and ulipristal, it is important to take the medicine as soon as possible after UPSI (ref: PI Postinor 1 and EllaOne). Ulipristal is more effective if taken in the first 24 hours following UPSI (PI EllaOne). More than a decade of experience with levonorgestrel has shown that pharmacy access enables women to use emergency contraception (EC) quickly and appropriately without medical supervision;
- Ulipristal acetate 30 mg tablet was approved in the European Union (EU) on 15 May 2009 and first marketed there on 1 October 2009, and as of 20 January 2016, in 89 countries including in the United States on 1 December 2010. It was re-classified as a non-prescription medicinal product in the EU (centralised procedure) on 7 January 2015 and in Switzerland on 15 January 2016. It is currently available without a doctor's prescription in 25 European countries;

- In Australia 'EllaOne ulipristal acetate 30 mg tablet blister pack' was approved by TGA on 6 March 2015 (AUST R 219535). It is now approved for supply on doctor's prescription as an alternative to levonorgestrel for EC. The TGA-approved Product Information (PI), the Australian Consumer Medicine Information (CMI) and the Australian Public Assessment Report (AusPAR) are included in this submission;
- While being comparable to levonorgestrel in adverse event profile, clinical and biological evidence demonstrate that ulipristal acetate 30 mg is more effective than levonorgestrel, especially when taken within the first 24 hours after UPSI, at the time when the vast majority of women ask for EC. In addition, it is effective within 5 days (120 hours) of UPSI compared to 3 days (72 hours) for levonorgestrel;
- In public health terms ulipristal offers a reduction in unintended pregnancies (and possibly abortions) and gives women additional options, for instance where more than 3 days has elapsed since UPSI (noting that for maximum efficacy ulipristal should be taken as soon as possible after UPSI). To put this in context we have calculated, based on sales of levonorgestrel to Australian pharmacies over 12 months to April 2014 and a meta-analysis of 2 comparative clinical trials conducted in the UK, Ireland and the USA, a theoretical figure of more than 5000 additional unintended pregnancies that could be prevented in Australia per year if ulipristal were to be used in place of levonorgestrel; and
- These benefits will only be realised in Australia if ulipristal is made available as a Schedule 3 medicine on the same basis as levonorgestrel. Even if women somehow become aware that a better alternative is available from doctors (noting that prescription medicines cannot be advertised to the general public), they are unlikely to go to a doctor for EC while levonorgestrel is conveniently available from pharmacies.

Substance summary

Ulipristal is an orally-active synthetic selective progesterone receptor modulator that acts via high affinity binding to the human progesterone receptor. When used for emergency contraception the mechanism of action is inhibition or delay of ovulation via suppression of the lutenising hormone (LH) surge.

Ulipristal is indicated for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

The structure of ulipristal is shown in Figure 1.1 and a summary of its chemical properties are described in Table 1.1.

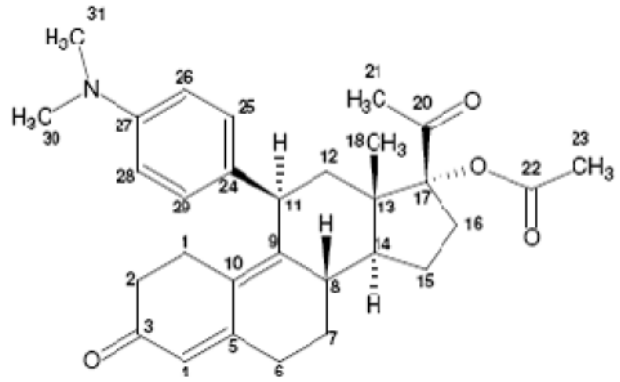


Figure 1.1: Structure of ulipristal

Table 1.1: General chemical information for ulipristal

Australian Approved Name (AAN)	ulipristal acetate
Chemical name	17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione
Molecular formula	$C_{30}H_{37}NO_4$
Molecular weight	475.62 g/mol
CAS No.	126784-99-4

Specific questions raised by the delegate

The delegate asked the committee if it was appropriate for ulipristal to be available as a Schedule 3 medicine for emergency post-coital contraception and, if not, how it differs from levonorgestrel for emergency post-coital contraception.

Current scheduling status

Ulipristal is currently listed in Schedule 4 of the SUSMP.

Schedule 4

ULIPRISTAL.

Relevant scheduling history

In May 2015, the delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of ulipristal, a new chemical entity for a human therapeutic medicine. The delegate decided to make a delegate-only decision to include ulipristal in Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted. Ulipristal was included in the SUSMP on 1 June 2015.

Pre-meeting public submissions

Sixteen (16) public submissions were received and all supported the application.

The key points made in the submissions were that rescheduling will provide more choice to women who require emergency contraception, that rescheduling would be consistent with the classification of the current available emergency contraception levonorgestrel, of which ulipristal has a similar safety profile, and that ulipristal is available without a doctor's prescription in at least 25 European countries.

The public submissions are available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the proposal to down-schedule ulipristal to Schedule 3 was appropriate.

The ACMS advised an implementation date of **1 February 2017**.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the committee 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.

The reasons for the advice included:

- Substantial benefit in providing another emergency contraception (EC) option for women with the ability to be used up to 5 days after unprotected sexual intercourse;
- Benefit outweighs risk for ulipristal's proposed use;
- Access to EC via a Schedule 3 listing has been established in Australia for over 10 years. There is no evidence of use outside of the intended or increased extent of use of EC as a result of a Schedule 3 listing;
- Consistent with overseas use and Schedule 4 use in Australia. Existing Schedule 3 alternative medicines are available, but they are less efficacious;
- The safety and toxicity profile of ulipristal is similar to levonorgestrel;
- The Product Information (PI) states that breastfeeding mothers need to cease to feed for 1 week post- exposure; this will need to be managed via the packaging, labelling and education of pharmacists;
- Toxicity is minimal in recommended dose (1 tablet);
- Single dose packaging and labelling are appropriate for Schedule 3;
- There is no evidence of potential for abuse; and
- There is minimal risk of use as an abortifacient with current doses.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate has considered and agrees with the advice and reasons of the ACMS to create a new Schedule 3 entry for ulipristal. There is substantial benefit in providing another, more effective, emergency contraception (EC) option for women with the ability to be used up to 5 days after unprotected sexual intercourse. The single dose packaging and labelling are appropriate for Schedule 3 given the safety and toxicity profile of ulipristal and its similarity to levonorgestrel. Over the 10 years in which EC has been available over the counter in Australia there has been no evidence of misuse or increased extent of use, and there is minimal risk of use as an abortifacient with currently available doses.

The proposed implementation date is **1 February 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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.

Schedule 4 – Amend Entry

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

Schedule 3 – New Entry

ULIPRISTAL for emergency post-coital contraception.

1.2 Fexofenadine

Referred scheduling proposal

An application was submitted to increase the pack size of unscheduled fexofenadine when in divided preparations for the treatment of seasonal allergic rhinitis (SAR) in adults and children 12 years of age and over when labelled with a recommended daily dose not exceeding 120 mg of fexofenadine from not more than 5 days' supply to not more than 10 days' supply.

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

Schedule 4 – Amend Entry

FEXOFENADINE except:

a) when included in Schedule 2; or

b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

i) in a primary pack containing ~~10~~ *20* dosage units or less and not more than ~~5~~ *10* days' supply; and

ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

Schedule 2 – Amend Entry

FEXOFENADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

a) in a primary pack containing ~~10~~ *20* dosage units or less and not more than ~~5~~ *10* days' supply; and

b) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

The applicant's reasons for the request are:

- With a well-defined risk profile, fexofenadine has been made available through grocery channels in many markets including Australia, UK, USA and NZ for a number of years;
- In other markets including the USA, both larger pack sizes and higher strengths (180mg) of fexofenadine are available through grocery channels with no evidence of any impact on the overall benefit/risk profile;
- This supports the proposal to revise the scheduling exemption conditions in Australia to allow consumers to benefit from the flexibility and convenience of access to larger packs, noting the proposed pack size still remains small;

- The benefits of a larger pack include having a more portable pack size for travel or work purposes as a 'top up' or to be 'on hand' to be able to relieve symptoms immediately exposure to a trigger is experienced; supporting treatment for multiple family members or for those sufferers experiencing intermittent episodes over a longer period;
- Larger pack sizes also help to decrease the economic burden of SAR considering sufferers can be exposed to allergens that trigger symptoms throughout the season and require ongoing relief; and
- A benefit-risk profile for unscheduled fexofenadine was completed which confirmed that the proposed increase in pack size had no impact on the existing favourable benefit-risk profile for unscheduled fexofenadine.

Substance summary

Fexofenadine hydrochloride is an equimolar mixture of two enantiomers. A summary of its chemical properties are described below in Table 1.2 and its structure is shown in Figure 1.2.

Table 1.2: General information for fexofenadine

INN/BAN	Fexofenadine hydrochloride
Chemical name	benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-a, a-dimethyl-, hydrochloride
Molecular formula	$C_{32}H_{39}N0_4.HCl$
Molecular Weight	538.12
CAS No.	153439-40-8

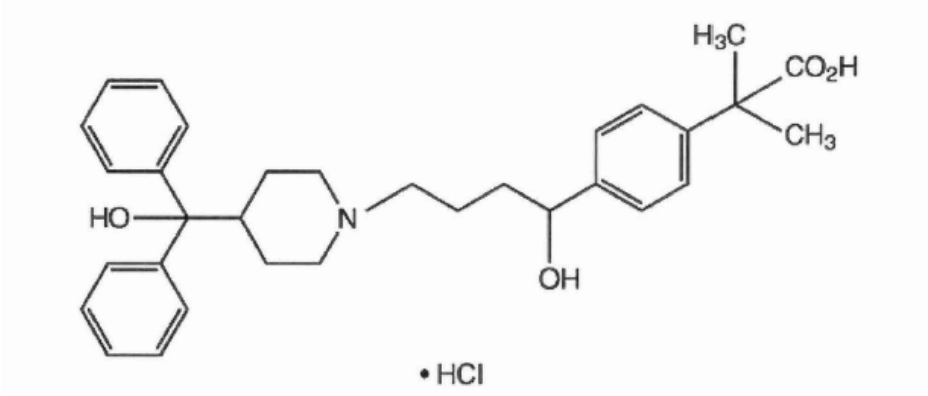


Figure 1.2: Structure of fexofenadine

Fexofenadine is an orally active non-sedating antihistamine with selective peripheral H1-receptor antagonist activity. It is a pharmacologically active carboxylic acid metabolite of terfenadine. Both enantiomers of fexofenadine hydrochloride display approximately equipotent antihistaminic effects. It has a rapid onset and long duration of action after oral administration. Further information on the pharmacology and mechanism of action of fexofenadine is included in the approved Product Information.

Specific questions raised by the delegate

The delegate asked the committee whether it is appropriate to increase the pack size of unscheduled fexofenadine to allow a maximum of 10 days' supply and whether there are increased benefits compared with risks with increasing the pack size.

Current scheduling status

Fexofenadine is currently listed in Schedules 4 and 2.

Schedule 4

FEXOFENADINE **except**:

a) when included in Schedule 2; or

b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

i) in a primary pack containing 10 dosage units or less and not more than 5 days' supply; and

ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

Schedule 2

FEXOFENADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

a) in a primary pack containing 10 dosage units or less and not more than 5 days' supply; and

b) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

It is also included under the entry:

ANTIHISTAMINES in Appendix F with the following statements:

APPENDIX F

Poisons	Warning statements
ANTIHISTAMINES not separately specified in this Appendix **except:** a) dermal, ocular, parenteral and paediatric preparations; b) oral preparations of astemizole, desloratadine, fexofenadine, loratadine or terfenadine; c) nasal preparations of azelastine; or d) preparations for the treatment of animals	39 or 40

Relevant scheduling history

National Drugs and Poisons Schedule Committee: May & August 1996

In May and August 1996, the NDPSC considered a request to initially schedule fexofenadine as per terfenadine (Schedule 3). It was agreed that as there was insufficient evidence to make a decision in regard to the toxicity of fexofenadine, a Schedule 4 entry was appropriate at that time. This scheduling was reconsidered in November 1996, where the NDPSC noted additional safety data, and decided that oral divided preparations of fexofenadine should be included in Schedule 3.

National Drugs and Poisons Schedule Committee: February 1997

In February 1997, the NDPSC considered a post-meeting request for a temporary Schedule 4 entry for all pack sizes so that the initial availability of fexofenadine would be under greater control. However, the NDPSC noted that a major reason for its November 1996 Schedule 3 decision was that it had been

satisfied that the available evidence indicated that fexofenadine was a safer drug than the prodrug, terfenadine. The NDPSC agreed that the decision to include fexofenadine as Schedule 3 remained appropriate.

National Drugs and Poisons Schedule Committee: August 1998

In August 1998, the NDPSC agreed that it was appropriate for fexofenadine to be included in Appendix H.

National Drugs and Poisons Schedule Committee: November 1998 & February 1999

In November 1998 and February 1999, following recommendations from the Trans-Tasman Harmonisation Working Party, the NDPSC agreed to reschedule fexofenadine from Schedule 3 to Schedule 2. The New Zealand and Australian entries for fexofenadine were then harmonised in November 1999.

National Drugs and Poisons Schedule Committee: October 2009 & February 2010

In October 2009, the NDPSC considered a request to exempt oral fexofenadine from scheduling for the short term treatment of SAR. The NDPSC decided that the current scheduling of oral fexofenadine (Schedule 2) remained appropriate. In February 2010, the NDPSC considered the same request referred from the NZ Medicine Classification Committee along with pre-meeting submissions and again decided that the current scheduling of fexofenadine remained appropriate.

Advisory Committee on Medicines Scheduling: February 2011

In February 2011, the ACMS considered a submission for exemption from scheduling requirements for oral fexofenadine (maximum 10 dosage units) when used for the short-term symptomatic relief (maximum 5 days of therapy) of SAR)\ in adults and children 12 years and over, with a maximum daily dose of 120 mg. The committee recommended that fexofenadine be exempt from scheduling when for the short-term symptomatic relief of SAR in adults and children 12 years of age and over when sold in small packs of 10 dosage units or less (i.e. not more than 5 days' supply at the current maximum recommended dose) with a maximum daily dose of 120 mg.

Pre-meeting public submissions

Three (3) public submissions were received.

One submission supported the proposal. The main points were:

- Given fexofenadine is used for the treatment of SAR, a patient could benefit from the proposal to increase pack size, as SAR typically can last up to 10 days. If SAR is left untreated, the patient's quality of life may be reduced;
- From a public health benefit perspective, it is logical that the pack size increases from a 5 day supply to a 10 day supply (containing 20 units or less) for unscheduled fexofenadine, as typically SAR can last up to 10 days;
- Patients already have an awareness of their allergic conditions (particularly with SAR) and/or knowledge of how to manage these allergies with little help or counselling from a pharmacist or doctor;
- Second generation antihistamines including fexofenadine, loratadine and cetirizine are a class of medicines that have been deemed safe and effective. They are considered low risk, have similar safety and efficacy profiles, similar indications and are well tolerated. Consideration should also be given to all other second generation antihistamines where pack sizes are limited to a 5 day supply, e.g. 10 mg cetirizine;
- While cetirizine includes a sedation warning according RASML and fexofenadine does not, it is well known that the sedation effect of cetirizine is mild to moderate;

- In New Zealand and Canada, cetirizine is considered to be non-drowsy at a maximum daily dose of 10 mg and have acknowledged that fexofenadine, loratadine and cetirizine 10 mg warrant the same labelling warnings with respect to sedation;
- Since cetirizine was down-scheduled to general sale, there has been no evidence to inappropriate or unsafe use. The submission believes this to be the same for other second generation antihistamines. Based on the pharmacology of the molecules in this class of medicine, it is assessed to have a very low abuse potential and is not expected to increase with a pack size increase; and
- The inclusion of appropriate warnings in the labelling of all second generation antihistamines prevents consumers from using it in clinical settings where such use is not advised.

Two (2) submissions opposed the proposal. The main points were:

- The current availability of small packs sufficiently accommodates the needs of consumers who may require rapid and short term relief and an increase is not warranted from a perspective of good clinical practice and optimal therapeutic outcomes;
- Irrespective of fexofenadine's reasonable safety profile, there are still public risks associated with its use; and
- It is not in the public interest to further increase the scheduling exemption to allow longer doses of fexofenadine to be available in general retail where there is no access to health professional advice.

The public submissions are available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the proposal to down-schedule fexofenadine was appropriate.

The ACMS advised an implementation date of **1 February 2017**.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the committee 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.

The reasons for the advice included:

- Lack of sedative effects. Low abuse potential. Ease of accessibility, consumer preference. Increase in pack size will support sufferers of seasonal allergic rhinitis (SAR) requiring more accessible, flexible and convenient pack size to self-manage their condition;
- Non-use of alternative treatments, misdiagnosis, potential use for other allergic disorders;
- Seasonal allergic rhinitis (SAR) can last up to 10 days;
- Fexofenadine has a wide therapeutic index and well-established toxicity profile. Has been shown to be safe at dosages of 800mg/day, which is six times the dose recommended for treatment of SAR;
- Current dosage, formulation, labelling and packaging for unscheduled fexofenadine remains unchanged except for the increase in pack size;
- The proposed increase pack size of fexofenadine would retain the statement to seek medical advice if symptoms persist after 5 days to ensure any consumers who may not be experienced users or who have not previously used it to mitigate the potential for misdiagnosis of any underlying serious symptoms;
- Seasonal allergic rhinitis (SAR) is a common, easily identified condition that is appropriate for self-management. Non treatment of SAR can affect a sufferer's quality of life; and

- The number of adverse events recorded on the TGA's Database of Adverse Event Notifications for the period before and after the availability of unscheduled fexofenadine show an unchanged safety profile.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, the ACMS advice and reasons to amend the Schedule 4 and Schedule 2 entries for fexofenadine. Seasonal allergic rhinitis (SAR) is a common, easily identified condition that is appropriate for self-management where non treatment can affect a sufferer's quality of life. Given fexofenadine's lack of sedative effects and low abuse potential, the increase in pack size will support sufferers of SAR who require more accessible, flexible and convenient pack size to self-manage their condition.

The proposed implementation date is **1 February 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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.

Schedule 4 – Amend Entry

FEXOFENADINE **except**:

a) when included in Schedule 2; or

b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

   i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and

   ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

Schedule 2 –Amend Entry

FEXOFENADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

a) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and

b) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

1.3 2,4-Dinitrophenol

Referred scheduling proposal

An application was submitted to list 2,4-dinitrophenol in Schedule 10 due to there being no appropriate therapeutic use and its high toxicity that it is a danger to health warrants prohibition of sale, supply and use.

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

> **Schedule 10 — New Entry**
>
> *2,4-DINITROPHENOL for human use.*

The applicant's reasons for the request are:

- 2,4-dinitrophenol is a highly toxic substance when ingested, inhaled or absorbed through the skin;
- 2,4-dinitrophenol inhibits efficient energy (ATP) production in cells and leads to rapid consumption of energy without generating ATP and consequently increased fat metabolism, increased oxygen consumption and production of heat;
- In the 1930s, 2,4-dinitrophenol was used as a weight loss agent in the treatment of obesity. Adverse effects included cataracts, renal failure and deaths due to hyperthermia;
- The US FDA banned therapeutic use of 2,4-dinitrophenol for weight loss in 1938;
- In the late 1990s, 2,4-dinitrophenol was promoted to the body building community as a 'fat burner'. There has been renewed interest in the use of 2,4-dinitrophenol among body builders and individuals who are anorexic or bulimic;
- There have been reports of intentional overdoses with 2,4-dinitrophenol;
- There has been a recent increase in deaths associated with the use of 2,4-dinitrophenol, particularly in the UK;
- In late 2015, a young woman died in South Australia after the voluntary consumption of around 50 tablets of an unspecified strength of 2,4-dinitrophenol;
- Users of 2,4-dinitrophenol are sourcing the substance and tablets/capsules via the internet;
- The current human use of 2,4-dinitrophenol is not under medical supervision and presents a significant risk to health; and
- 2,4-Dinitrophenol for human use presents such a danger to health as to warrant prohibition of sale, supply and use.

Substance summary

Developed in the late 19th century, 2,4-dinitrophenol is a synthetic organic disubstituted nitro derivative of phenol, produced by hydrolysis of 2,4-dinitrochlorobenzene. It is used non-medically in manufacturing dyes, as a wood preservative, insecticide and as an indicator. 2,4-Dinitrophenol is a chemical intermediate in the production of sulfur dyes and is also used as an antiseptic, as a herbicide (such as Dinoseb (2,4-dinitro-6-sec-butylphenol) and Dinoterb (2-(2-methyl-2-propanyl)-4,6-dinitrophenol)), as a photographic developer and in the manufacture of explosives.

All dinitrophenols are highly toxic when ingested, inhaled or absorbed through the skin. 2,4-Dinitrophenol inhibits efficient energy adenosine triphosphate (ATP) production in cells and leads to rapid consumption of energy without generating ATP and consequently increased fat metabolism, increased oxygen consumption and production of heat.

The mechanism of action of dinitrophenols involves the uncoupling of mitochondrial oxidative phosphorylation resulting in increased metabolism of lipids. This effect led to use of 2,4-dinitrophenol in weight loss tablets in the early 1930s. Adverse effects including cataracts, renal failure and deaths due to hyperthermia were attributed to use of 2,4-dinitrophenol. It was banned for weight loss purposes by the US Food and Drugs Administration (FDA) in 1938. The epidemiological features of the cataracts suggest an idiosyncratic reaction more than toxicity. There has been renewed interest in the use of 2,4-Dinitrophenol as a 'fat burner' among body builders. There have been reports of misuse of 2,4-Dinitrophenol by anorexic and bulimic individuals and in intentional overdoses.

The use of high doses as a dieting aid has been associated with severe side-effects, including death. 2,4-Dinitrophenol is rapidly absorbed through the gastrointestinal tract, respiratory tract and intact skin. Potential symptoms of overexposure include: marked fatigue, tremendous thirst, profuse sweating, flushing of face, nausea, vomiting, abdominal pain, diarrhoea, restlessness, anxiety, excitement, rise in body temperature, tachycardia, hyperpnoea, dyspnoea, cyanosis, muscle cramps, kidney and liver injury.

Acute oral exposure to 2,4-dinitrophenol has resulted in hyperthermia, nausea, vomiting, sweating, dizziness and headache. Subacute oral exposure can cause weight loss. Chronic oral exposure can lead to formation of cataracts and skin lesions and effects on the bone marrow, central nervous system and cardiovascular system.

There has been an increase in the number of deaths associated with use of 2,4-dinitrophenol since 2001. The main effects seen in patients who die as a result of poisoning with 2,4-dinitrophenol include profuse sweating, tachycardia, tachypnoea and hyperthermia.

2,4-Dinitrophenol is a yellow crystalline solid. It is volatile with steam and is soluble in most organic solvents as well as aqueous alkaline solutions. The chemical structure of 2,4-dinitrophenol is shown in Figure 1.3 and a summary of its chemical properties are described in Table 1.3.

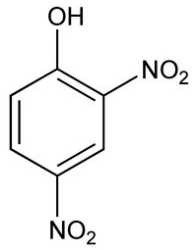


Figure 1.3: Structure of 2,4-Dinitrophenol

Table 1.3 General chemical information 2,4-dinitrophenol

IUPAC name	2,4-Dinitrophenol
Molecular formula	$HOC_6H_3(NO_2)_2$
Molecular weight	184.106 g/mol
CAS No.	51-28-5

Specific questions raised by the delegate

The delegate asked the committee (based on toxicity, morbidity and evidence of misuse) whether 2,4-dinitrophenol should be listed in Schedule 10 or whether another schedule was more appropriate.

Current scheduling status

2,4-Dinitrophenol (CAS No. 51-28-5) is not specifically scheduled in the SUSMP.

There are three class entries for dinitrophenols in the SUSMP as follows:

Schedule 7

DINITROPHENOLS except when included in Schedule 4 or 6.

Schedule 6

DINITROPHENOLS and their homologues in preparations containing 5 per cent or less of such compounds except:

a) when included in Schedule 4; or

b) when separately specified in this Schedule.

Schedule 4

DINITROPHENOLS for therapeutic use.

Appendix E, Part 2 – A, G1, E1, S1

Appendix F, Part 3 except when for therapeutic use – 1, 4, 8

Appendix J, Part 2 – 1

Relevant scheduling history

2,4-Dinitrophenol (CAS No. 51-28-5) is not specifically scheduled in the SUSMP.

In January 1955, dinitrophenols were considered by the National Drugs and Poisons Schedule Committee (NDPSC) and included Schedule 4 and in Schedule 6 for agricultural and horticultural purposes. In November 1955 dinitrophenols were included in Schedule 7 by the NDPSC. In May 1956, dinitrophenols were included in Schedule 1 (substances which are extremely dangerous to human life), Schedule 2 and Schedule 4. In February and April 1963 the NDPSC recommended amendment to Schedule 6 and 7 for dinitrophenols and amended the Schedule 4 entry to include the words 'for therapeutic use'. The Schedule 2 entry was deleted in November 1969. In February 1979, first aid statements A, B, F were included. In February 1983, the first aid statement Q was added.

International regulations

US FDA banned therapeutic use of 2,4-dinitrophenol for weight loss in 1938.

The United Kingdom's Food Standards Agency identifies DNP as "an industrial chemical known to have serious short-term and long-term effects, which can be extremely dangerous to human health." and advises "consumers not to take any product containing DNP at any level. This chemical is not suitable for human consumption."

Pre-meeting public submissions

No submissions were received.

Summary of ACMS advice to the delegate

The committee advised that the proposal to include 2,4-dinitrophenol in Schedule 10 was appropriate.

The ACMS advised an implementation date of **1 February 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act1989* 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 comprised the following:

- Serious and common adverse effects causing significant toxicity, including death;
- Legitimate industrial uses – pesticide, wood preservative, dyes, photographic developer, and explosive;
- No legitimate therapeutic use;
- Serious evidence of misuse; and
- Education at state level is needed due to the high toxicity of the substance.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes and accepts the ACMS advice and reasons to create a new Schedule 10 entry for 2,4-dinitrophenol for human use. Schedule 10 is the most appropriate schedule for 2,4-dinitrophenol owing to its range of serious acute and chronic adverse effects causing significant toxicity and morbidity. Furthermore, although there are legitimate uses of 2,4-dinitrophenol – pesticide, wood preservative, dyes, photographic developer, and explosive – there are no legitimate therapeutic uses. There is also evidence of serious misuse of 2,4-dinitrophenol.

The proposed implementation date is **1 February 2017.**

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989:* (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.

Schedule 10 – New Entry

2,4-DINITROPHENOL for human use.

Schedule 7 – Amend Entry

DINITROPHENOLS except when included in Schedule 4, 6 or 10.

1.4 *N,N*-Dimethyltrypamine

Referred scheduling proposal

An application was submitted to amend the Schedule 9 entry for *N,N*-dimethyltryptamine (DMT) to be for human or therapeutic use except for oral use in liquid form where the concentration of naturally occurring DMT is 0.25 mg/mL or less.

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

> **Schedule 9 – Amend Entry**
>
> *N,N*-DIMETHYLTRYPTAMINE (DMT) *for human or therapeutic use* ***except*** *for oral use in liquid form where the concentration of naturally occurring DMT is 0.25 mg/mL or less.*
>
> The applicant's reasons for the request are that DMP is an entheogen within Hoasca Tea and is a necessary and essential part of the manifestation of the The Beneficient Spiritist Centre Uniao do Vegetal (UDV) religious group. Members of the UDV receive communion through Hoasca tea. It is a sacrament in their religion and orally ingested at UDV ceremonies.

Substance summary

N,N-Dimethyltryptamine is a psychedelic tryptamine alkaloid with an indole ring structure. The substance occurs naturally in plants with hallucinogenic properties. A summary of its chemical properties are described below in Table 1.4 and its structure is shown in Figure 1.4.

Table 1.4: General information for N,N-dimethyltryptamine

INN/BAN	*N,N*-Dimethyltryptamine
Chemical name	*N,N*-Dimethyl-1*H*-indole-3-ethanamine; 3-[2-(dimethylamino)ethyl]indole; DMT
Molecular formula	$C_{12}H_{16}N_2$
Molecular Weight	188.27
CAS No.	61-50-7

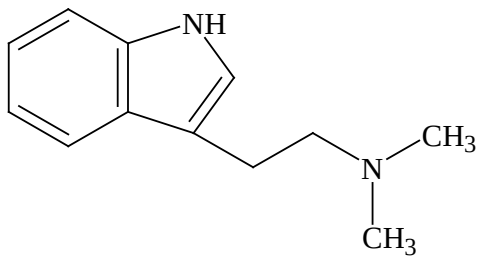


Figure 1.4: Structure of *N,N*-dimethyltryptamine

The basis of this application is that the entheogen Hoasca tea is a sacrament which has been used in religious ceremonies by The Beneficent Spiritist Centre Uniao do Vegetal (UDV) religious society for over 50 years.

Hoasca

- Hoasca is produced by boiling parts of the bark of the plant *Banisteriopsis caapi* (known as Mariri) which contains B-carboline alkaloids, with the leaves of a companion plant namely, the shrub *Psychotria viridis* (known as Chacrona). The maceration of the plants takes place during a ceremony called a "preparo";
- The companion plant; Chacrona, contains a substance called DMT. When sections of Mariri are boiled with the leaves of the companion plant, the resulting brew is considered a "union of the plants'' and is consumed orally;
- It is believed that the harmala alkaloids contained in the tea, namely harmine, harmaline and tetrahydroharmine, inhibit monoamine oxidase (MAO) in the body that would ordinarily destroy orally administered DMT, making it orally active. If DMT were to be ingested without an MAO inhibitor, the MAO contained in the gastrointestinal tract and liver would metabolise the DMT before it reached the brain. The MAO inhibitor in Hoasca has the effect of delaying this process by inhibiting the enzyme MAO. The scientists Goodman & Gilman (The Pharmacological Basis of Therapeutics, 8th. edition): "DMT is a psychoactive substance with hallucinogenic effects when it's smoked, snorted or injected, but it's inactive when orally ingested"; and
- A number of religious movements use a similar, but not identical substance as a sacrament. Those substances are commonly referred to as Ayahuasca; meaning "vine of the soul" in the language of the Quechua people who are indigenous to the Amazonian regions of Peru and Ecuador. The various sacraments are also referred to as Daime, Vegetal, Caapi, Yagé, Mihi, Dapa, Naterma and Pinde.

Specific questions raised by the delegate

The delegate asked the committee the following questions:

1. Is it appropriate to exclude DMT for oral use in liquid form where the concentration of naturally occurring DMT is 0.25 mg/mL or less?
2. What is the risk of low concentration DMT?
3. If the request is supported how would a strength solution be regulated or should it have a maximum amount of DMT as well?

Current scheduling status

N,N-Dimethyltryptamine (DMT) is currently listed in Schedule 9.

Relevant scheduling history

In June 1967, DMT was placed in a new Schedule 7 entry. In July 1976, the committee recommended numerous hallucinogenic substances be included in a prohibited list. This included DMT.

National Drugs and Poisons Schedule Committee: June 2010

The NDPSC considered the scheduling of entheogenic substances (psychoactive substances used in a religious, shamanic or spiritual context) used in a religious, shamanic or spiritual context. Entheogens are used to supplement various practices for healing and transcendence, including in meditation, psychonautics, art projects, and psychedelic therapy. Historically, entheogens were mostly derived from plant sources, however there now exist many synthetic substances with similar psychoactive properties. Examples of traditional entheogens were included ayahuasca and acacia (both containing *N,N*-dimethyltryptamine [DMT]), cannabis, and kava.

Members of the NDPSC recalled the 2007 Hanes v Human Rights and Equal Opportunity Commission (HREOC) and Commonwealth of Australia legal proceedings, where the November 2001 NDPSC decision to include Salvia divinorum in Schedule 9 was challenged. The applicant in these proceedings claimed that the committee's action manifested a restriction on his human rights to access Salvia divinorum as part of the practice of his spiritual beliefs.

The judgement upheld the committee's action, noting that the Schedule 9 decision was based upon considerations of public health and safety and that the manifestation of one's religion or belief may be subject to limitations prescribed by law and which are necessary to protect public health and safety.

Members noted that a majority of substances with potential entheogenic uses were included in Schedules 4, 8 and 9.

It was generally agreed that in scheduling a substance, the committee gives extensive consideration to the substance's risk profile and potential use patterns prior to making a decision. Members agreed that the use of a substance in an entheogenic context would not diminish a substance's potential associated risk to public health.

The committee further noted that the 2007 Hanes v HREOC and the Commonwealth decision confirmed that the committee could schedule entheogenic substances in order to protect public health and safety.

In June 2010, the committee agreed that the current scheduling of entheogenic substances remained appropriate.

Pre-meeting public submissions

Fifteen (15) Public submissions were received.

All 15 submissions supported the proposal. The main points were that federal regulation required the allowance for religious/spiritual use of DMT under a controlled safe environment, that the current scheduling places restrictions on religious freedoms and that there are potential medical benefits.

The public submissions are available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the current scheduling for DMT remained appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the committee 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 advice comprised the following:

- The proposed use of naturally occurring DMT at low concentrations is for religious purposes as an entheogen. However, managing safety risks within this context is not clear;
- Toxicity - the evidence is not clear for low doses. At high concentrations DMT has been reported to have marked psychotropic responses as well as common physical effects such as diarrhoea and vomiting;
- There is a lack of safety data regarding consumption of low doses of naturally occurring DMT at concentrations of than 0.25mg/mL used in a religious context. It is unlikely that psychoactive effects occur with DMT in the absence of harmaline alkaloids of which concentrations probably need to be approximately 2%;

- The potential interaction with other foods and common medicines (such as SSRI antidepressants) presents a significant risk that needs further investigation. To what extent that they are problematic at low concentrations is unclear. Further safety studies are required for low dose toxicity;
- No information was provided on how brewing the tea would ensure levels of DMT would not exceed 0.25%. International evidence suggests levels of 0.25% would be exceeded;
- Potential for abuse has been reported and is likely to be similar to other compounds such as mescaline, peyote etc. Risks of dependence are unknown when used at low concentrations;
- DMT and harmala alkaloids should be considered as entheogens together in the same application; and
- It is unclear that the proposed use justifies the public health risks of this substance.

Delegate considerations

The delegate considered the following in regards to this application:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, the ACMS advice and reasons that the current Schedule 10 entry for *N,N*-dimethyltryptamine remains appropriate. The proposed use of naturally occurring *N,N*-dimethyltryptamine is for religious purposes at low concentrations as an entheogen. While the evidence of toxicity of *N,N*-dimethyltryptamine consumption at low concentrations is lacking, at high concentrations *N,N*-dimethyltryptamine has been reported to have marked psychotropic responses as well as common physical effects such as diarrhoea and vomiting. It is not clear how the safety risks within the religious context will be managed. Furthermore, the potential for abuse has been reported and is likely to be similar to other compounds such as mescaline, peyote etc. Risks of dependence and food interactions are unknown when used at low concentrations. It is unclear that the proposed use justifies the public health risks of this substance.

An implementation date is not relevant given there will be no change to the SUSMP as a result of this interim decision.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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.

1.5 Piper methysticum (kava)

Referred scheduling proposal

An application was submitted to amend part a) of the Schedule 4 entry for piper methysticum (kava) to exempt powdered and liquid preparations of piper methysticum (kava) dosage forms not exceeding 3 g, and where containing more than 25 mg of kavalactones per dose, compliant with the requirements

of the Medicines Advisory Statements Specification. It is also proposed that there is the addition of the mandatory warning statement "Do not exceed recommended daily dose" to be added to all kava packaging.

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

Schedule 4 – Amend Entry

PIPER METHYSTICUM (kava) in preparations for human use except when included on the Australian Register of Therapeutic Goods in preparations:

a) for oral use when present in tablet, capsule, *powder, liquid* or teabag form that is labelled with a recommended maximum daily dose of 250 mg or less of kavalactones and:

i) the tablet or capsule form contains 125 mg or less of kavalactones per tablet or capsule; or

ii) the amount of dried whole or peeled rhizome in the teabag does not exceed 3 g; and, where containing more than 25 mg of kavalactones per dose, compliant with the requirements of the Required Advisory Statements for Medicine Labels; or

iii) the amount of dried whole or peeled rhizome in the unit dose of powder does not exceed 3 g; and

where containing more than 25 mg of kavalactones per dose, compliant with the requirements of the Medicines Advisory Statements Specification 2014;

and is packaged with a dose controlled measuring device (Scoop);

and is limited to a maximum quantity of 200 g of powder per package; or

iv) the liquid form contains 125 mg or less of kavalactones per unit dose of liquid;

and, where containing more than 25 mg of kavalactones per dose, compliant with the Medicines Advisory Statements Specification 2014;

and is packaged in a single serve packaging.

b) in topical preparations for use on the rectum, vagina or throat containing dried whole or peeled rhizome or containing aqueous dispersions or aqueous extracts of whole or peeled rhizome; or

c) in dermal preparations.

It is also proposed that there is the addition of the mandatory warning statement "Do not exceed recommended daily dose" to be added to all kava packaging as follows:

Medicines Advisory Statements Specification - New warning statement

WARNING: Do not exceed recommended daily dose.

The applicant's reasons for the request are:

- Current regulations in Australia pertaining to kava are the result of both the potential for hepatotoxicity and reported abuse in Indigenous communities in Australia;
- The rhizome of piper methysticum (kava), indigenous to the South Pacific, has a proven history of use as an effective treatment for anxiety through folk and contemporary medicine;

- The yearly state-of-the-nation survey Stress and wellbeing in Australia 2014, has highlighted a yearly incremental increase in the levels of stress and anxiety in the Australian population since it began in 2011;
- This increase in stress and anxiety in the Australian population calls for assessment of effective strategies for helping to manage anxiety and promote greater health and wellbeing within the community;
- Evidence suggests that some specific dosage forms are more difficult for members of the community suffering from stress and anxiety to adhere to due to difficulties swallowing tablets and capsules meaning less access to effective treatment;
- Current exceptions to the SUSMP exclude powder and liquid preparations for kava;
- The proposed new dosage form poses no further risk to the community than those currently approved for use; and
- The use of kava as an effective anxiolytic is well established, with benefits to the community particularly in relation to stress and anxiety.

Substance summary

Kava is the rhizome of piper methysticum (piperaceae), a shrub indigenous to islands of the South Pacific.

The major chemical constituents of kava are kava lactones (also known as kava pyrones) with the major lactones being kawain (1.8%), methysticin (1.2%), dihydromethysticin (0.5%), emethyoxyyangonin (1.0%), yagonin (1.0%) and dihydrokawain (1.0%). At least 13 other lactones, two chalcones and a number of free aromatic acids are known.(1) The structures of the representative lactones are presented below in Figure 1.5.

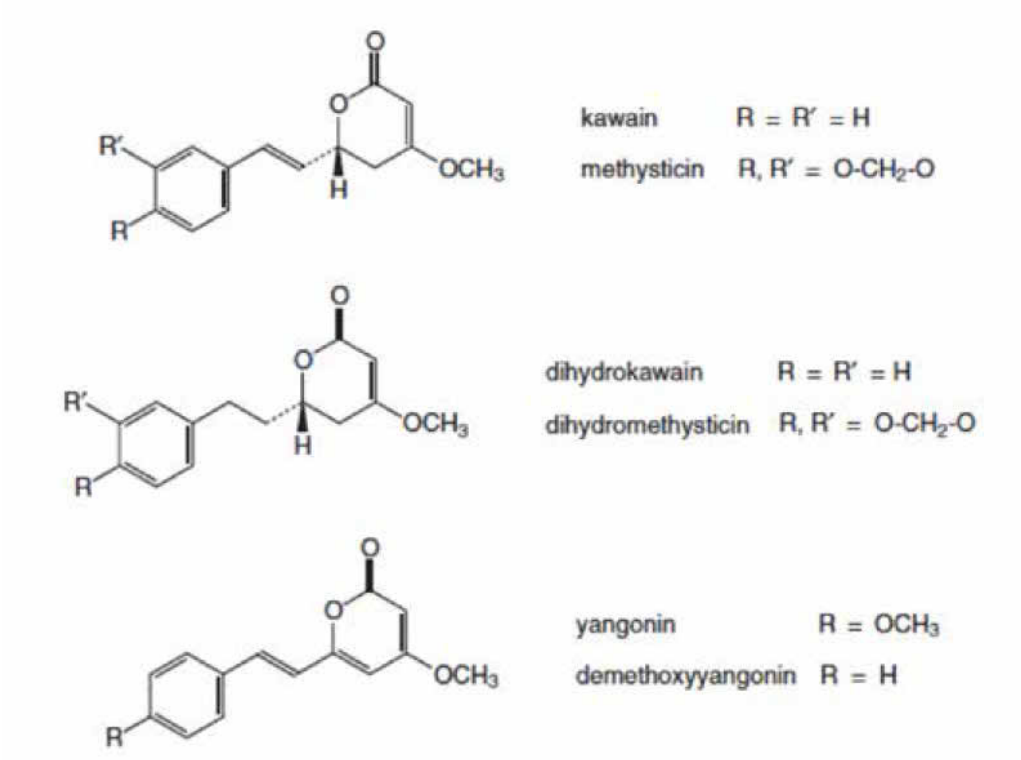


Figure 1.5: Chemical structure of isolated kava lactones

There have been concerns over hepatotoxicity, which have lead to kava's use being restricted in Australia by way of addition to Schedule 4 of the SUSMP and it has also been withdrawn or restricted for use in other parts of the world.

Hepatotoxicity was not an established health issue of kava, over the centuries of traditional kava use, and it appears that the primary cause of toxicity is most likely attributable to poor quality of the raw material caused by bacterial and/or mould hepatotoxins. Other issues may be the forms, including plant parts and incorrect cultivars of kava and potential adulteration however further research is required to elucidate the exact cause and currently the most convincing argument is for a plan for rigorous testing of kava raw materials as well as kava standardisation and manufacturing quality standards put forward by kava researchers Teschke and Sarris (2011).

Kava is a psychotropic plant medicine that has anxiolytic activity. This effect is achieved through modulation of GABA activity via alteration of lipid membrane structure and sodium channel function, monoamine oxidase B inhibition, and noradrenaline and dopamine re-uptake inhibition.

Kava has been used in the South Pacific to produce an intoxicating beverage for recreational purposes and during convalescence. Traditionally, a beverage is prepared, then drunk before the evening meal. It is reported to have sedative, skeletal muscle relaxant, and anaesthetic properties. It is given in some anxiety and stress related disorders. Kawain has also been used for nervous disorders and as a tonic.

Specific questions raised by the delegate

The delegate asked the committee the following questions:

1. Does the application provide any new information from that considered by ACMS in 2011?
2. Is it appropriate for liquid and powder preparations of PIPER METHYSTICUM (kava) as in the proposal to be exempt from Schedule 4 of SUSMP?
3. Does the risk of misuse and abuse of liquid and powder preparations of kava that are not for medicinal use fit an unscheduled product?
4. Do the current jurisdictional controls still allow appropriate access for traditional use?

Current scheduling status

Piper methysticum is currently listed in Schedule 4 of the SUSMP.

Schedule 4

PIPER METHYSTICUM (kava) in preparations for human use except when included on the Australian Register of Therapeutic Goods in preparations:

a) for oral use when present in tablet, capsule or teabag form that is labelled with a recommended maximum daily dose of 250 mg or less of kavalactones and:

   i) the tablet or capsule form contains 125 mg or less of kavalactones per tablet or capsule; or

   ii) the amount of dried whole or peeled rhizome in the teabag does not exceed 3 g;

   and, where containing more than 25 mg of kavalactones per dose, compliant with the requirements of the Required Advisory Statements for Medicine Labels;

b) in topical preparations for use on the rectum, vagina or throat containing dried whole or peeled rhizome or containing aqueous dispersions or aqueous extracts of whole or peeled rhizome; or

c) in dermal preparations.

Relevant scheduling history

National Drugs and Poisons Schedule Committee: October 2003

The committee noted a safety evaluation report prepared by the Kava Evaluation Group/ Office of Complementary Medicines on kava containing medicines, which made recommendations on the regulation of kava as an ingredient in Listed Medicines. Due to the potential risk of liver toxicity from use of non-aqueous extracts of kava plants at high doses, the committee considered there was a need to restrict the use of alcohol/acetone extracts of kava, including those for bulk supply to health care practitioners for use in extemporaneous compounding.

National Drugs and Poisons Schedule Committee: February 2004

The committee was advised that the Complementary Medicines Evaluation Committee (CMEC) Recommendation 41.3 regarding the listing and registration of kava had been included in Schedule 4 of the Therapeutic Goods Regulations 1990 (TG Regulations). This recommendation only allowed specified concentrations of aqueous kava extracts in Listed Medicines and required that all other kava products be cancelled from the ARTG. The committee agreed to foreshadow the inclusion of kava in Schedule 4 of the SUSDP with exemptions consistent with those specified in the TG Regulations.

National Drugs and Poisons Schedule Committee: June 2004

The committee, on the grounds of public health and safety, agreed to include kava in Schedule 4, as well as adopting exemptions as specified in the TGA Regulations 1990. The decision made all kava Schedule 4 except dried whole or peeled rhizome, its aqueous dispersions or extracts, tablets of 125 mg or less of kavalactones per tablet, teabags of up to 3 g kava, and not more than 25 mg of kavalactones per dose.

National Drugs and Poisons Schedule Committee: October 2005

The committee confirmed that all parts of the Schedule 4 exemption for oral use for kava required the mandatory warning statement. The committee agreed that the only exception to this should be for preparations containing less than 25 mg kavalactones and agreed to amend the Schedule 4 entry for kava to clarify this ambiguity.

National Drugs and Poisons Schedule Committee: October 2007

The committee considered a proposal from the Office of Chemical Safety (OCS) which requested the removal of the current exemption from scheduling for the whole or peeled rhizome of kava. This request was part of the Australian Government's efforts to reduce the abuse of the substance in some indigenous communities. The committee agreed to foreshadow consideration of this issue at the February 2008 NDPSC Meeting.

National Drugs and Poisons Schedule Committee: February 2008

The committee considered the Schedule 4 entry for piper methysticum (kava). In light of an Australian Government kava policy decision, the committee reconsidered the restrictions for kava and concluded that the potential for abuse and the hazard to public health of the whole or peeled rhizome meant that this form of kava should no longer be exempt from scheduling. The committee therefore amended the Schedule 4 entry so that only some products on the ARTG were not captured.

National Drugs and Poisons Schedule Committee: June 2009

The committee considered the scheduling of piper methysticum (kava) and decided that the current scheduling for piper methysticum remains appropriate.

Pre-meeting public submissions

Four (4) public submissions were received.

All 4 submissions supported amendment (iii) of the proposal. The main points were that kava has a long history of use, well-researched toxicity, low relative potential for abuse, and very significant positive benefits, both demonstrated and potential.

Two (2) submissions provided alternative wording for amendment (iv) and the additional mandatory warning label. The main points were:

- Consideration regarding ability to provide packs for extemporaneous dispensing larger than the proposed limitation; and
- Mandatory warning label potentially problematic as it is unclear if it refers to bulk supplies or dispensed product in the extemporaneous context.

The public submissions are available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the delegate that the current scheduling remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the committee 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; (e) the potential for abuse of a substance; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- Cultural use has a long history where the drink is consumed for sense of relaxation, tranquillity and to manifest sociable attitude, however there is a high potential of recreational misuse in localised communities;
- Liver toxicity is a known adverse effect with kava. Elevated liver enzymes on exposure return to normal levels upon ceasing or reducing kava consumption;
- Long term consumption of kava can lead to toxic effects, such as dry and scaly skin which is reversible on cessation;
- There are serious concerns that kava powder and liquid forms would be misused and does not support down-scheduling of kava powder from Schedule 4. Several jurisdictions have had historical problems with misuse, especially with the powder forms and liquid form, but the latter to a lesser extent;
- There are concerns that people ingesting drinks prepared from either liquid or powdered forms would not know the level of kava contained in the preparations. In comparison, an individual would be able to readily identify the number of tablets they consume;
- Pre-packaged liquid doses might promote the mixing of the liquid dose in other drinks, and this may lead to serious concerns about the ability of children to access mixed drinks;
- In 2008, the whole or peeled rhizomes and aqueous dispersions of kava were removed from the SUSMP, and despite reconsideration by the scheduling committee in 2011, the scheduling of kava has remained unchanged. In this proposal, no further information was provided to support a change in the scheduling of kava; and
- Kava would be more open to misuse, with no particular health benefit, by permitting kava to become available in powder or liquid form.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes and accepts the ACMS advice and reasons that the current Schedule 4 entry for piper methysticum (kava) remains appropriate. The scheduling application has presented no further information to support a change in the scheduling of kava. There is a long history of cultural use for piper methysticum (kava) where the drink is consumed for sense of relaxation, tranquillity and to manifest sociable attitude. However, there is a high potential of recreational misuse in localised communities. Long term consumption of kava can lead to toxic effects, such as liver toxicity and dry/scaly skin, which is reversible on cessation. There are serious concerns that kava would be more open to misuse, with no particular health benefit, by permitting kava to become available in powder or liquid form. Several jurisdictions have had historical problems with misuse, especially with the powder and liquid (to a lesser extent) forms. While an individual would be able to readily identify the number of kava tablets they consume, there are concerns that people ingesting drinks prepared from either liquid or powdered kava forms would not know the level of kava contained in the preparations. Furthermore, pre-packaged liquid doses might promote the mixing of the liquid dose in other drinks, and this leads to serious concerns about the ability of children to access mixed drinks.

An implementation date is not relevant given there will be no change to the SUSMP as a result of this interim decision.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989:* (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; (e) the potential for abuse of a substance; (f) any other matters that the Secretary considers necessary to protect the public health.

2. Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (ACCS/ACMS#13)

Summary of delegates' interim decisions

Substance	Interim decision
Geraniol and related compounds	**Schedule 6 – New Entry** 3,7-DIMETHYL-2,6-OCTADIEN-1-OL and its isomers **except** in products containing 5 per cent or less 3,7-dimethyl-2,6-octadien-1-ol and its isomers. **Index – New Entry** 3,7-DIMETHYL-2,6-OCTADIEN-1-OL cross reference: GERANIOL, NEROL, CITROL Schedule 6 Appendix E, Part 2 Appendix F, Part 3 **Appendix E –** 3,7-DIMETHYL-2,6-OCTADIEN-1-OL 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), S1 (if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water). **Appendix F** – 3,7-DIMETHYL-2,6-OCTADIEN-1-OL Warning statement: 5 (irritant). Safety directions: 1 (avoid contact with eyes), 4 (avoid contact with skin). Proposed implementation date: **1 June 2017**
Hexachlorophene	**Schedule 6 – Amend Entry** HEXACHLOROPHENE: a) in preparations for the treatment of animals; or b) for cosmetic use. **Schedule 2 – Amend Entry** HEXACHLOROPHENE in preparations for human use containing 3 per cent or less of hexachlorophene **except**: a) in preparations containing 0.75 per cent or less of hexachlorophene; or b) in preparations for use on infants, as specified in Schedule 4; or

	c) when separately specified in these Schedules. Proposed implementation date: **1 February 2017**
Phenol	**Schedule 6 – Amend Entry** PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, **except**: a) when separately specified in these Schedules; or b) in preparations containing 1 per cent or less of phenols, and in preparations containing 3 per cent or less of cresols and xylenols and other homologues of phenol. **Schedule 5 – Amend Entry** PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, when in animal feed additives containing 15 per cent or less of such substances, **except** in preparations containing 1 per cent or less of phenol and in preparations containing 3 per cent or less of cresols and xylenols and other homologues of phenol. **Schedule 2 – Amend Entry** PHENOL, or any homologue boiling below 220°C for human therapeutic use, **except**: a) when included in Schedule 4; or b) in preparations for external use containing 1 per cent or less of phenol and in preparations for external use containing 3 per cent or less of cresols and xylenols and other homologues of phenol. **Appendix E** – PHENOL when included in Schedule 6. 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). Warning statements: 3 (corrosive liquid), 51 (irritant to skin, eyes, mucous membranes and upper respiratory tract). **Appendix F** – PHENOL when included in Schedule 6. Safety directions: 2 (attacks eyes - protect eyes when using), 4 (avoid contact with skin), 8 (avoid breathing dust (or) vapour (or) spray mist). The committee advised an implementation date of **1 February 2017**.

2.1 Geraniol and related compounds

Referred scheduling proposal

An application was submitted to create a new Schedule 5 or Schedule 6 entry for geraniol and related compounds and to investigate whether an appropriate exemption cut-off is required.

Scheduling history

Geraniol has not been previously considered for scheduling; therefore no scheduling history is available.

Other restrictions for use

Geraniol

Geraniol is a permissible excipient ingredient under subsection 26BB(1) of the *Therapeutic Goods Act 1989* when in topical medicines for dermal application.

This group of chemicals includes geraniol, nerol and citrol. Geraniol (not to be confused with geranial) and nerol are *trans* and *cis* isomers respectively of 3,7-dimethyl-2,6-octadien-1-ol. Citrol (not to be confused with citral) is a 1:1 mixture of geraniol and nerol. They are grouped together here because of their similarity of end use and chemical structures.

The current usage of geraniol and related compound in Australia, outside of cosmetics and OTC medicines, is unclear. Overseas however, these compounds are used as fragrances in cosmetic, domestic, commercial and non-commercial products, including pharmaceuticals. Some restrictions apply to these products.

In EU and New Zealand the use of geraniol and related compounds in cosmetics requires label declaration for levels >0.001% in leave-on products and >0.01% in rinse-off products. In toys, geraniol and related compounds is permitted in EU when 'technically unavoidable' up to 100 mg/kg. In Australia, geraniol is listed as a permitted excipient for topical products for dermal application under the Therapeutic Goods Act and a number of complementary medicines that contain it are listed in the ARTG. In USA, geraniol and nerol are listed as safe for human consumption.

Geranial

Geranial (an oxidised form of geraniol) and related compounds were considered for scheduling by a joint meeting of the ACCS and ACMS in July 2014. At that meeting, the committee advised that cosmetic and household cleaning preparations containing more than 5% of citral be listed in Schedule 5.

The delegates' final decision on geranial was to create a new Schedule 5 entry as follows:

> 3,7-DIMETHYL-2,6-OCTADIENAL and its isomers in cosmetic and household cleaning preparations **except** in preparations containing 5 per cent or less of 3,7-DIMETHYL-2,6-OCTADIENAL isomers.

Other relevant considerations

Public exposure

Although the extent of use in cosmetic and domestic products in Australia is not well known, geraniol is contained within formulations of cosmetic and domestic products (at unspecified concentrations in aerosol/pump spray, liquid, cream and gel personal care products).

The main route of exposure for these products is through skin and eye contact.

Geraniol is listed on the following:

- EU Cosmetics Regulation 1223/2009 Annex III - List of substances which cosmetic products must not contain except subject to the restrictions laid down. '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.
- New Zealand Cosmetic Products Group Standard - Schedule 5: Components cosmetic products must not contain except subject to the restrictions listed above.
- Directive 2009/48/EC of the European parliament and of the Council on the safety of toys – Annex II lists allergenic fragrances toys shall not contain, stating 'however, the presence of traces of these fragrances shall be allowed provided that such presence is technically unavoidable under good manufacturing practice and does not exceed 100 mg/kg.

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

Schedule 6 – New Entry

GERANIOL AND RELATED COMPOUNDS.

The applicant's reasons for the request are:

- Currently, there are no restrictions on introducing or using these chemicals in Australia. In the absence of any regulatory controls, the characterised critical health effects (particularly skin and eye irritation and skin sensitisation) have the potential to pose an unreasonable risk if used in cosmetic products. Whilst domestic use of the chemicals will result in lower levels of exposure, there is sufficient uncertainty regarding the safety of such products to warrant some restriction;
- Although use in cosmetic and/or domestic products in Australia is not known, the chemicals are reported to be used (at unspecified concentrations) in cosmetic and/or domestic products overseas, such as perfumes, hair conditioners and colourants that could result in exposure of the general population;
- The presence of the chemicals in essential oils, the use of which is not subject to existing controls;
- Geraniol, has a labelling restriction under international jurisdictions European Union (EU) Cosmetics Regulation 1223/2009 Annex III – List of substances which cosmetic products must not contain except subject to the restrictions laid down;
- The chemicals have been shown to cause local effects (skin and eye irritation and particularly skin sensitisation) which may occur following exposure to the chemicals;
- Exemptions to scheduling might be applicable at low concentrations;
- Acute oral and dermal toxicity – LD_{50} >2000 (for geraniol and nerol);
- No information on inhalational toxicity. It is a moderate skin irritant in rabbits and a severe irritant in humans. It is a severe eye irritant in rabbits. It is a skin sensitizer in mice (LLNA); and
- Repeat dose toxicity is likely to be associated with local effects (corrosion/irritation). It is not considered to be genotoxic. No data on carcinogenicity. Not considered to be specific reproductive or developmental toxins.

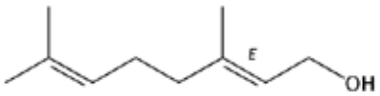
Substance summary

Please refer to the publically available NICNAS IMAP Human Health Tier II group assessment report for geraniol and related compounds.

Grouping rationale

The chemicals in this group (geraniol and related compounds) are the (E)- (geraniol, Figure 2.1A) and (Z)- (nerol, Figure 2.1B) isomers of 3,7-dimethyl-2,6-octadien-1-ol (other names include: i) 2,6-octadien-1-ol, 3,7-dimethyl-; ii) 3,7-dimethyl-2,6,-octadienol and iii) citrol. Citrol (CAS No. 624-15-7) is an approximate 50:50 mixture of the two isomers. The chemicals have been grouped due to their related end-uses and their close chemical relationship based on:

- Structural similarity, where orientation of the substituents differs only around the double bond at C2; and
- Similarity of the physico-chemical properties including melting points, boiling points and water solubility.



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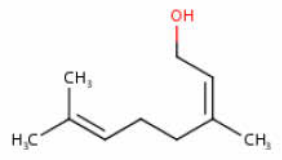

B

Figure 2.1: Geraniol (CAS No. 106-24-1) (A) and nerol (CAS No. 106-25-2) (B)

Acute toxicity

The acute toxicity endpoints for these chemicals are listed in Table 2.1. Briefly, geraniol and nerol have low oral (LD_{50} >2000 mg/kg bw) and dermal toxicity (LD_{50} >2000 mg/kg bw). Based on the available animal data for geraniol and nerol and observations in humans, the chemicals in this group are considered to be moderate to severe skin irritants, severe eye irritants and skin sensitisers (LLNA, EC = 11.4-23%). Geraniol and nerol are not considered to be genotoxic nor a reproductive or developmental toxin. No animal toxicity data are available on the carcinogenicity of the chemicals in this group; however the chemicals in this group present no alerts for mutagenicity or carcinogenicity based on molecular structure as profiled by the OECD Quantitative Structure–Activity Relationship (QSAR) Toolbox v3.2.

Table 2.1: Acute toxicity end-points for geraniol and related compounds

Toxicity	Species	Geraniol and nerol	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	N/A	> 2000 (for geraniol and nerol)	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	> 2000 (for geraniol and nerol)	Appendix B or Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	N/A

Toxicity	Species	Geraniol and nerol	SPF (2015) Classification
Skin irritation	Rabbit	Moderate irritant (geraniol of 90.7 % purity and nerol of unspecified purity)	Schedule 5
	Humans	Severe irritant (conc. 32%) (geraniol of unspecified purity), occlusive patch test (see below)	Schedule 6
Eye irritation	Rabbit	Severe irritant (geraniol and nerol of unspecified purity); irreversible symptoms evident after 7 days post-treatment in all animals	Schedule 6
Skin sensitisation (LLNA)	Mice	Moderate sensitiser with (EC = 11.4-23%) (geraniol of 98.5 % purity and nerol of unspecified purity)	Schedule 6
Genotoxicity	Various	Not genotoxic*	–
Carcinogenicity	–	No animal data Not considered to be carcinogenic based on QSAR*	–
Reproduction and developmental toxicity	Rats	Nerol is negative*; limited data available for other chemicals	–

* See the NICNAS IMAP Human Health Tier II group assessment report for geraniol and related compounds for more information.

Skin irritation

- Geraniol was applied (0.2 mL) in a closed patch test conducted on the upper outer arm of 25 subjects (male and female) between the ages of 18 and 65 years old over four hours (at 15 and 30 minute intervals and also after 1, 2, 3 and 4 hours). Reactions were assessed at 24, 48 and 72 hours after patch removal. Dermal exposure to the substance in humans resulted in irritant effects in 2 out of 25 subjects.
- In another test, 0.05 g of a solution containing 32 % geraniol was applied to the back of each subject for 48 hours. The reactions were read 30 minutes after patch removal and if necessary at 72, 96 and 120 hours after patch removal. The substance was determined to be a severe irritant at 32 % concentration and given an irritation score of 3.

Eye irritation

Based on the available animal data for geraniol and nerol, the chemicals in this group are considered to be severe eye irritants.

- In an acute eye irritation and corrosion study, 0.1 mL of geraniol (purity unspecified) was instilled into the eyes of four female Specific Pathogen Free (SPF) white rabbits which were observed for 21 days (at 1, 24, 48 and 72-hours as well as after 7, 14 and 21 days). Well defined signs of eye

irritation reported 24 hours after exposure included corneal opacity, iris lesion, swelling and crimson red colouration of the conjunctivae. No Draize scores were available. Irreversible symptoms in two out of the four animals were reported after the 21 day observation period.

- In a similar study, 0.1 mL of undiluted nerol was instilled into the eyes of six female New Zealand White rabbits and observed for a period of 7 days (at 24, 48 and 72-hour intervals and then after 4 and 7 days). Nerol was reported to be irritating to the eyes of rabbits, with Draize scores for days 1, 2, 3, 4 and 7 of 31, 21, 15, 5 and 1 (out of a maximum score of 110), respectively. Irreversible effects were reported after the seven day observation period.

Skin sensitisation

Based on the available animal data for geraniol and nerol, the chemicals in this group are considered to be skin sensitisers.

- In a study (OECD TG 429), geraniol (98.5 % purity) was reported to be positive for skin sensitisation in a mouse local lymph node assay (LLNA). Female CBA mice (4/dose) were administered daily applications of 2.5 %, 5 %, 10 %, 25 % or 50 % (w/v) of geraniol in ethanol:diethyl phthalate (ratio of 1:3) for three consecutive days. Stimulation indices of 1.7, 2.4, 2.8, 4.8 and 6.0 were reported, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was reported to be 11.4 %.

- In an additional skin sensitisation study using geraniol (purity unspecified), positive results for skin sensitisation in a CBA mouse LLNA were reported. Mice (3/dose) were administered daily applications of 0 %, 12.5 %, 25 % (w/v) of geraniol in acetone:olive oil (4:1 v/v) for three consecutive days (after being pre-exposed with 50 % of geraniol). No stimulation indices or EC3 values were provided. However, increases of lymph node cell proliferation and lymph node weights were reported at the highest dose.

- Positive results for skin sensitisation were reported for nerol (98.5 % purity) in a mouse local lymph node assay (LLNA). Female CBA/J mice (4/dose) were administered daily applications of 5 %, 10 %, 25 %, 50 % and 100% (w/v) of nerol in acetone/olive oil (4/1; v/v) to the dorsal surface of both ears for three consecutive days. Stimulation indices of 1.10, 1.77, 3.16, 5.12 and 2.47 were reported, respectively. The EC3 value was reported to be 23 %.

- There are limited human data available for the chemicals in this group. Geraniol was reported to cause skin sensitisation in 1 out of 35 subjects (13 male, 22 female) in a human patch test study (where 8 subjects had previous history of eczematous skin and 12 subjects had cosmetic sensitivity). Subjects were dermally exposed under occlusive conditions to geraniol at 5 % over a 48 hour period. Reactions were recorded at 48 and 96 hours post-exposure. However, it was reported that the positive subject had previous signs of eczematous skin (redness, itching and inflammation).

Repeat-dose toxicity

Based on the available animal data for geraniol, repeated oral exposure to the chemicals in this group is not expected to cause adverse systemic toxic effects, but repeated dermal exposure with local effects have been noted.

No information was available for repeated dose toxicity by inhalation route.

Pre-meeting public submissions

One (1) public submission was received that opposed the scheduling on the basis that all companies comply with the International Fragrance Association standard of 0.3-8.6% geraniol, depending on usage. However, if scheduling is deemed necessary, the submission suggests a reverse scheduling entry to include geraniol (excluding salts and derivatives) in Schedule 6 for leave-on products containing >0.0001% and rinse-off products containing >0.001% unless the products are listed on the label. They also request a long lead time to permit label changes.

The public submission is available on the TGA website.

Summary of joint ACMS/ACCS advice to the delegates

The committee advised that a new Schedule 6 entry for geraniol and its isomers be created in the SUSMP as follows:

> **Schedule 6 – New Entry**
>
> *3,7-DIMETHYL-2,6-OCTADIEN-1-OL and its isomers **except** in products containing 5 per cent or less 3,7-dimethyl-2,6-octadien-1-ol and its isomers.*

The committee advised that a cross reference to geraniol, nerol and citrol be created as follow:

> *3,7-DIMETHYL-2,6-OCTADIEN-1-OL*
>
> *cross reference: GERANIOL, NEROL, CITROL*
>
> *Schedule 6*

The committee advised Appendix E and F entries be created as follows:

> **Appendix E** – *3,7-DIMETHYL-2,6-OCTADIEN-1-OL*
>
> *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), S1 (if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).*
>
> **Appendix F** – *3,7-DIMETHYL-2,6-OCTADIEN-1-OL*
>
> *Warning Statement: 5 (irritant).*
>
> *Safety Directions: 1 (avoid contact with eyes), 4 (avoid contact with skin).*

To allow sufficient time for implementation the committee advised an implementation date of **1 June 2017**.

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; and (c) the toxicity of a substance.

The reasons for the advice included:

- Geraniol and nerol are moderate skin irritants and severe eye irritants (consistent with Schedule 6 criteria). Furthermore, there is a risk of skin sensitisation at concentrations greater than 5 per cent;
- There are currently no restrictions on the use of geraniol and related compounds in Australia; and
- Overseas these substances are used in consumer products including cosmetics and household cleaning products. There is the potential for skin and eye contact with these types of products. The extent of use in Australia is not known.

Delegates' considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS/ACMS advice;
- Public Submissions received;

- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegates' interim decision

The delegates note and accept the ACMS-ACCS advice to create a new Schedule 6 entry for 3,7-dimethyl-2,6-octadien-1-ol and its isomers with a cross reference to geraniol, nerol and citrol in the index. The skin and eye irritation data for geraniol and nerol (moderate skin irritant and severe eye irritant) are consistent with the SPF criteria for Schedule 6. Furthermore, there is a risk of skin sensitisation at concentrations greater than 5 per cent. Whilst the extent of use of geraniol and related compounds is not known in Australia, internationally these substances are common in cosmetics and household cleaning consumer products. With products such as these, there is potential for skin and eye contact.

The proposed implementation date is **1 June 2017**. A later implementation date is proposed, in line with the request included in the submission from industry, to allow sufficient time for implementation.

The delegate considered the relevant matters under section 52E (1) of *the Therapeutic Goods Act 1989*: (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; and (c) the toxicity of a substance.

Schedule 6 – New Entry

3,7-DIMETHYL-2,6-OCTADIEN-1-OL and its isomers **except** in products containing 5 per cent or less 3,7-dimethyl-2,6-octadien-1-ol and its isomers.

Index – New Entry

3,7-DIMETHYL-2,6-OCTADIEN-1-OL

cross reference: GERANIOL, NEROL, CITROL

Schedule 6

Appendix E, Part 2

Appendix F, Part 3

Appendix E – 3,7-DIMETHYL-2,6-OCTADIEN-1-OL

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), S1 (if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F – 3,7-DIMETHYL-2,6-OCTADIEN-1-OL

Warning statement: 5 (irritant).

Safety directions: 1 (avoid contact with eyes), 4 (avoid contact with skin).

2.2 Hexachlorophene

Referred scheduling proposal

An application was submitted to create a new Schedule 10 entry to prohibit the use of hexachlorophene in cosmetics.

Scheduling history

Hexachlorophene was originally considered for scheduling in March 1972 by the National Health and Medical Research Council's Poisons Schedule Sub-committee and has been considered a number of times since. In March 1972, the committee considered and advised on new entries for hexachlorophene in Schedules 3 and Schedule 4 with an Appendix A statement given its use as a topical antiseptic. Appendix A imposed a warning statement '*for external washing only, rinse skin thoroughly after use*', for preparations other than that for use on infants, containing 0.75 per cent or less for skin cleansing purposes. In July 1972, the Poisons Schedule Sub-committee considered topical uses of hexachlorophene and advised a new Schedule 2 entry. In November 1974, the Poisons Schedule Sub-committee agreed to amend the existing Schedule 3 and 4 entries and create a new Schedule 6 entry for veterinary use of hexachlorophene. Amendments to the Appendix A warning statements were advised, where the concentration was raised from 0.75 per cent to 3 per cent.

In November 1980, the National Health and Medical Research Council's Poisons Schedule (standing) committee (PSStC) agreed to amend the Schedule 3 entry by removing the clause relating to use as a preservative and an inclusion of a new pregnancy warning statement in Appendix A (*women likely to become pregnant should avoid the use of this product*) was considered. In May 1981, the PSStC noted a report by PHAC that there was an absence of detailed data on absorption through intact skin and teratogenicity of hexachlorophene. The PSStC also considered that a mandatory warning on products containing hexachlorophene may result in their withdrawal from the market, which was of concern due to their use in hospitals as surgical preparations.

In November 1983, PSStC again considered advising on a 15 ppb limit for TCDD in hexachlorophene to align with the British Pharmacopoeia Commission. However in the absence of data on the practicalities of production or the toxicological implications of various levels, no agreement was made.

In August 1984, PSStC considered amending Schedule 2 to limit hexachlorophene to 3 per cent or less in skin cleansing products, and Schedule 4 in preparations for use on infants. In November 1984, the PSStC noted that Victorian Poisons Advisory Committee advised on the inclusion of a warning statement on hexachlorophene products for use in pregnancy, which had been previously raised several times (considerations of teratogenicity and risks to women of child-bearing age were considered in the November 1978, August 1980, February 1982 and November 1983 meetings). The PSStC decided that no alteration to the scheduling of hexachlorophene was warranted.

Current scheduling status

Hexachlorophene is currently listed in Schedules 2, 4 and 6 and Appendix E and F as follows:

Schedule 6

HEXACHLOROPHENE in preparations for the treatment of animals.

Schedule 4

HEXACHLOROPHENE:

a) in preparations for use on infants; or

b) in other preparations **except**:

   i) when included in Schedule 2 or 6; or

   ii) in preparations containing 0.75 per cent or less of hexachlorophene.

Schedule 2

HEXACHLOROPHENE in preparations for human use containing 3 per cent or less of hexachlorophene **except**:

a) in preparations containing 0.75 per cent or less of hexachlorophene; or

b) in preparations for use on infants, as specified in Schedule 4.

Appendix E – HEXACHLOROPHENE when included in Schedule 6.

Standard statement: A [for advice, contact a Poisons Information Centre (e.g. phone Australia 131126; New Zealand 0800 764 766) or a doctor (at once)]

Appendix F – HEXACHLOROPHENE in preparations for skin cleansing purposes containing 3 per cent or less of hexachlorophene.

Warning statement: 24 (for external washing only. Rinse skin thoroughly after use)

Other relevant regulations

Public exposure

Although use in cosmetic and domestic products in Australia is not clearly known, hexachlorophene is available for use in consumer products (not intended for infants) at concentrations up to 0.75% as per the current SUSMP entries.

Non-industrial use is reported for hexachlorophene in Australia, including in medicinal cleansing lotions.

Internationally, the use of hexachlorophene in cosmetics is prohibited in several countries, while use of hexachlorophene as a preservative (at up to 0.1%) in cosmetics is conditionally permitted in the United States of America.

Non-industrial uses of hexachlorophene have been identified internationally, including therapeutic use as a topical anti-bacterial medicine, veterinary use as an anthelminthic (parasite treatment) drug in animals, and agricultural use as a soil fungicide.

Historical use of hexachlorophene as an anti-bacterial ingredient in soaps, lotions and detergents is reported. However, this use is now prohibited in several countries. Notable historical use in detergents is also reported in hospital settings for surgical scrubbing and for washing newborn babies to reduce bacterial infections.

International regulations

Hexachlorophene is prohibited for use in cosmetic products in several countries as according to inclusion in the following listings:

- European Union (EU) Cosmetics Regulation 1223/2009 Annex II - List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard - Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist').

Additionally, there are severe restrictions on use of hexachlorophene in cosmetics in the United States, as according to the following listing by the United States Food and Drug Administration (US FDA):

> 'Hexachlorophene may be used as a preservative in cosmetic products other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available'.

Scheduling application

General application.

The applicant's proposal is to amend the entries in the SUSMP for hexachlorophene to prohibit its use in cosmetic products.

The applicant's reasons for the request are:

- The potential for use of hexachlorophene in cosmetic products in Australia (up to 0.75 % concentration is currently unscheduled);
- Hexachlorophene causes neurotoxic effects following short-term or repeated oral and dermal exposure;
- Hexachlorophene is a suspected developmental toxin;
- Hexachlorophene is acutely toxic following oral or dermal exposure; and
- Hexachlorophene is prohibited for use in cosmetic products in Canada, New Zealand and the European Union, with severely restricted use in cosmetics in the United States of America.

Substance summary

Hexachlorophene (CAS No. 70-30-4) is a white to light-tan, odourless, crystalline powder. While no specific Australian industrial use, import, or manufacturing information has been identified for hexachlorophene, the TGA has identified several non-industrial uses of hexachlorophene in Australia including in medicinal cleansing lotions.

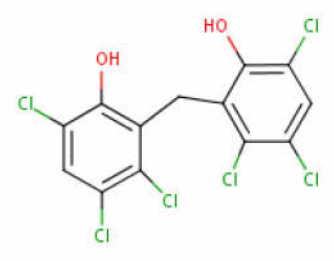

Figure 2.2: Structure of hexachlorophene

Acute toxicity

The acute toxicity end-points for hexachlorophene (Figure 2.2) are listed in the Table 2.2 and are publically available in the NICNAS IMAP Human Health Tier II assessment report for phenol, 2,2'-methylenebis[3,4,6-trichloro-. Briefly, hexachlorophene is classified as hazardous for both oral and dermal exposure routes, with the risk phrases 'Toxic if swallowed' (T; R25) and 'Toxic in contact with skin' (T; R24) in the HSIS. The available data (LD_{50} values and observations in humans) support these classifications. Additionally, hexachlorophene is reported to cause severe (irreversible) sub-lethal effects following short-term oral or dermal exposure to products containing hexachlorophene (at 3 – 6.3 % concentrations). There is no acute inhalation toxicity data available for hexachlorophene and limited data from animal studies and human observations which indicate that hexachlorophene is a potential skin irritant. There is no reliable data available for eye irritation or skin sensitisation. There are several repeat insult patch tests conducted with hexachlorophene in humans, however specific study details are limited. While skin irritation is reported in these studies, no significant effects indicative of skin sensitisation have been observed.

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity assays, hexachlorophene is not considered to be genotoxic; and based on the available data, there is no evidence to indicate that hexachlorophene is carcinogenic.

Table 2.2: Acute toxicity end points for hexachlorophene

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	56 - 66	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	1180	Schedule 6
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	-
Skin irritation	Human, rabbit, guinea pig	Insufficient data	-
Eye irritation	N/A	No data	-
Skin sensitisation	Human	Insufficient data*	-
Genotoxicity	Mice, Human	Not genotoxic*	-
Carcinogenicity	Rats, Mice	Not carcinogenic*	-

* See the NICNAS IMAP Human Health Tier II assessment report for phenol, 2,2'-methylenebis[3,4,6-trichloro-. for more information

Reproduction and developmental toxicity

Hexachlorophene does not show specific reproductive toxicity based on the available information. The reproductive effects were only observed at maternally toxic dose levels. However, based on the available data from experimental studies in animals, hexachlorophene has the potential to cause developmental effects. Reduced survival rate of offspring, in addition to the detection of lesions in the brain of offspring (similar to those reported in repeated oral and dermal toxicity studies in animals and observations in humans), support this conclusion.

Observation in humans

Cases of poisoning, caused by ingestion of products containing hexachlorophene, have been reported. In one case, a product containing hexachlorophene at 3 % in emulsion was mistakenly swallowed by 10 preoperative patients. Reported toxic effects included food aversion, nausea, vomiting, abdominal cramps and diarrhoea. Severe dehydration was also observed.

Dermal application of hexachlorophene to patients with burns, or to infants, has resulted in circulatory failure, effects on the central nervous system (twitching and convulsions) and, in some cases, death. In one notable incident in 1972, hexachlorophene was reported to have been inadvertently added to a talc baby powder product at 6.3 %. Encephalopathy (displayed symptoms of brain dysfunction) and skin lesions were observed in 204 infants and small children exposed to the product, with deaths occurring in 36 children within a few days of exposure. Similar to findings reported in animal studies, brain lesions were commonly reported following autopsy of children that have died following exposure to hexachlorophene.

There are several studies that have examined the prevalence of birth defects and malformations in children of hospital staff who had been regularly exposed to hexachlorophene through hand washing. Some concluded that exposure-related association was observed, while others concluded that there is no association between exposure to hexachlorophene and malformations at birth. However, deficiencies in the study methodologies have been noted in most cases.

Use of hexachlorophene in cosmetic and domestic products in Australia is not known.

Repeat-dose toxicity

There are consistent reports of neurotoxic effects following exposure to hexachlorophene (leg weakness in animals, and tremors and convulsions in humans). Additionally, brain lesions were commonly reported at necropsy in animal exposure studies, including in the offspring of animals exposed to hexachlorophene (in reproductive or developmental toxicity studies), and at autopsy of children that have died following exposure to hexachlorophene.

Pre-meeting public submissions

One (1) public submission was received that supported the scheduling proposal.

The public submission is available on the TGA website.

Summary of joint ACMS/ACCS advice to the delegates

The committee advised that the proposal to create a new Schedule 10 entry for hexachlorophene was inappropriate. The committee advised that the current hexachlorophene Schedule 6 and Schedule 2 entries for hexachlorophene in the SUSMP be amended as follows:

Schedule 6 – Amend Entry

HEXACHLOROPHENE:

a) in preparations for the treatment of animals; *or*

b) *for cosmetic use.*

Schedule 2 – Amend Entry

HEXACHLOROPHENE in preparations for human use containing 3 per cent or less of hexachlorophene **except**:

a) in preparations containing 0.75 per cent or less of hexachlorophene; or

b) in preparations for use on infants, as specified in Schedule 4; or

c) *when separately specified in these Schedules.*

The committee suggested an implementation date of **1 February 2017**.

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 included:

- Hexachlorophene is considered hazardous and acutely toxic;
- Human adverse events have been recorded from both oral and dermal exposure showing neurotoxic side effects (leg weakness in animals, twitching ad convulsions in humans), poisoning (resulting nausea, vomiting, abdominal cramps, diarrhoea and severe dehydration) and death;
- Hexachlorophene is used as a disinfectant and a preservative; and
- The chemical is prohibited for use in cosmetic products in Canada, New Zealand, the European Union, and severely restricted for use in cosmetics in the United States, a similar level of restriction in Australia to mitigate the risks would be appropriate.

Delegates' considerations

The delegate considered the following in regards to this proposal:

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

Delegates' interim decision

The delegates note and accept the ACCS-ACMS advice to amend the Schedule 6 and Schedule 2 entries for hexachlorophene. Given hexachlorophene is considered hazardous and acutely toxic – with human adverse events recorded from both oral and dermal exposure showing neurotoxic side effects (leg weakness in animals, twitching ad convulsions in humans), poisoning (resulting nausea, vomiting, abdominal cramps, diarrhoea and severe dehydration) and death – adding a restriction to preclude its use in cosmetics is appropriate. Furthermore, the amendment to the Schedule 6 entry for hexachlorophene will align Australian regulations for this chemical in regards to its use in cosmetics, with Canada, New Zealand, the United States and the European Union.

The proposed implementation date is **1 February 2017.**

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989:* (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.

Schedule 6 – Amend Entry

HEXACHLOROPHENE:

a) in preparations for the treatment of animals; or

b) for cosmetic use.

Schedule 2 – Amend Entry

HEXACHLOROPHENE in preparations for human use containing 3 per cent or less of hexachlorophene **except**:

a) in preparations containing 0.75 per cent or less of hexachlorophene; or

b) in preparations for use on infants, as specified in Schedule 4; or

c) when separately specified in these Schedules.

2.3 Phenol

Referred scheduling proposal

An application was submitted to amend the existing Schedule 6 entry for phenol to include cosmetic use with an appropriate concentration cut-off and to consider appropriate Appendix E and F statements.

Scheduling history

Phenols were first included in Schedule 2 in January 1955 as carbolic acid (phenol), cresylic acid and other homologues containing 3% or more by weight of such poison except (a) in the provisions of Schedules 5 or 6; (b) in smelling salts; (c) a compound of a phenol with a metal. The Schedule 5 entry for carbolic acid was for all liquid substances containing less than 3% by weight of phenol or its homologues for use as a disinfectant. An entry was also included in Schedule 5 as phenyle when containing less than 3% phenol or its homologues for use as a disinfectant. Phenol and homologues (all preparations containing more than 3% of such substance) were also included in Appendix 1, advising on a statement requirement for the poison. There was no specific entry for phenol or carbolic acid in Schedule 6.

In February 1991, the Drugs and Poisons Schedule Standing Committee (DPSSC) considered an apparent conflict between entries in Appendix E for phenols and xylenols. The committee advised that standard statement 'J' be modified by the addition of "do not induce vomiting" in order to make it clearer. The committee felt that this proposal should be brought back to committee when a review of the issue of first aid for phenolic substances had been completed.

In August 1994, editorial amendments were made to the Schedule 2 entry for phenol to specify preparations for external use containing 3 per cent or less of phenol for human therapeutic use.

In November 1998, the National Drugs and Poisons Committee (NDPSC) agreed with working party recommendations to the New Zealand Ministry of Health to amend the Schedule 1 entry for phenol. The recommendations included adoption into Part 1, Schedule 1 of the Medicines Act of Phenol in medicines for injection, amendment of the part III entry to include phenol, in medicines other than for injection, containing more than 3 per cent of phenol. The committee deferred advice to remove the words ‘for therapeutic use’ from the current Schedule 4 entry for phenol, remove the wording ‘For Human therapeutic use’ in Schedule 2 and temperature references were replaced with separate entries for phenol, cresol and xylenol and replace the Schedule 6 entry with phenol, (including cresols and xylenols) or any homologue of phenol boiling below 220 degrees Celsius, except (a) for therapeutic use (b) in preparations containing 3 per cent or less of such substances.

Between February 1999 and February 2000, the National Drugs and Poisons Schedule Committee (NDPSC) considered a proposal to delete the words ‘therapeutic use’ from Schedule 4 and 2 entries for numerous substances, including phenols. It was agreed to amend the entries to remove this wording in February 2000.

Between February 2001 and October 2002, the National Drugs and Poisons Schedule Committee (NDPSC) considered the first aid instruction Appendix E Part 2 statements for phenols, replacing a,c,j,s with A, G3, E2, with S3 for concentrations below 25% phenols. The committee also agreed that the statement S4 should be included in first aid instructions (instead of S3) for phenols at concentrations above 25 per cent.

Current scheduling status

Phenol is currently listed in Schedule 6 for industrial use with a number of exceptions. It is also listed in Schedules 2, 4 and 5 for non-industrial uses. The Schedule 5 entry relates to use in animal feed.

Phenol

Schedule 6

PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, **except**:

a) when separately specified in these Schedules;

b) when included in Schedule 5; or

c) in preparations containing 3 per cent or less of such substances.

Schedule 5

PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, when in animal feed additives containing 15 per cent or less of such substances, **except** in preparations containing 3 per cent or less of such substances.

Schedule 4

PHENOL in preparations for injection.

Schedule 2

PHENOL, or any homologue boiling below 220°C, for human therapeutic use **except**:

a) when included in Schedule 4; or

b) in preparations for external use containing 3 per cent or less of such substances.

Appendix E

PHENOLS:

Standard statements:

- at 25 per cent and less: 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)], G3 (If swallowed, do NOT induce vomiting), 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), S3 (If on skin, remove any contaminated clothing, wash skin thoroughly with soap and water, then methylated spirit if available. Contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor)
- above 25 per cent: 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)], G3 (If swallowed, do NOT induce vomiting), 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), S4 (If on skin, immediately remove any contaminated clothing, wash skin with methylated spirit or PEG (polyethylene glycol) 300 or 400 if available, then flush under running water until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor)

PHENOLS in pressurised spray packs:

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

PHENOL and any other homologue of phenol:

Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin)

Safety direction: 5 (Wear protective gloves when mixing or using)

Creosote

Schedule 6

CREOSOTE derived from wood other than beechwood **except**:

a) when included in Schedule 2;

b) in preparations for human therapeutic use containing 10 per cent or less of creosote derived from wood other than beechwood; or

c) in other preparations containing 3 per cent or less of phenols and homologues of phenol boiling below 220°C.

Cresols

Appendix E

CRESOLS

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)], G3 (If swallowed, do NOT induce vomiting), 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), S3 (If on skin, remove any contaminated clothing, wash skin thoroughly with soap and water, then methylated spirit if available. Contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor)

CRESOLS in pressurised spray packs:

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)], G6 (If sprayed in mouth, rinse mouth with water), 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)

Other relevant information

Public exposure

Although use in cosmetic and domestic products in Australia is not known, phenol has reported cosmetic and domestic uses overseas, where the general public may be exposed to phenol through dermal and/or inhalation routes.

Internationally phenol has reported potential domestic use including as a general disinfectant and in adhesives, paints, lacquers and varnishes. Phenol has reported cosmetic use with the following functions:

- antimicrobial;
- deodorant;
- denaturants;
- masking;
- oral care; and
- preservative.

Whilst use in cosmetics is prohibited in some countries there is reported use of phenol in cosmetics in the United States of America.

Phenol has reported non-industrial uses including in medical preparations including lotions, ointment, mouthwashes etc., and in pesticides.

International regulations

Phenol is listed on the following:

- European Union Cosmetic Directive 76/768/EEC Annex II - List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard - Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of Prohibited and Restricted Cosmetic Ingredients ("Hotlist").

Scheduling application

General application.

The applicant's proposed amendments to the SUSMP are as follows:

Schedule 6 – Amend Entry

PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, **except**:

a) when separately specified in these Schedules;

b) when included in Schedule 5; ~~or~~

c) in preparations for cosmetic use containing 1 or less of such substances; or

d) in preparations *other than for cosmetic use* containing 3 per cent or less of such substances.

The applicant's reasons for the request are:

- Given the risk characterisation, it is advised that phenol remain in Schedule 6, but the allowable concentration of phenol in cosmetics/personal care products and domestic products be further restricted. The safety directions and warning statements should also be reviewed; and
- The current entry for phenol is complex and includes additional chemicals, including cresols and xylenols. Any change to the scheduling of phenol will have flow on effects to these other chemicals. Within the cresols and xylenols, cresols are expected to represent worst case toxicity. The IMAP assessment for cresols (which is supportive of the current controls for cresols) should be taken into account in determining whether changes in cut-off concentrations should apply to the current entry as written in the SUSMP, or whether separate entries for phenol and homologues of phenols should be created.
- In Australia, for industrial uses, phenol is currently listed in Schedule 6 of the SUSMP for preparations containing greater than 3 %. At concentrations greater than 3 %, a number of first aid instructions and safety directions relating to skin and eye contact apply. The current Schedule entry covers phenol and a number of substituted phenols;
- Given that necrosis has been seen in humans following exposure to solutions diluted as 1 %, phenol may pose an unreasonable risk to public health, particularly in cosmetic products when purposely applied to the skin. The risks could be mitigated by reducing the concentration limit permitted in products without the need for safety directions. Typically, the risk of systemic effects would also be reduced for products containing lower concentrations of phenol; and
- As vapours can readily penetrate the skin surface, safety directions relating to the use of phenol in the presence of adequate ventilation may also minimise risk associated with the use of products with higher phenol concentrations that come under Schedule 6.

- although use in cosmetic and domestic products in Australia is not known, phenol has reported cosmetic and domestic uses overseas;
- phenol has been reported to cause poisoning in humans by ingestion, skin absorption, and by inhalation;
- necrosis of human skin has been reported at concentrations as low as 1 %;
- local exposure to phenol may diminish the sensation of pain, possibly leading to less awareness and thus higher degrees of local damage; and
- With respect to cresol, the use of the cresols in cosmetic and consumer products is not anticipated in Australia. Hence, the public risk from these chemicals is not considered to be unreasonable. In addition, cresols are less corrosive than phenol with corrosive effects not seen at or below 3 %.

Substance summary

Phenol (Figure 2.3) is colourless to light pink crystalline solid with a distinct aromatic, and somewhat sickening sweet and acrid odour.

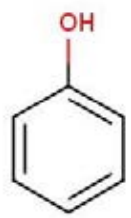

Figure 2.3: Structure of phenol

Acute toxicity

The acute toxicity end-points for phenol are listed in Table 2.3 and are publically available in the NICNAS Human Health Tier II assessment report for phenol. Briefly, based on available data, phenol has moderate to high acute oral and dermal toxicity in animals. Limited data are available on acute inhalation toxicity. However, phenol is classified as hazardous with the risk phrase 'Toxic by inhalation' (T; R23) in HSIS (Safe Work Australia). Median lethal concentration (LC_{50}) values on acute inhalation toxicity tests with animals are not available (ECB, 2006). Rats are reported to have tolerated phenol concentrations as high as 236 ppm (900 mg/m^3) for eight hours, resulting in ocular and nasal irritation, loss of coordination, tremors, and prostration. Phenol has been reported to cause poisoning in humans from ingestion, skin absorption, and by inhalation. Signs and symptoms of acute toxicity of phenol in laboratory animals and humans are similar regardless of the route of administration. Oral toxicity of phenol in humans leading to the death of the victim is reported for doses as low as 140-290 mg/kg bw. Death following dermal application of phenol has been reported. Following skin contact, absorption is very rapid and the symptoms develop rapidly (within 15-20 minutes). Death can occur within 30 minutes to several hours. Skin necrosis and irreversible effects on the eyes have been observed in irritation studies in rabbits. Signs of respiratory irritation have been observed in a number of animal studies following acute and repeat inhalation exposure to phenol. There have been frequent reports of human experience with occupational exposure to phenol (since 1871). Based on these experiences, phenol has been reported to cause burns in humans. While a 10 % solution of phenol has been reported to produce corrosion in humans, occasionally skin necrosis has also been seen with solutions as dilute at 1 % (ECB, 2006). It has been noted that, due to the local anesthetic properties of phenol, no pain is experienced at initial contact with skin and a white wrinkled discolouration is formed.

Table 2.3: Acute end-points for phenol

Toxicity	Species	Phenol	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats Humans	340–530 mg/kg bw 140–290 mg/kg bw	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	660–707 mg/kg bw	Schedule 6
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rats, Humans	Limited data available*	-
Skin irritation	Humans, Rabbits	Corrosive	Schedule 7
Eye irritation	Rabbits	Corrosive	Schedule 7
Skin sensitisation (Buehler)	Guinea Pig	Not sensitising*	Appendix B or Schedule 5
Genotoxicity	Mice	Positive (intraperitoneal) Negative/equivocal (orally)	N/A
Carcinogenicity	Rats, Mice	Negative*	N/A
Reproduction and developmental toxicity	Rats, Mice	Negative*	N/A

* For more information see the NICNAS Human Health Tier II assessment report for phenol.

Genotoxicity

Phenol tested positive in several *in vitro* genotoxicity assays. For *in vivo* studies, while generally positive results have been obtained with the intraperitoneal route, negative or equivocal results have been obtained with the oral route. This route-related difference is likely to be due to the potential for first-pass detoxification of phenol when it is administered by the oral route, but not when administered intraperitoneally. The genotoxic potential of phenol appears to depend on the competing processes of activation to a genotoxic form and metabolic inactivation (e.g., by conjugation).

Carcinogenicity

Phenol was not carcinogenic in rats and mice up to and including the highest doses tested (450 and 375 mg/kg bw/d, respectively). Based on the extensive use of phenol over the years, there are no epidemiological data that reveals an association of exposure to phenol with increased tumour rates in humans (ECB, 2006).

Reproduction and developmental toxicity

There is no evidence of reproductive toxicity. Developmental effects were only observed secondary to maternal toxicity. Therefore, phenol is not expected to have specific developmental toxicity in humans.

Repeat-dose toxicity

Repeated dose studies in animals showed toxic effects on target tissues such as the kidneys, liver, lungs, the haematopoietic system and nervous system, although effects were not consistent between studies. Based on the available data it appears that the toxicity of phenol is related to peak blood levels rather than total dose delivered.

Pre-meeting public submissions

One public submission was received that supported the scheduling proposal. However, the submission suggested a new entry for phenol, with exclusion to salts and derivatives, to apply for cosmetics except in preparations containing 0.1% or less of phenol. This would align with the EU standards and allow for products that contain phenol as an impurity.

The main points were:

- No objection to the ban of phenol in cosmetics;
- Phenols are currently listed in Annex II of the EU Cosmetic Regulations (banned in cosmetics in the EU); however, xylenol and cresol and potentially other derivatives of phenol with boiling points below 220°C are used in cosmetics with no regulatory restrictions;
- A new entry for phenol, excluding salts and derivatives, be created to apply specifically to cosmetics; and
- In line with EU requirements, propose that products containing up to 0.1% phenol be exempt from scheduling.

The public submission is available on the TGA website.

Summary of joint ACMS/ACCS advice to the delegates

The committee advised that the current Schedule 6, 5 and 2 entries for phenol be amended as follows:

Schedule 6 – Amend entry

PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, **except**:

a) when separately specified in these Schedules; *or*

b) ~~when included in Schedule 5; or c)~~ in preparations *containing 1 per cent or less of phenols, and in preparations* containing 3 per cent or less of ~~such substances~~ *cresols and xylenols and other homologues of phenol.*

Schedule 5 – Amend Entry

PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, when in animal feed additives containing 15 per cent or less of such substances, **except** in preparations containing *1 per cent or less of phenol and in preparations containing* 3 per cent or less of ~~such substances~~ *cresols and xylenols and other homologues of phenol.*

Schedule 2 – Amend Entry

PHENOL, or any homologue boiling below 220°C for human therapeutic use, **except**:

a) when included in Schedule 4; or

b) in preparations for external use *containing 1 per cent or less of phenol and in preparations for external use* containing 3 per cent or less of ~~such substances~~ *cresols and xylenols and other homologues of phenol.*

The committee advised that Appendix E and F entries be created as follows:

> **Appendix E** – *PHENOL when included in Schedule 6.*
>
> *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).*
>
> *Warning Statements: 3 (corrosive liquid), 51 (irritant to skin, eyes, mucous membranes and upper respiratory tract).*
>
> **Appendix F** – *PHENOL when included in Schedule 6.*
>
> *Safety Directions: 2 (attacks eyes - protect eyes when using), 4 (avoid contact with skin), 8 (avoid breathing dust (or) vapour (or) spray mist).*

The committee advised an implementation date of **1 February 2017**.

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; and (c) the toxicity of a substance.

The reasons for the advice included:

- Phenol displays human systemic toxicity, orally, by inhalation and through dermal absorption;
- Necrosis of human skin has been reported at concentrations as low as 1 %;
- Local exposure to phenol may diminish the sensation of pain, possibly leading to less awareness and thus higher degrees of local damage;
- European Union and New Zealand have banned its used in cosmetic products, and it is included on Health Canada List of Prohibited and Restricted Cosmetic Ingredients;
- Phenol is corrosive and is reported to induce skin necrosis in humans at a concentration of 1 %. This is especially problematic in the case of accidental skin exposure because the local anaesthetic properties of phenol may result in a delayed pain response resulting in chemical burns; and
- Phenol has widespread industrial and minor therapeutic use.

Delegates' considerations

The delegate considered the following in regards to 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.

Delegates' interim decision

The delegates note and accept the ACCS-ACMS advice to amend the Schedule 6, Schedule 5 and Schedule 2 entries for phenol. The delegates note that this advice is primarily based on the acute toxicity profile for phenol including reports of human systemic toxicity orally, by inhalation and through dermal absorption. Phenol is corrosive and is reported to induce skin necrosis in humans at

concentrations as low as 1 per cent. This is especially problematic in the case of accidental skin exposure because the local anaesthetic properties of phenol may result in a delayed pain response resulting in a higher degree of local damage.

The proposed implementation date is **1 February 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989:* (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; and (c) the toxicity of a substance.

3. Advisory Committee on Chemicals Scheduling (ACCS#17)

Summary of Delegate's interim decisions

Substance	Interim Decision
Direct Red 254	**Schedule 6 – New Entry** DIRECT RED 254 **except** when included in Schedule 5. **Schedule 5 – New Entry** DIRECT RED 254 in preparations containing 30 per cent or less of Direct Red 254. **Index – New Entry** DIRECT RED 254 cross reference: 2-NAPHTHALENESULFONIC ACID, 7-AMINO-4-HYDROXY-3-[[P-[(P-SULFOPHENYL)AZO]PHENYL]AZO]-, BIS(TRIETHANOLAMINE) SALT Schedule 5 Schedule 6 Proposed implementation date: **1 February 2017**
Aminopyralid	**Schedule 6 – Current Entry** AMINOPYRALID **except** when included in Schedule 5. **Schedule 5 – Amend Entry** AMINOPYRALID in preparations containing 22 per cent or less of aminopyralid. Proposed implementation date: **1 February 2017**
Metazachlor	**Schedule 5 – New Entry** METAZACHLOR. Proposed implementation date: **1 February 2017**
Quinoline	**Schedule 6 – New Entry** QUINOLINE and its salts (excluding other derivatives). **Index – New Entry** QUINOLINE. cross reference: 2,3-BENZAPYRIDINE

Substance	Interim Decision
	Schedule 6 Appendix E, Part 2 Appendix F, Part 3 **Appendix E** – QUINOLINE 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), S1 (if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water). **Appendix F** – QUINOLINE Warning Statement: 79 (will irritate eyes). Safety Directions: 1 (avoid contact with eyes), 4 (avoid contact with skin). Proposed implementation date: **1 February 2017**
Phenoxymethyl oxirane	**Schedule 6 – New Entry** PHENOXYMETHYL OXIRANE. **Appendix E –** PHENOXYMETHYL OXIRANE 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 –** PHENOXYMETHYL OXIRANE Warning Statements: 12 (vapour is harmful to health on prolonged exposure), 28 [(Over) (Repeated) exposure may cause sensitisation], 51 (irritant to skin, eyes, mucous membranes and upper respiratory tract). Safety Directions: 1 (avoid contact with eyes), 3 (wear eye protection when mixing or using), 4 (avoid contact with skin), 5 (wear protective gloves when mixing or using), 7 (wash hands thoroughly after use), 8 (avoid breathing vapour), 9 (use only when in well-ventilated areas). Proposed implementation date: **1 February 2017**
n-Hexane	The current scheduling remains appropriate for *n*-hexane.
Amyl and hexyl cinnamaldehyde	**Appendix B – New Entries** AMYL CINNAMALDEHYDE HEXYL CINNAMALDEHYDE Proposed implementation date: **1 February 2017**
Isoeugenol	**Schedule 6 – Amend Entry**

Substance	Interim Decision
	ISOEUGENOL **except:** a) when included in Schedule 5; or b) in preparations intended for contact with skin containing 0.5 per cent or less of isoeugenol. **Schedule 5 – Amend Entry** ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol **except** in preparations intended for contact with skin containing 0.5 per cent or less of isoeugenol. Proposed implementation date: **1 June 2017**

3.1 Direct Red 254

Referred scheduling proposal

An application was submitted to create a new Schedule 7 entry for Direct Red 254 while providing consistency with the current scheduling of other azo-based dyes.

Current scheduling status and relevant scheduling history

Direct red 254 has not been previously considered for scheduling and is not separately listed in the SUSMP. There is a group entry for specific azo dyes in Schedule 7. There is a group entry for phenylenediamine and its derivatives in Schedule 6 and 10, and Appendix E and F.

Other azo dyes have been considered for scheduling on two separate occasions. At the August and November 2015 Advisory Committee on Chemicals Scheduling (ACCS) meetings, the committee advised that a range of azo dyes requires scheduling. The delegate agreed with the ACCS advice, and a group entry for azo dyes was included in Schedule 7 in the SUSMP in 2016. The fundamental reasons for the scheduling of the azo dyes were due to the potential to be metabolised to carcinogenic and/or genotoxic aromatic amines.

The azo dyes considered by the delegate and published in November 2015, include derivatives by diazotisation of o-anisidine, o-toluidine, p-aminoazobenzene, o-aminoazotoluene, 2,4-toluenediamine, 5-nitro-o-toluidine, p-chloroaniline and 4-chloro-o-toluidine, to be included in Schedule 7 and implemented on 1 February 2016. Further information is available at: https://www.tga.gov.au/sites/default/files/final-decisions-and-reasons-decisions-delegate-chemicals-secretary-department-health-november-2015_1.pdf.

The azo dyes considered by the delegate and published in March 2016, include derivatives by diazotisation of 2-napthylamine, 2,4,5-trimethylaniline and 6-methoxy-m-toluidine (p-cresidine) to be included in Schedule 7 and implemented on 1 June 2016. Further information is available at https://www.tga.gov.au/sites/default/files/reasons-scheduling-delegates-final-decisions-march-2016.

Scheduling application

General application.

The application's proposed amendments to the SUSMP are as follows:

Schedule 5 – New Entry

DIRECT RED 254.

The applicant's reasons for the request are:

- An application to register a product 'Envirodye' containing Direct Red 254, an azo dye derivative;
- Direct Red 254 has an estimated oral LD50 of 750 mg/kg bw (low toxicity). On this basis the applicant sought a Schedule 6 classification for the substance; and
- Although Direct Red 254 is an azo dye, it is not listed as a benzidine based azo dye, but a sulphonated dye and as such, is considered to have a low potential for genotoxicity and carcinogenicity. Therefore, the APVMA instead suggested a Schedule 5 classification.

Substance summary

Direct Red 254 has been put forward for scheduling by the APVMA in relation to an application for the registration of an AgVet product. Direct Red 254 is a sulfonated diazo dye, and is intended for use in a liquid marking dye for use in non-crop situations with herbicide spray solutions to assist in clearer identification of sprayed areas.

The APVMA proposed a Schedule 5 entry based on the submitted acute oral toxicity studies supporting the combined toxicity of the product being of low acute toxicity. The proposal does not include a cut-off.

Direct Red 254 (Figure 3.1) is a sulfonated diazo dye with a molecular weight of approximately 826 g/mol. It is a water soluble substance with sulfonic acid substituents and amine / hydroxyl functional groups that are ionisable. The following information has been extracted from the HHRA technical report for toxicology of the Direct Red 254.

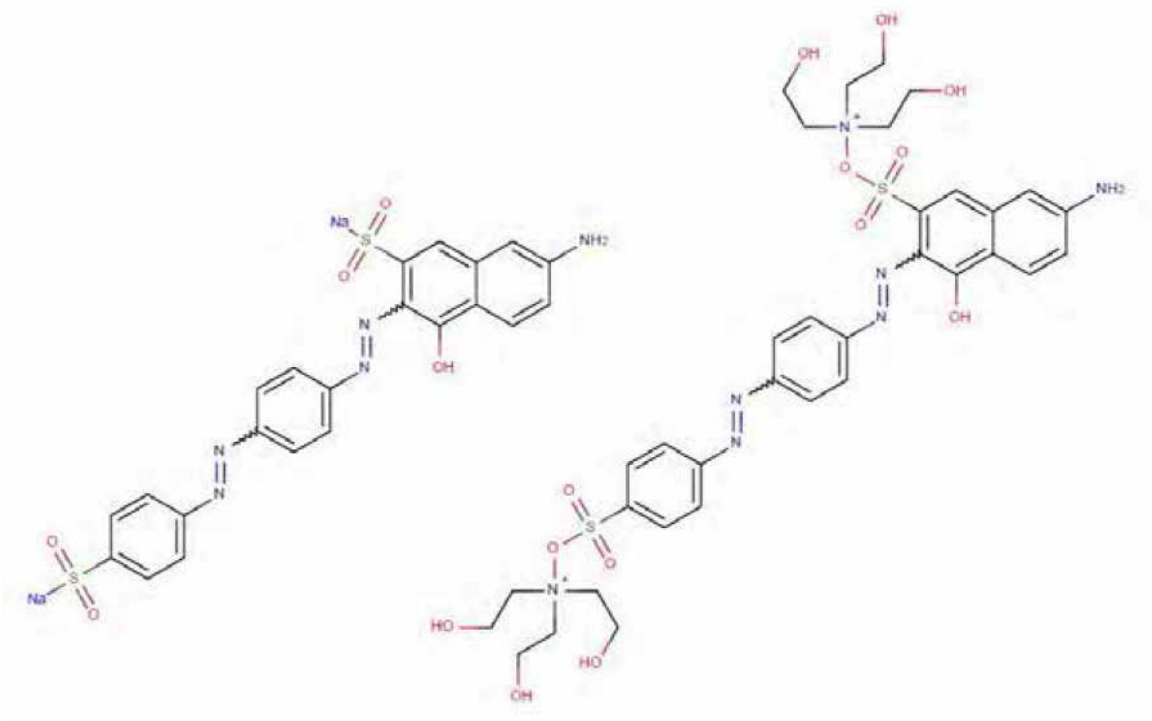

Figure 3.1: Structures of Direct Red 254 as the disodium salt (CAS No. 6300-50-1) and as the triethanolamine salt (CAS No. 64683-40-5)

Acute toxicity

The acute toxicity end-points for Direct Red 254 (CAS No. 64683-40-5) are listed in Table 3.1. The toxicological database for Direct Red 254 is limited to acute toxicity and genotoxicity studies. However the toxicological database for the group of azo dyes to which Direct Red 254 belongs (Direct / Reactive

Dyes, PMRA 2015) is considered sufficient to determine the toxicological profile of Direct Red 254 and characterise the risk to humans.

The toxicology assessment of Direct / Reactive Dyes was conducted by Health Canada (2015).

Table 3.1: Acute toxicity end-points for Direct Red 254

Toxicity	Species	Results	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>5000	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	No data	No data	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	No data	No data	N/A
Skin irritation	Rabbit	Non-irritant	Appendix B
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation	Guinea pig	Non-sensitive	Schedule 5

Acute studies

Aqueous solutions (8.7% and 15%) have been tested for acute toxicity (LD_{50} > 5000 mg/kg bw).

Dermal and inhalation toxicity studies were not available. Direct Red 254 was not a skin irritant in rabbits but is a slight eye irritant in the same species. Direct Red 254 was not a dermal sensitiser in the guinea pig maximisation test.

Systemic effects

Subacute, chronic, developmental and *in vivo* genotoxicity studies were not submitted for Direct Red 254. A Health Canada (2015) evaluation of direct dyes included consideration of data for 37 diazo direct dyes within their evaluation. The Health Canada evaluation was used to consider missing endpoints (repeat dose toxicity, reproductive toxicity and developmental toxicity) and to source acute and repeat dose NOAELs suitable for conducting a worker risk characterisation. Direct Red 254 is not intended for crop uses.

Health Canada concluded a low carcinogenic and genotoxic potential for sulfonated aromatic amines (Direct Red 254 can be reduced to a sulfonated aromatic amine). In particular Health Canada state: Available data indicate that sulfonated aromatic amines generally have low carcinogenic and genotoxic potential owing to their high electronegativity and water solubility (Marchisio et al. 1976; Lin and Solodar 1988; Jung et al. 1992; OECD QSAR Toolbox 2013).

Health Canada considered a range of subacute, chronic, developmental and reproductive toxicity studies for direct and reactive dyes. A range of NOAELs, 26 - 300 mg/kg bw/d, was identified from oral repeat-dose toxicity studies for Direct Orange 39 and the six additional substances. Data from the dermal route were limited; only a single test dose level was used in each of the available short-term and chronic dermal toxicity studies.

Pre-meeting public submissions

No pre-meeting submissions were received for Direct Red 254.

Summary of ACCS advice to the delegate

The committee advised that Direct Red 254 should remain unscheduled and an Appendix B entry for Direct Red 254 was appropriate with a cross reference in the index.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the committee included: (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 advice comprised the following:

- Toxicity is low via the oral and dermal routes due to the high molecular weight, water solubility and electronegativity of Direct Red 254 in comparison to some other azo-dyes;
- Health Canada have previously identified sulfonated aromatic amines to have low carcinogenic and genotoxic potential and Direct Red 254 does not form carcinogens as part of the metabolism pathways; and
- Its use pattern as a molecular dye for application of herbicides to vegetation suggests that the already low toxicity profile of Direct Red 254 is further mitigated by the use of appropriate personal protective equipment (PPE).

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Public Submissions received;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information:
  - Following the ACCS meeting in July 2016, the APVMA submitted further information (19 August 2016) to help inform the delegate's interim decision.

    The APVMA confirmed the following CAS numbers for Direct Red 254:

    CAS 64683-40-5 = Direct Red 254 (triethanolamine salt)

    CAS 101380-00-1 = Direct Red 254
  - The new proposal for Direct Red 254 suggested by the APVMA:

    Schedule 6 with a cut-off at 30% (w/v) into Schedule 5.

    This proposal is based on the theoretical oral LD50 of 750 mg/kg bw for Direct Red 254 which was calculated from the oral LD50 of 5000 mg/kg bw for a diluted formulation containing Direct Red 254 at a concentration of 15% (i.e. 5000 mg/kg bw x 15% = 750 mg/kg bw).

Delegate's interim decision

The delegate notes the ACCS advice and reasons to keep Direct Red 254 unscheduled, however the theoretical oral LD_{50} of 750 mg/kg bw for Direct Red 254 is consistent with the criteria for Schedule 6 in the SPF. The acute toxicity data is only available for a diluted formulation of Direct Red 254 (8.7-5%) and not for the active ingredient alone. Skin sensitisation and genotoxicity studies were

performed using Direct Red 254 in 'powdered' form which in some cases was stated to be 'pure' however the exact concentration of active is unknown. The interim decision to create new entries for Direct Red 254 in Schedule 5 and Schedule 6 is appropriate based on SPF criteria with the new schedules providing adequate control for any preparations in current use that would contain more than 30% of Direct Red 254.

The proposed implementation date is **1 February 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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.

Schedule 6 – New Entry

DIRECT RED 254 except when included in Schedule 5.

Schedule 5 – New Entry

DIRECT RED 254 in preparations containing 30 per cent or less of Direct Red 254.

Index – New Entry

DIRECT RED 254

cross reference: 2-NAPHTHALENESULFONIC ACID, 7-AMINO-4-HYDROXY-3-[[P-[(P-SULFOPHENYL)AZO]PHENYL]AZO]-, BIS(TRIETHANOLAMINE) SALT

Schedule 5

Schedule 6

3.2 Aminopyralid

Referred scheduling proposal

An application was submitted to amend the Schedule 5 and Schedule 6 entries for aminopyralid to include reference to the triisopropanolamine (TIPA) salt and to investigate whether an appropriate exemption cut-off is required.

Scheduling history

Aminopyralid was first considered by the National Drugs and Poisons Schedule Committee (NDPSC) in June 2005. At that time, the committee agreed aminopyralid be included in Schedule 6 of the SUSMP based on the assessment of toxicity and having regard to severe eye irritancy.

Aminopyralid was considered again in November 2013 by the Advisory Committee on Chemicals Scheduling (ACCS) following an application for rescheduling the current Schedule 6 entry for aminopyralid to provide a cut-off to Schedule 5 at 0.5 per cent for the product. The application sought to include aminopyralid, present as the TIPA salt, in Schedule 5.

In its deliberations, the committee noted that the Office of Chemical Safety (OCS) had recently evaluated studies that were provided to support the rescheduling application for the TIPA salt, and indicated that data provided did not use 100% aminopyralid TIPA, but rather a 459.4 g/L aqueous solution of aminopyralid TIPA. The OCS, therefore, considered there was insufficient information to provide advice on a Schedule 5 entry for aminopyralid TIPA as a separate active constituent from aminopyralid to the scheduling delegate.

The ACCS agreed that there was a lack of data to support a Schedule 5 entry for aminopyralid TIPA and that the Schedule 6 entry for aminopyralid be amended to provide a cut-off to Schedule 5 at 0.5 per cent (as in the current entries).

Current scheduling status

The current scheduling of aminopyralid is:

Schedule 6

AMINOPYRALID **except** when included in Schedule 5.

Schedule 5

AMINOPYRALID in water soluble gel formulations containing 0.5 per cent or less of aminopyralid.

Scheduling application

General application.

The application's proposed amendments to the SUSMP is to amend the existing entry in Schedule 5 for aminopyralid to include the TIPA salt, in concentrations equivalent to more than 5% of aminopyralid and less than 20% aminopyralid and exempt concentrations of 5% or less from the scheduling.

The applicant's reasons for the request are:

- The current Poisons Schedule for Foragemax Herbicide is determined by the Schedule 6 listing for aminopyralid acid which is driven primarily by severe eye irritancy;
- The other active constituent in the product, halauxifen-methyl, is included in Appendix B of the SUSMP, based on its low toxicity profile, when used as a herbicide;
- The APVMA has indicated that the toxicology profile of aminopyralid TIPA at 40% or less (approx. 20 % aminopyralid active ingredient or less) does not appear to be consistent with the SPF factors identified for inclusion in a schedule of the SUSMP; and
- The delegate may wish to consider either an exemption from scheduling for aminopyralid as the TIPA salt at specified concentrations equivalent to 20 % or less of aminopyralid, OR inclusion in Schedule 5 at 20% or less, with a cut-off to exempt at 5% or less of aminopyralid, to be appropriate.

Substance summary

Aminopyralid (CAS No. 150114-71-9) (Figure 3.2) belongs to the picolinic acid family of herbicides, which also includes clopyralid, picloram and triclopyr. It is a synthetic auxin and selective herbicide used for control of broadleaf weeds, woody weeds, wild tobacco trees, rhizomatous plants, wandering jew and herbaceous weeds.

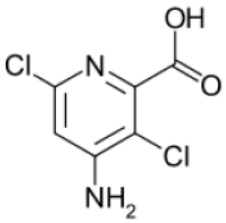

Figure 3.2: Structure of aminopyralid

Acute toxicity

The acute toxicity end-points for aminopyralid are listed in Table 3.2. Aminopyralid has low acute oral toxicity in rats (LD_{50} >5000 mg/kg bw; 1/10 died at 5000 mg/kg bw/d), low acute dermal toxicity (LD_{50} >5000 mg/kg bw; no deaths) and low acute inhalation toxicity (LC_{50} >5500 mg/m3; no deaths) in male and female rats. Aminopyralid is non-irritating to rabbit skin and non-sensitising to guinea pig skin but a severe eye irritant in rabbits. Aminopyralid is neither, a teratogen in rats or rabbits, a

reproductive toxin in rats, a genotoxin, nor a carcinogen in life time studies in rats or mice. Aminopyralid was not neurotoxic in a 1 year rat study.

Table 3.2: Acute end-points for aminopyralid

Toxicity	Species	Results	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	> 5000, low toxicity	Appendix B
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	> 5000, low toxicity	Appendix B
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rats	> 5500, low toxicity	Appendix B
Skin irritation	Rabbits	Non-irritant	Appendix B
Eye irritation	Rabbits	Severe eye irritant, Moderate irritation	Schedule 6
Skin sensitisation (Magnusson and Kligman)	Guinea Pigs	Non-sensitiser	Appendix B
Neurotoxicity	Rats	Not neurotoxic	N/A
Genotoxicity	Rats	Not genotoxic	N/A
Reproduction and developmental toxicity	Rats, Rabbits	Negative	N/A
Carcinogenic	Rats, Mice	Not carcinogenic	N/A

Repeat-dose toxicity

Effects on various organs were observed in oral repeat-dose studies using aminopyralid or aminopyralid TIPA. In the case of the liver, there was an increase in hepatocyte size with altered cytoplasmic staining and decreased liver glycogen at 1000 mg/kg bw/d in mice. Higher relative liver weights, associated in some cases with very slight hypertrophy of centrilobular to midzonal hepatocytes, were observed at 967 mg/kg bw/d in male dogs and at 1038 mg/kg bw/d in females. A dermal repeat-dose study found slight chronic focal inflammation of the liver in male rats at 500 mg/kg bw/d.

The caecum was affected in a number of rat studies. Increased caecum size and/or weight was observed in four studies in rats, at dose levels between 500 mg/kg bw/d and 1000 mg/kg bw/d. In two of these studies, increased caecum weights were associated with very slight hyperplasia of the caecal mucosal epithelium of the rats at 1000 mg/kg bw/d.

In dogs, effects on the stomach included a slight, diffuse hyperplasia and hypertrophy of the mucosal epithelium of the stomach at 1070 mg/kg bw/d in males and at 929 mg/kg bw/d in females. Another study found diffuse thickening of the stomach mucosa, slight diffuse mucosal hyperplasia and hypertrophy, slight chronic mucosal inflammation and slight lymphoid hyperplasia of the stomach mucosa, in male and females at 967 mg/kg bw/d and 1038 mg/kg bw/d, respectively.

No kidney pathology was observed. However there were reductions in urine pH and decreased urine protein and ketones at 1000 mg/kg bw/d in rats. In another rat study, there was increased urine volume, with decreased urine specific gravity, pH, protein and ketones at 1000 mg/kg bw/d. A study

using aminopyralid TIPA found increased urine volume and decreased urine specific gravity at 1000 mg/kg bw/d in rats.

Pre-meeting public submissions

No pre-meeting submissions were received for aminopyralid.

Summary of ACCS advice to the delegate

The committee advised the following amendments to the SUSMP:

Schedule 6 – Amend Entry

AMINOPYRALID **except** ~~when included in Schedule 5~~ *in preparations containing aminopyralid triisopropanolamine (TIPA) salt equivalent to 22 per cent or less of aminopyralid.*

Schedule 5 – Delete Entry

~~AMINOPYRALID in water soluble gel formulations containing 0.5 per cent or less of aminopyralid.~~

Index – Amend Entry

AMINOPYRALID

Schedule 6

~~Schedule 5~~

The committee suggested an implementation date of **1 February 2017**.

Members agreed that the relevant matters under Section 52E (1) of the *Therapeutic Goods Act 1989* included: (c) the toxicity of a substance.

The reasons for the advice included:

- Aminopyralid is a severe eye irritant; and
- Negligible eye irritation potential of the TIPA salt at 22%.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes the ACCS advice and reasons to amend the Schedule 6 entry to include the aminopyralid triisopropanolamine (TIPA) salt and to delete the Schedule 5 entry for aminopyralid. However, the delegate's interim decision is that the Schedule 6 entry for aminopyralid remains appropriate and that the Schedule 5 entry for aminopyralid be amended to include preparations containing 22 per cent or less of aminopyralid. While the toxicity profile of the pure chemical is

consistent with the SPF factors for listing in Schedule 6, the reduction in eye irritancy associated with the diluted preparation is consistent with the SPF factors for Schedule 5. The data for aminopyralid TIPA referred to in the JMPR report and used in the APVMA HHRA has previously been evaluated by the OCS (67378/55918 (2013)). The acute toxicity studies were performed with the formulated product GF-871 (41.3%-42% TIPA, corresponding to 21.7% aminopyralid). GF-871 has low acute oral (LD_{50} >5000 mg/kg), dermal (LD_{50} >5000 mg/kg) and inhalational toxicity (LC_{50} >5.79 mg/L). It is a slight skin and eye irritant and is not a skin sensitiser. The data available to the committee for aminopyralid TIPA did not use 100% aminopyralid TIPA, but rather formulated products containing 0.5-45% aminopyralid TIPA. It was therefore, considered that there was a lack of data to support a Schedule 5 entry for aminopyralid TIPA as a separate active constituent from aminopyralid (as was concluded in previous deliberations by the Advisory Committee for Chemicals Scheduling in 2013).

An early implementation date of **1 February 2017** is proposed in order to bring the regulation of this ingredient in products sold in Australia into alignment with international regulations.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (c) the toxicity of a substance.

Schedule 6 – Current Entry

AMINOPYRALID except when included in Schedule 5.

Schedule 5 – Amend Entry

AMINOPYRALID in preparations containing 22 per cent or less of aminopyralid.

3.3 Metazachlor

Referred scheduling proposal

An application was submitted to create a new Schedule 5 entry for metazachlor with an appropriate exemption cut-off concentration.

Scheduling history

Metazachlor is not specifically scheduled and has not been previously considered for scheduling.

Scheduling application

General application.

The application's proposed amendments to the SUSMP are as follows:

Schedule 5 – New Entry

*METAZACHLOR **except** in preparations containing 50 per cent or less of metazachlor.*

The applicant's reasons for the request are:

- BASF Australia Ltd have submitted a data package seeking approval of the new active constituent metazachlor and registration of the new product containing 500 g/L metazachlor in a suspension concentrate formulation;
- Metazachlor belongs to the chloroacetamide chemical class and acts by inhibition of lipid biosynthesis. As a new chemical it will require scheduling consideration for SUSMP listing prior to final registration of products containing this active constituent;
- BASF Australia Ltd have proposed that metazachlor be listed in Schedule 5 of the SUSMP; and
- Metazachlor is a skin sensitiser in a guinea pig maximisation test and a slight skin irritant in rabbits.

Substance summary

Metazachlor (Figure 3.3) belongs to the chloroacetamide chemical class and acts by inhibition of lipid biosynthesis.

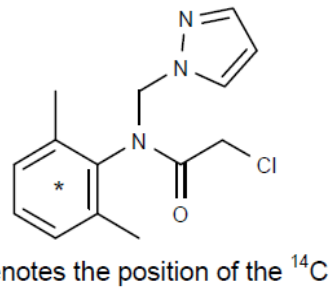

Figure 3.3: Structure of metazachlor

Acute toxicity

The acute toxicity end-points for metazachlor are listed in Table 3.3A. Briefly, in acute toxicity studies in rodents, metazachlor was of low acute oral toxicity in rats (LD_{50} = 2160/2140 mg/kg (M/F)) and mice (LD_{50} = 2010 mg/kg bw); low acute dermal toxicity in rats (LD_{50} > 6810 mg/kg bw; no deaths) and low acute inhalational toxicity in rats (LC_{50} >3450 mg/m^3, 4 hour exposure, no deaths). Regarding irritation, metazachlor was found to be a slight irritant to the skin, and non-irritating to the eye in rabbits. Metazachlor was found to be a sensitiser in a Guinea Pig Maximisation Test (GPMT).

Metazachlor displays no evidence of mutagenic/genotoxic potential in vitro (with and without metabolic activation), or a genotoxic potential *in vivo*. Furthermore, there was no evidence of a reproductive toxicity potential in a two-generation reproductive (dietary) toxicity study in rats and shows no evidence of a developmental toxicity potential in developmental toxicity studies conducted with rats and rabbits. No neurotoxicity or immunotoxicity studies were submitted. Regarding carcinogenicity, the OCS considers the evidence for potential carcinogenicity arising from metazachlor administration in mice and rats to be weak and that the overall lack of treatment-related neoplastic findings in long term mouse and rat studies and the lack of genotoxicity in a battery of tests conducted with metazachlor and its metabolites supports the conclusion that metazachlor is unlikely to be a carcinogen. For more information see the OCS human health risk assessment report for metazachlor.

Table 3.3A: Acute toxicity end-points for metazachlor

Toxicity	Species	Results	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats, Mice	LD_{50} > 2000	Appendix B
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} > 6810	Appendix B
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	LC_{50} > 34500	Appendix B
Skin irritation	Rabbit	Slight irritant	Schedule 5
Eye irritation	Rabbit	Non-irritant	Appendix B
Skin sensitisation (GPMT)	Guinea Pig	Sensitiser	Schedule 5

Toxicity	Species	Results	SPF (2015) Classification
Genotoxicity/Mutagenic	Mice	Not genotoxic/mutagenic	N/A
Carcinogenicity	Mice, Rats	Carcinogenicity unlikely	N/A
Reproduction and developmental toxicity	Rats, Rabbits	Negative	N/A

Repeat-dose toxicity

The primary target organs for toxicity in short-term, sub-chronic and chronic toxicity studies with metazachlor were the liver, kidney and red blood cells. Effects observed in these studies also included non-specific toxicity (i.e. decreases in food consumption, body weight, or body weight gain), clinical signs (e.g. piloerection, ataxia, salivation, vomiting) and effects on the liver or kidney (e.g. serum liver enzyme changes, increased liver and/or kidney weights, or fatty degeneration of hepatocytes, renal parenchymal cell damage).

Toxicity of metazachlor metabolites

A large number of metabolites were identified and subjected to further investigations in a variety of studies, including acute oral toxicity, 13-week (dietary) repeat-dose and developmental studies, as well as a battery of genotoxicity studies including: *in vitro* mammalian chromosome aberration test; in vitro mammalian cell gene mutation test (HPRT), *in vitro* bacterial reverse mutation and *in vivo* mouse (erythrocyte) micronucleus test. Six metabolites were tested in genotoxicity assays and were found to be negative. In acute oral studies, all metabolites were of low acute oral toxicity (oral LD_{50} > 500 mg/kg bw) and clinical signs observed in some of these studies were similar to those observed with the parent compound. No toxicologically significant findings were noted in oral sub-chronic or developmental studies in rats on the metabolites.

Toxicity of Butisan Herbicide (containing 50% w/v metazachlor)

The acute toxicity end-points for Butisan Herbicide, based on data for the proposed formulation and a reference formulation (containing 500 g/L metazachlor), are listed in Table 3.3B. Comparison of the findings for the formulation with results for the active constituent suggest that the increased acute oral toxicity and change in eye irritation potential are not due to the toxicity of metazachlor, but rather the product excipients.

Table 3.3B: Acute toxicity end-points for Butisan Herbicide

Toxicity	Species	Butisan Herbicide
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	500 < LD_{50} < 2000
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	LD_{50} > 4000
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	LC_{50} > 6200 (no deaths)
Skin irritation	Rabbit	Non-irritant
Eye irritation	Rabbit	Slight irritant
Skin sensitisation (GPMT)	Guinea Pig	Non-sensitiser

Pre-meeting public submissions

No pre-meeting submissions were received for metazachlor.

Summary of ACCS advice to the delegate

The committee advised that a new Schedule 5 entry be created in the SUSMP for metazachlor.

The committee advised an implementation date of **1 February 2017**.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the committee included: (c) the toxicity of a substance.

The reasons for the advice included:

- Metazachlor exhibits low acute toxicity by all routes. It is not an eye irritant but is a slight skin irritant and a skin sensitiser; and
- The European Food Safety Authority (EFSA) considered that any carcinogenic effects were non-genotoxic, only observed at high doses and within the historical control range, therefore the relevant human risk is low.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes and accepts the advice of the ACCS to create a new Schedule 5 entry for metazachlor. Metazachlor exhibits low acute toxicity by all routes. It is not an eye irritant, but is a slight skin irritant and a skin sensitiser. The European Food Safety Authority (EFSA) considered that any carcinogenic effects were non-genotoxic, only observed at high doses and within the historical control range, therefore the relevant risk of metazachlor to humans is low.

An early implementation date of **1 February 2017** is proposed in order to bring the regulation of this ingredient in products sold in Australia into alignment with international regulations.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (c) the toxicity of a substance.

Schedule 5 – New Entry

METAZACHLOR.

3.4 Quinoline

Referred scheduling proposal

An application was submitted to create a new Schedule 6 entry for quinoline in preparations for use in cosmetics and domestic uses with an appropriate cut-off to exempt from scheduling for preparations with low concentration levels.

Current scheduling status and relevant scheduling history

Quinoline is not specifically scheduled and has not been previously considered for scheduling; therefore, scheduling history is not available.

Other relevant regulations

Public exposure

Although use in cosmetic or domestic products in Australia is not known, quinoline is reported to be used in cosmetic/domestic products as fragrance compounds overseas. However, information on the maximum use concentrations in consumer products as fragrance ingredients is not available.

The EU has prohibited the use of quinoline in cosmetics. Currently, there are no restrictions on using this chemical in Australia. In the absence of any regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk under the identified uses.

Scheduling application

General application.

The application's proposed amendments to the SUSMP are as follows:

Schedule 6 – New Entry

QUINOLINE in preparations for domestic use.

The applicant's reasons for the request are:

- Quinoline has reported cosmetic and domestic use as a fragrance compound overseas;
- Quinoline is a Category 2 carcinogen and Category 3 mutagen;
- Quinoline has moderate acute oral and dermal toxicity;
- Quinoline is an irritant to the skin and a severe eye irritant;
- There are no data on reproductive and developmental toxicity;
- There are overseas restrictions for the use of quinoline in cosmetics; and
- Scheduling is an effective way of controlling the use of quinoline in cosmetic and domestic products.

Substance summary

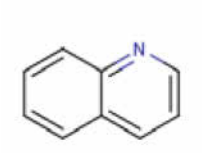

Figure 3.4: Structure of quinoline

The following has been extracted from the NICNAS IMAP Human Health Tier II group assessment report for quinoline.

Acute toxicity

The acute toxicity end-points for quinoline (Figure 3.4) are listed in Table 3.4. Briefly, quinoline has moderate acute oral and dermal toxicity. It is classified as harmful if swallowed or in contact with skin. This is supported by the median lethal dose (LD_{50}) values for oral and dermal exposure. Data for acute inhalation toxicity are insufficient to derive a conclusion. Quinoline is classified as irritating to the skin

and eyes. Only limited data are available for skin irritation, showing moderate effects in rabbits. In an eye irritation study in rabbits (n = 6), 0.1 mL of quinoline was applied to one eye of each animal for 24 hours and the animals were observed for seven days. The combined irritation scores 72 hours after application were 0.8/1 for corneal irritation, 0.5/1 for iris irritation, 2/3 for conjunctival redness and 2.2/3 for conjunctival chemosis. Effects were not reversible within the 7-day observation period. Quinoline was reported to be severely irritating to the eyes. Based on the available data, quinoline is considered a non-skin sensitiser. Quinoline is a Category 3 mutagenic substance and a Category 2 carcinogenic substance. No information was available on reproductive and developmental toxicity.

Table 3.4: Acute toxicity end-points for quinoline

Toxicity	Species	Results	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	262–460	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit Rat	590 1377	Schedule 6
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	Insufficient data	N/A
Skin irritation	Rabbits	Moderate (Classified as irritant; only limited data available)	Schedule 5
Eye irritation	Rabbits	Severe (not reversible within the observation period of seven days)	Schedule 6
Skin sensitisation (LLNA)	Mouse	Not sensitising	N/A
Genotoxicity	Hamster, Mice, Rats	Genotoxic	N/A
Carcinogenicity	Rats, Mice	Carcinogenic	N/A

* See the NICNAS IMAP Human Health Tier II group assessment report for quinoline for more information

Repeat-dose toxicity

Based on the available data, quinoline is not considered to cause serious health effects from repeated oral exposure. No information was available for repeated dose toxicity by dermal and inhalation exposure.

In a repeated dose oral toxicity study (similar to OECD TG 407), male rats (n = 5/dose) were administered quinoline at 0, 25, 50, 100 or 200 mg/kg bw/day for 28 days. One death was reported in the highest dose group on day 12, and body weight gain was significantly decreased by approximately 24 % and 53 % in the 100 and 200 mg/kg bw/day groups, respectively, compared with controls. Clinical signs of toxicity included diarrhoea, reduced activity, and staining around the eyes and nose in the 200 mg/kg bw/day group.

In a repeated dose oral toxicity study (similar to OECD TG 453), male SD rats (n = 6 for control and n = 20/dose) were exposed to quinoline at 0, 0.05, 0.10 or 0.25 % (estimated to be equivalent to 0, 25, 50 or 125 mg/kg bw/day) in the diet for 40 weeks. Final body weights were reduced by 17.9, 33.4 or 51.2 % in rats exposed to quinoline at 0.05, 0.10 or 0.25 %, respectively, compared with controls. Absolute liver weights were increased in all treated rats. The non-neoplastic changes observed in rats at all doses included infiltration of liver progenitor (oval) cells, bile duct proliferation and fatty liver.

Pre-meeting public submissions

One (1) public submission was received which did not object to the proposal to schedule quinoline for cosmetic and domestic preparations if derivatives (specifically, 2- and 4-methyl quinoline) of quinoline are excluded from scheduling.

The public submission is available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that the proposal to include quinoline and its salts in Schedule 6 was appropriate with a cross reference to 2,3-benzapyridine in the index.

The ACCS advised an implementation date of **1 February 2017**.

Members agreed that the relevant matters under Section 52E (1) of the *Therapeutic Goods Act 1989* included: (c) the toxicity of a substance.

The reasons for the advice comprised the following:

- Moderate to high acute oral and dermal toxicity; and
- Severe eye irritancy.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Public submissions received;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes and accepts the advice and reasons of the ACCS that the moderate to high acute oral and dermal toxicity and severe eye irritancy of quinoline is consistent with Schedule 6 criteria in the SPF. Accordingly, a new Schedule 6 entry for quinoline will be created for quinoline with a cross reference to 2,3-benzapyridine in the index and appropriate Appendix E and F statements and warnings to reflect its toxicity profile.

An early implementation date of **1 February 2017** is proposed in order to bring the regulation of this ingredient in products sold in Australia into alignment with international regulations.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989:* (c) the toxicity of a substance.

Schedule 6 – New Entry

QUINOLINE and its salts (excluding other derivatives).

Index – New Entry

QUINOLINE

cross reference: 2,3-BENZAPYRIDINE

Schedule 6

Appendix E, Part 2

Appendix F, Part 3

Appendix E and F – New Entries

Appendix E – QUINOLINE

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), S1 (if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water)

Appendix F – QUINOLINE

Warning statement: 79 (will irritate eyes).

Safety directions: 1 (avoid contact with eyes), 4 (avoid contact with skin).

3.5 Phenoxymethyl oxirane

Referred scheduling proposal

An application was submitted to create a new Schedule 6 entry for phenoxymethyl oxirane.

Scheduling history

Phenoxymethyl oxirane is not specifically scheduled and has not been previously considered for scheduling; therefore, scheduling history is not available.

Other relevant regulations

Public exposure

No specific Australian use, import or manufacture information have been identified. Phenoxymethyl oxirane is however, known to be used in domestic and commercial products overseas.

International regulations

Phenoxymethyl oxirane is listed in:

- EU regulation (EC) No 1223/2009 Annex II: List of substances which must not form part of the composition of cosmetic products; and
- New Zealand Cosmetic Products Group Standard - Schedule 4: Components cosmetic products must not contain.

Scheduling application

General application.

The application's proposed amendments to the SUSMP are as follows:

Schedule 6 – New Entry

PHENOXYMETHYL OXIRANE for domestic use.

The applicant's reasons for the request are:

- Although there is no information to confirm that phenoxymethyl oxirane is currently used in domestic products in Australia, use in domestic products such as paints and varnishes has been identified overseas;
- The main critical effects to human health are carcinogenicity following long-term occupational exposure, potential for mutagenicity and sensitisation from dermal contact. Phenoxymethyl oxirane also possesses other hazardous properties such as skin, eye and respiratory tract irritation; and
- Adverse skin effects including sensitisation have been reported in humans from long-term exposure to phenoxymethyl oxirane; and the European Union and New Zealand have banned the use of this chemical in cosmetics. There are no restrictions in Australia to prevent this chemical being used in cosmetics or domestic products. However, no cosmetic use for this chemical has been identified in Australia.

Substance summary

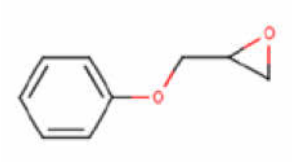

Figure 3.5: Structure of phenoxymethyl oxirane

The following is extracted from the NICNAS IMAP Human Health Tier II assessment report for phenoxymethyl oxirane.

Acute toxicity

The acute toxicity end-points for phenoxymethyl oxirane (Figure 3.5) are listed in Table 3.5. Briefly, phenoxymethyl oxirane has low acute toxicity via oral and dermal route of exposure and is currently classified with the risk phrase 'Harmful by inhalation' (R20) (Safe Work Australia). Although the data available do not warrant a hazard classification, in the absence of more reliable data and considering the local effects seen in the repeat dose inhalation toxicity study (See below), the existing hazard classification was not amended. Phenoxymethyl oxirane is an eye irritant and respiratory irritant upon single or repeated inhalation exposure and is classified as hazardous with the risk phrase 'Irritating to skin' (R38) (Safe Work Australia). Phenoxymethyl oxirane has skin sensitising effects in guinea pigs (Buehler Patch test) and is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) (Safe Work Australia). Based on the available data, phenoxymethyl oxirane is not considered to have reproductive or developmental toxicity.

Table 3.5: Acute toxicity end-points for phenoxymethyl oxirane

Toxicity	Species	Results	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	3850 mg/kg bw	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	2100 mg/kg bw	Schedule 5
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rats, Mice	>100 ppm/4 hour	Schedule 5
Skin irritation	Rabbit, Human	Irritating	Schedule 5
Eye irritation (Standard Draize test)	Rabbit, Human	Mild to severe irritation	Schedule 5/6
Skin sensitisation (Buehler)	Guinea pig	Sensitising	Schedule 6
Skin sensitisation (HRIPT)	Humans	Sensitising, allergic dermatitis reaction	–
Genotoxicity	*In vivo* (bacterial and mammalian cells)	Genotoxic	–
Carcinogenicity	Rats	Carcinogenic	–
Reproduction and developmental toxicity	Rats	Negative*	–

* See the NICNAS IMAP Human Health Tier II assessment report for phenoxymethyl oxirane for more information.

Genotoxicity

Phenoxymethyl oxirane is classified as hazardous in the HSIS with the risk phrase 'Possible risk of irreversible effects' (R68) (Safe Work Australia). The available *in vitro* genotoxicity data support this classification.

In vitro genotoxicity assays with phenoxymethyl oxirane were conducted using bacterial and mammalian cells. Positive results were observed in bacterial assays and some assays with mammalian cells. There are no *in vitro* studies conducted in germ cells showing positive results.

Phenoxymethyl oxirane has been reported to alkylate nucleic acid bases *in vitro*; however, it did not bind to DNA in *Escherichia coli* with or without metabolic activation (HSDB). All epoxide-containing compounds including glycidyl ethers elicited alkylation activity and mutagenic potency. There was no correlation between rate of alkylation and mutagenic potency.

Most *in vivo* genotoxicity assays with phenoxymethyl oxirane showed negative results, except for one host-mediated assay.

Carcinogenicity

Phenoxymethyl oxirane is classified with the risk phrase 'May cause cancer' (R45 Category 2 carcinogen) in HSIS (Safe Work Australia).

Phenoxymethyl oxirane is classified by the International Agency for Research on Cancer (IARC) as Group 2B (possibly carcinogenic to humans) based on sufficient evidence of carcinogenicity in experimental animals (IARC 1989).

Phenoxymethyl oxirane is classified by American Conference of Governmental Industrial Hygienists (ACGIH) as A3 carcinogen (confirmed animal carcinogen with unknown relevance to humans).

In a chronic inhalation carcinogenicity bioassay, 100 rats were exposed to phenoxymethyl oxirane for 6 hours/day, 5 days/week for 24 months at 0, 1 or 12 ppm. After 621 exposure days, malignant nasal tumours were found in 9/85 (11 %) males and 4/89 (4.4 %) females exposed at 12 ppm (average latent period was 688 days). No nasal tumours were found in the rats exposed at 1 ppm (even up to 24 months). A nasal tumour was found in 1/89 male controls, while none were found in the female controls. Nasal tumours were primarily epidermoid carcinomas sharply limited to the anterior nasal cavity. Tumours were derived from respiratory epithelium and nasal glands (both of which revealed squamous metaplasia or dysplasia). Squamous metaplasia was seen in 72 % rats at 12 ppm, 4.7 % rats at 1 ppm, and 3.4 % in controls; rhinitis was observed in 78 % at 12 ppm, 22 % at 1 ppm, and 19 % in controls.

Repeat-dose toxicity

No data are available on its oral or dermal repeat-dose toxicity.

In a subchronic study, rats which inhaled aerosols of phenoxymethyl oxirane at a concentration of 29 ppm for 4h/day, 5 days/week for two weeks, showed weight loss, atrophic changes in the liver, kidneys, spleen, thymus, and testes, depletion of hepatic glycogen, and chronic catarrhal tracheitis (inflammation of mucous membrane lining the trachea). Local effects included respiratory irritation. The estimated NOAEC was 29 ppm in rats.

Pre-meeting public submissions

One (1) public submission was received which did not object to the scheduling proposal.

The public submission is available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that the proposal to create a Schedule 6 entry for phenoxymethyl oxirane was appropriate.

The ACCS advised an implementation date of **1 February 2017**.

Members agreed that the relevant matters under Section 52E (1) of the *Therapeutic Goods Act 1989* included: (c) the toxicity of a substance.

The reasons for the advice included:

- Acute toxicity profile indicating low oral and dermal toxicity within the range of a Schedule 5 substance;
- Skin and eye irritant;
- Skin sensitiser; and
- Genotoxic and potential carcinogen as indicated by respiratory tract tumours in rodent studies.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;

- Public submissions received;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes, and accepts, the ACCS advice to create a new entry for phenoxymethyl oxirane in Schedule 6 with appropriate listings in Appendices E and F. While the acute toxicity profile of phenoxymethyl oxirane indicates low oral and dermal toxicity within the range of a Schedule 5 substance, the delegate agrees with the ACCS that on the basis of the skin sensitisation and eye irritation data, a Schedule 6 entry for phenoxymethyl oxirane is more appropriate. Furthermore, phenoxymethyl oxirane is a potential genotoxin and carcinogen as indicated by respiratory tract tumours in rodent studies.

An early implementation date of **1 February 2017** is proposed in order to bring the regulation of this ingredient in products sold in Australia into alignment with international regulations.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989:* (c) the toxicity of a substance.

Schedule 6 – New Entry

PHENOXYMETHYL OXIRANE.

Appendix E – PHENOXYMETHYL OXIRANE

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 – PHENOXYMETHYL OXIRANE

Warning statements: 12 (vapour is harmful to health on prolonged exposure), 28 [(Over) (Repeated) exposure may cause sensitisation], 51 (irritant to skin, eyes, mucous membranes and upper respiratory tract).

Safety directions: 1 (avoid contact with eyes), 3 (wear eye protection when mixing or using), 4 (avoid contact with skin), 5 (wear protective gloves when mixing or using), 7 (wash hands thoroughly after use), 8 (avoid breathing vapour), 9 (use only when in well-ventilated areas).

3.6 *n*-Hexane

Referred scheduling proposal

An application was submitted to amend the Schedule 5 entry and create a specific Schedule 7 entry for *n*-hexane except when packed and labelled for industrial use.

Scheduling history

Historically in Australia, the scheduling of *n*-hexane has always been covered within another schedule entry and is therefore not separately specified in the SUSMP.

In July 1963, the Poisons Schedule sub-committee decided to include kerosene, mineral turpentine, oil of turpentine, petrol, white spirits, solvent derived from petroleum or coal in Schedule 5.

In November 1991, the National Drugs and Poisons Schedule Committee (NDPSC) agreed that liquid hydrocarbons, when used as a solvent in writing correction fluids packed in containers having a capacity of 20 mL or less, would be exempt from scheduling.

In February 1998, the NDPSC agreed to exempt from scheduling liquid hydrocarbons when used as thinners for writing correction fluids packed in containers having a capacity of 20 mL or less.

In February 2004, the NDPSC considered amending the Schedule 5 liquid hydrocarbon entry to specifically exclude isohexadecane and isododecane, noting that both hydrocarbons are lipophilic and therefore able to dissolve fats present in the skin thereby leading to skin irritation and/or dermatitis. Isododecane is also an eye irritant and both hydrocarbons present as aspiration hazards. The NDPSC therefore decided that the scheduling of isohexadecane and isododecane remain appropriate under the Schedule 5 entry for liquid hydrocarbons and not to amend the Schedule 5 entry to exclude these two hydrocarbons.

Most recently, in June 2007, the NDPSC decided to amend the Schedule 5 liquid hydrocarbon entry to exempt from scheduling liquid hydrocarbon preparations when packed in containers with a capacity of 2 mL or less.

Current scheduling status and other relevant regulations

n-Hexane is not separately specified or listed in the SUSMP. However, it is covered by the following general entries:

Schedule 5

HYDROCARBONS, LIQUID, including kerosene, diesel (distillate), mineral turpentine, white petroleum spirit, toluene, xylene and light mineral and paraffin oils (but excluding their derivatives), **except**:

a) toluene and xylene when included in Schedule 6;

b) benzene and liquid aromatic hydrocarbons when included in Schedule 7;

c) food grade and pharmaceutical grade white mineral oils;

d) in solid or semi-solid preparations;

e) in preparations containing 25 per cent or less of designated solvents;

f) in preparations packed in pressurised spray packs;

g) in adhesives packed in containers each containing 50 grams or less of adhesive;

h) in writing correction fluids and thinners for writing correction fluids packed in containers having a capacity of 20 mL or less; or

i) in other preparations when packed in containers with a capacity of 2 mL or less.

Appendix E

HYDROCARBONS, liquid

Standard statements: A, G3.

Existing work health and safety controls for n-hexane

Hazard classification

The chemical is classified as hazardous in the Hazardous Substances Information System (HSIS) (Safe Work Australia), with the following risk phrases for human health:

- Xi; R38 (irritation);
- Xn; R48/20 (repeated dose toxicity);
- Repr. Cat. 3; R62 (reproductive toxicity);

- Xn; R65 (aspiration hazard); and
- R67 (Vapours may cause drowsiness and dizziness).

Exposure standards

Australian: The chemical has an exposure standard of 72 mg/m^3 (20 ppm) time weighted average (TWA).

International (Galleria Chemica): Exposure limits of 72-1800 mg/m3 (20-500 ppm) TWA and 180-3600 mg/m^3 (50-1000 ppm) short-term exposure limit (STEL)/MAK/occupational exposure limit (OEL) in different countries such as Canada, Egypt, France, Netherlands, Norway, Spain, Switzerland and the US.

Scheduling application

General application.

The application's proposed amendments to the SUSMP are as follows:

Schedule 5 – Amend Entry

HYDROCARBONS, LIQUID, including kerosene, diesel (distillate), mineral turpentine, white petroleum spirit, toluene, xylene and light mineral and paraffin oils (but excluding their derivatives), **except**:

a) toluene and xylene when included in Schedule 6;

b) *n-hexane*, benzene and liquid aromatic hydrocarbons when included in Schedule 7;

c) food grade and pharmaceutical grade white mineral oils;

d) in solid or semi-solid preparations;

e) in preparations containing 25 per cent or less of designated solvents;

f) in preparations packed in pressurised spray packs;

g) in adhesives packed in containers each containing 50 grams or less of adhesive;

h) in writing correction fluids and thinners for writing correction fluids packed in containers having a capacity of 20 mL or less; or

i) in other preparations when packed in containers with a capacity of 2 mL or less.

Schedule 7 – New Entry

n-HEXANE ***except*** *when packed and labelled for industrial use.*

The applicant's reasons for the request are:

- *n*-Hexane may cause lung damage following inhalation exposure;
- *n*-Hexane is a skin irritant;
- *n*-Hexane is a neurotoxin;
- *n*-Hexane causes testicular damage in males;
- Prohibition for use of n-hexane in cosmetic products internationally. *n*-Hexane is listed on the following:

- 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;
- The EU Cosmetics Regulation 1223/2009 Annex II - List of substances prohibited in cosmetic products; and
- The New Zealand Cosmetic Products Group Standard - Schedule 4: Components cosmetic products must not contain.

· Alternative chemicals, such as cyclohexane are readily available.

Substance summary

n-Hexane (CAS No. 110-54-3) (Figure 3.6) (synonyms include hexyl hydride and hexane) is a colourless liquid with a gasoline-like odour, used in a wide range of commercial goods in Australia including adhesives (at concentrations up to 60%) and roof cleaning agents, and in the fuel, oil, textiles, furniture, shoemaking and printing industries. Consumer exposure internationally has been identified through its inclusion in cosmetics and in various domestic and commercial products as a solvent and viscosity-decreasing agent (thinner). Also reported are non-industrial uses of *n*-hexane in non-agricultural pesticides and preservatives. (For the extensive use pattern see the NICNAS IMAP Human Health Tier II assessment report for *n*-hexane). Exposure may therefore occur by contact with products containing *n*-hexane and the main routes of exposure are via inhalation and skin contact.

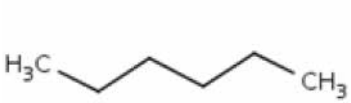

Figure 3.6: Structure of *n*-hexane

Acute toxicity

Acute toxicity for *n*-hexane is outlined in Table 3.6. Briefly, acute oral, dermal and inhalation toxicity for *n*-hexane is low, with LD_{50}'s of >15800 mg/kg bw (oral, rat), >2000 mg/kg bw (dermal, rat) and 48000 mg/m^3 / 4h (inhalation, rat and mice). As a hydrocarbon with low viscosity, *n*-hexane is an aspiration hazard with inhalation exposure (5000 ppm/ ~17.6 mg/L, 10 minutes) in humans resulting in vertigo and giddiness, and occupational exposure (1000–25500 ppm = ~3.52-89.76 mg/L, 30-60 min) resulting in drowsiness. Mild skin irritation was observed in humans and eye irritation was seen in rabbits but not observed in humans. Neither mice (local lymph node (LLN) assay), nor humans (25% solution, 25 volunteers), displayed positive skin sensitisation to *n*-hexane. Repeat-dose toxicity is low based on oral and dermal exposure in animal tests. Neurotoxicity was observed in several animal and human studies and although effects on the central nervous system have been reported, the primary neurotoxic effect of *n*-hexane is peripheral neuropathy. Peripheral neuropathy was also reported in humans exposed industrially to *n*-hexane or solvent mixtures containing *n*-hexane.

The Human Substance Information system (HSIS) classification of *n*-hexane is hazardous with the risk phrase 'Harmful: danger of serious damage to health by prolonged exposure through inhalation' (Xn; R48/20). In a human inhalation study, approximately 28 % of the inhaled chemical was absorbed from the lungs. The chemical is able to cross the alveolar-capillary membrane and enter the bloodstream easily, with an average half-life of 1.5-2 hours in blood. The final absorption rate is 15-17 % in relation to the total respiratory uptake. In workers exposed to 180 mg/m3 of the chemical, a net lung uptake of 112 mg over eight hours was reported. Approximately 17 % and 20 % of the inhaled chemical was exhaled unchanged in rats and humans, respectively.

n-Hexane is not considered to be genotoxic or carcinogenic (see the NICNAS IMAP Human Health Tier II assessment report for *n*-hexane for more information) but reproductive toxicity was positive according to a repeat dose study in male rats. *n*-Hexane is therefore classified as hazardous – Category 3 substance toxic to reproduction – with the risk phrase 'Possible risk of impaired fertility' (Xn; R62) in the HSIS.

Table 3.6: Acute toxicity of *n*-hexane

Toxicity	Species	Results	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>15800	Appendix B
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	Appendix B
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat, Mice	48000 ppm (~169.2 mg/L)	Schedule 7
Inhalation exposure (5000 ppm/ ~17.6 mg/L, 10 min)	Humans	Vertigo, giddiness	N/A
Occupational exposure (1000-25500 ppm or approximately 3.52-89.76 mg/L)	Humans	Drowsiness	N/A
Skin irritation	Human	Mild irritant	Schedule 5
Eye irritation	Rabbit	Not irritating*	Appendix B
Skin sensitisation (LLNA)	Mice	Not sensitising*	Appendix B or Schedule 5
Skin sensitisation (Maximisation Test)	Human	Not sensitising*	Appendix B or Schedule 5
Genotoxicity	Rat	Not genotoxic*	N/A
Carcinogenicity	Rats, Mice	Not carcinogenic*	N/A
Reproduction and developmental toxicity	Rats	Positive	N/A

* See the NICNAS IMAP Human Health Tier II assessment report for *n*-hexane for more information

Pre-meeting public submissions

Four (4) public submissions were received and all were opposed to the proposed Schedule 7 entry because of the substances wide use. Two (2) advocated the use of exemptions to manage the risks of the varied and diversified end-use products. One (1) proposal states that, because there are no proposed concentration limits, any product containing even trace amounts of *n*-hexane, including vegetable oil, would need to be labelled as a Dangerous Poison.

The public submissions are available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that the current scheduling for *n*-hexane remains appropriate.

Members agreed that the relevant matters under Section 52E (1) of the *Therapeutic Goods Act 1989* 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; and (e) the potential for abuse of a substance.

The reasons for the advice included:

- Limited data surrounding *n*-hexane-induced neurotoxicity in humans. The risks are not consistent with the creation of a new Schedule 7 entry;
- Use patterns indicate limited exposure to *n*-hexane in the domestic market. Multiple industrial uses of *n*-hexane including in petrol and some foods (in small quantities);
- Low acute toxicity via the oral, dermal and inhalation routes; and
- Mild skin irritant.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Public submissions received;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes and accepts the ACCS advice that the current scheduling for *n*-hexane remains appropriate. Owing to the limited data surrounding *n*-hexane-induced neurotoxicity in humans, the risks are not consistent with the creation of a new Schedule 7 entry. *n*-Hexane is currently covered by the general Schedule 5 entry for hydrocarbons owing to *n*-hexane's low acute toxicity via the oral, dermal and inhalation routes and status as a mild skin irritant. Furthermore, the use patterns of *n*-hexane (including industrial uses in petrol and some foods) indicate limited exposure in the domestic market.

An implementation date is not relevant given the substance is already covered by the generic hydrocarbons Schedule 5 entry.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989:* (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; and (e) the potential for abuse of a substance.

3.7 Amyl & hexyl cinnamaldehyde

Referred scheduling proposal

An application was submitted to create new Schedule 6 entries for amyl cinnamal (amyl cinnamaldehyde) and hexyl cinnamal (hexyl cinnamaldehyde) with an appropriate cut-off to exempt from scheduling for preparations with low concentrations.

Current scheduling status and relevant scheduling history

Amyl and hexyl cinnamaldehyde are not specifically scheduled.

Amyl and hexyl cinnamaldehyde have not been previously considered for scheduling; therefore, scheduling history is not available.

Other relevant regulations

Public exposure

Although the uses of amyl and hexyl cinnamaldehyde in cosmetic and domestic products in Australia are not known, the chemicals are reported to have widespread use in cosmetic and domestic products overseas, which introduce the potential availability of these chemicals for use in Australia (US HHPD and CIUCUS). While the European Union (EU) and New Zealand (NZ) have outlined restrictions on the use of amyl and hexyl cinnamaldehyde in cosmetics (see International Restrictions below) there are no restrictions currently in Australia regarding the use of these chemicals in cosmetic products. In the absence of any regulatory controls, the characterised critical local health effects have the potential to pose an unreasonable risk under the identified uses. It is suggested that the risk could be mitigated by implementing concentration limits and restricting uses to limit dermal exposure.

International regulations

Amyl and hexyl cinnamaldehyde are restricted for cosmetic use in the EU. They are listed on the EU Cosmetics Regulation 1223/2009 Annex III - the presence of the chemical 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.

Amyl and hexyl cinnamaldehyde are listed on the following:

- The New Zealand Cosmetic Products Group Standard - Schedule 5, with the same use restrictions as described above for the EU; and
- The International Fragrance Association (IFRA) Standards - Restricted.

Scheduling application

General application.

The application's proposed amendments to the SUSMP are as follows:

Schedule 6 – New Entries

AMYL CINNAMALDEHYDE

HEXY CINNAMALDEHYDE

The applicant's reasons for the request are:

- Amyl and hexyl cinnamaldehyde have reported uses in a range of cosmetic and domestic products;
- Amyl and hexyl cinnamaldehyde are potential sensitisers with an LLNA derived EC3 of 6.6 –11.5%; and
- There are overseas restrictions for the use of amyl and hexyl cinnamaldehyde in cosmetic products, where the presence of the chemical 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

Alpha-amyl cinnamaldehyde (CAS No. 122-40-7) and alpha-hexyl cinnamaldehyde (CAS No. 101-86-0) (Figure 3.7A and 3.7B) are alkyl-substituted cinnamaldehydes, grouped together because of their close structural relationship and the resulting physico-chemical and toxicological properties. Amyl and hexyl cinnamaldehyde are identified as GRAS ('generally regarded as safe') for use as flavouring

substances by the United States Food and Drug Administration (US FDA) and World Health Organisation (WHO).

A **B**

Figure 3.7: Amyl cinnamaldehyde (A) and hexyl cinnamaldehyde (B)

Acute toxicity

The acute toxicity profile for amyl and hexyl cinnamaldeyde is outlined in Table 3.7. Briefly, amyl and hexyl cinnamaldehyde display low oral toxicity based on animal test results following oral exposure with the lethal dose (LD_{50}) in rats reported to be >2000 mg/kg bw. Amyl and hexyl cinnamaldehyde display low acute dermal toxicity based on results from animal tests in rabbits following dermal exposure (LD_{50} >2000 mg/kg bw). The concentrations used in the animal studies for skin sensitisation are above the reported concentrations of up to 0.1%, used in cosmetic and domestic products available on the domestic market. Based on the limited available data, these chemicals are expected to have low acute inhalation toxicity based on results from animal tests following inhalation exposure. Based on the available data from animal studies in rabbits the chemicals in this group are irritating to the skin and cause slight eye irritation. Amyl and hexyl cinnamaldehyde are considered to be weak to moderate skin sensitisers (Mice LLN assay EC = 6.6-11.5%) according to the SPF classification with hexyl cinnamaldehyde being commonly used as a positive control in skin sensitisation studies. Human data for hexyl cinnamaldehyde using the Human Repeat Insult Patch Test (HRIPT) do not indicate sensitisation. Amyl and hexyl cinnamaldehyde are not considered to be genotoxic and are not expected to cause reproductive or developmental toxicity. No information is available regarding the carcinogenicity of these chemicals. (See the NICNAS IMAP Human Health Tier II group assessment report for amyl & hexyl cinnamaldehyde for more information.)

Table 3.7: Acute toxicity end-points of amyl and hexyl cinnamaldehyde

Toxicity	Species	Results	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	-
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	>2000	-
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rat	Low**	-
Skin irritation	Rabbits	Irritant (amyl cinnamaldehyde) (Classified as irritant)	-
Eye irritation	Rabbits	Slight irritant	Schedule 5
Skin sensitisation (LLNA)	Mice, Guinea pigs	Weak to moderate skin sensitisers (EC = 6.6-11.5%)	Schedule 6

Toxicity	Species	Results	SPF (2015) Classification
Skin sensitisation (HRIPT)	Human	Not sensitising* Mild erythema with moderate oedema was seen in 1 volunteer out of 138, which subsided after 96 hrs.	–
Genotoxicity	*Salmonella typhimurium*, Mice	Not genotoxic*	N/A
Carcinogenicity	N/A	N/A	N/A
Reproduction and developmental toxicity	Rats	Not expected*	N/A

* See the NICNAS IMAP Human Health Tier II group assessment report for amyl & hexyl cinnamaldehyde for more information

Repeated dose toxicity

While no data is available regarding repeat exposure through inhalation, based on the available data, repeated oral exposures to the amyl and hexyl cinnamaldehyde are not considered to cause serious damage to health (see the NICNAS IMAP Human Health Tier II group assessment report for amyl & hexyl cinnamaldehyde for more information). In contrast, repeated dermal exposure to the chemicals in this group at high doses can cause systemic and local effects according to animal studies in male rats. The lowest LOAEL was reported to be 125 mg/kg bw/day based on changes in the liver and local effects on the skin.

Pre-meeting public submissions

One (1) public submission was received which proposed that scheduling is not required due to international regulation through IFRA. The submission also proposed that, if scheduling is determined necessary then, a Schedule 6 entry with different cut-offs for leave-in and rinse off products should be used, specifically 0.001% in leave-on cosmetics and > 0.01% in rinse-off cosmetics. The submission also requested a prolonged implementation date.

The public submission is available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that amyl and hexyl cinnamaldehyde do not require scheduling in the SUSMP. The committee advised that the Delegate list amyl and hexyl cinnamaldehyde in Appendix B.

Members agreed that the relevant matters under Section 52E (1) of the *Therapeutic Goods Act 1989* 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; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

- Public exposure is only likely to occur through the use of these substances as fragrances in cosmetic and household cleaning products containing up to 0.1%;

- Low acute toxicity; and
- Slight/mild skin sensitization data observed in animal studies and absence of skin sensitisation observed in human studies.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Public submissions received;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes and accepts the advice of the ACCS that amyl and hexyl cinnamaldehyde do not require scheduling in the SUSMP, but that an Appendix B listing for amyl and hexyl cinnamaldehyde is more appropriate. The delegate notes that amyl and hexyl cinnamaldehyde have low acute toxicity; and although slight/mild skin sensitization data is observed in animal studies, there was an absence of skin sensitisation observed in humans. Furthermore, public exposure to amyl and hexyl cinnamaldehyde is only likely to occur through their use as fragrances in cosmetic and household cleaning products containing up to 0.1%.

The proposed implementation date is **1 February 2017**. Since listing in Appendix B is not equivalent to a decision to list a substance in a schedule, an implementation date is not strictly relevant. However, amendment of Appendix B at the earliest revision of the SUSMP is recommended.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989:* (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; and (f) any other matters that the Secretary considers necessary to protect public health.

Appendix B – New Entries

AMYL CINNAMALDEHYDE

HEXYL CINNAMALDEHYDE

3.8 Isoeugenol

Referred scheduling proposal

An application was submitted to amend the existing Schedule 6 entry for isoeugenol to lower the concentration cut-off from 10 to 1 per cent.

Current scheduling status and relevant scheduling history

Isoeugenol was considered for scheduling by the National Drugs and Poisons Schedule Committee (NDPSC) in November 1996 and at that time, the acute toxicity profile of isoeugenol warranted inclusion in Schedules 5 and 6 due to skin and eye irritancy, the potential for skin sensitisation and the level of oral toxicity.

Schedule 5

ISOEUGENOL in preparations containing 25 per cent or less of isoeugenol except in preparations containing 10 per cent or less of isoeugenol.

Schedule 6

ISOEUGENOL except:

a) when included in Schedule 5; or

b) in preparations containing 10 per cent or less of isoeugenol.

Other relevant regulations

Public exposure

Although the use of isoeugenol in cosmetic/domestic products in Australia is not known isoeugenol is reported to be used overseas in cosmetic products (as a perfuming agent) and in domestic products (including in cleaning and surface treatment products).

International regulations

Isoeugenol is listed on the following:

- European Union (EU) Cosmetics Regulation 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 - maximum authorised concentration in the finished cosmetic product: 0.02%;
- 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; and
- Based on qualitative risk assessment, the International Fragrance Association (IFRA) has indicated an acceptable concentration for isoeugenol in skin contact products should be 0.02%.

Scheduling application

General application.

The application's proposed amendments to the SUSMP are as follows:

Schedule 6 – Amend Entry

ISOEUGENOL except:

a) when included in Schedule 5; or

b) in preparations containing ~~10~~ *1* per cent or less of isoeugenol.

The applicant's reasons for the request are:

- Isoeugenol is classified as a carcinogen;
- It is a strong skin sensitiser with Local Lymph Node Assay estimated concentration to produce a three-fold increase in lymphocyte proliferation (EC3) values as low as 0.54 %;
- It has induced sensitisation in Human Repeat Insult Patch Tests at 1 %;
- It may be widely present due to it being a constituent of a range of essential oils; and
- Isoeugenol is restricted to 0.02 % in cosmetics in the European Union.

Substance summary

The following has been extracted from the NICNAS IMAP Human Health Tier II assessment report for phenol, 2-methoxy-4-(1-propenyl)-.

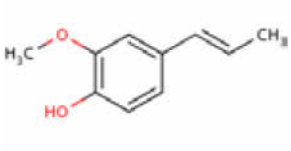

Figure 3.8: Structure of isoeugenol (2-methoxy-4-(1-propenyl)phenol)

Acute toxicity

The acute toxicity end-points for isoeugenol (Figure 3.8) are listed in Table 3.8. Briefly, isoeugenol is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS (Safe Work Australia). The available data support the existing classification for isoeugenol as 'harmful if swallowed: (Xn; R22)'. A review of the literature by the US National Toxicology Program (2010) found that oral LD_{50} values for isoeugenol ranged from 1290 to 1880 mg/kg bw for rats and 1130 to 1780 mg/kg bw for guinea pigs. Isoeugenol has been identified as a severe skin irritant in a number of animal studies. Isoeugenol is also considered to be a skin sensitiser based on human data (HRIPT), positive results seen in guinea pig maximisation tests (GPMT) and LLNAs. Isoeugenol is not considered to be genotoxic and does not show specific reproductive or developmental toxicity.

Table 3.8: Acute toxicity end-points of isoeugenol

Toxicity	Species	Results	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1290-1880	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	1910	Schedule 6
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	N/A	N/A
Skin irritation	Rabbit	Evidence of severe irritation (non-guideline study)	Schedule 6
Eye irritation	Rabbit	Evidence of irritation	Schedule 5
Skin sensitisation (LLNA)	Various	2 % (weighted mean from over 40 tests)	Schedule 6
Genotoxicity	Various	Not genotoxic*	–
Carcinogenicity	Rats, Mice	Carcinogenic	–
Reproduction and developmental toxicity	Rats	Negative*	–

* See the NICNAS IMAP Human Health Tier II assessment report for phenol, 2-methoxy-4-(1-propenyl)- for more information

Carcinogenicity

Isoeugenol is classified as hazardous - Category 3 carcinogenic substance - with the risk phrase 'Limited evidence of carcinogenic effect' (Xn; R40) in the HSIS (Safe Work Australia). The available data support this classification.

In a two-year carcinogenicity study, Fischer 344 (F344) rats (50/sex/group) were dosed with isoeugenol by oral gavage at 0, 75, 150 or 300 mg/kg bw, five days per week for 105 weeks. Survival rates of the exposed animals were comparable to controls. Mean body weights of males in the high dose group were increased compared with controls. Two males in the high dose group developed thymomas, while two other males in this group developed mammary gland carcinomas. Some animals in the mid and high dose groups showed olfactory epithelial metaplasia and mild atrophy of the olfactory nerves.

A similar experiment was conducted in B6C3F1 mice (50/sex/group) where animals were dosed with isoeugenol by oral gavage at 0, 75, 150 or 300 mg/kg bw, 5 days/week for 104 weeks (females) and 105 weeks (males). Survival was decreased in males in the high dose group and body weights were reduced in both males and females in this group. In all groups, males exhibited increased incidences of hepatocellular adenoma, hepatocellular carcinoma and hepatocellular carcinoma and adenoma (combined). Incidences of hepatic clear cell foci were also increased in the male mice that received 75 or 150 mg/kg bw/day. There was also a significant increase in the incidence of histiocytic sarcomas (at multiple tissue sites) in females across all groups. Olfactory epithelial metaplasia was observed in all exposed groups. Bowman's gland hyperplasia was also significantly increased in all exposed groups. Mild renal papillary necrosis and renal tubule necrosis were also significantly increased in the high dose group females. There were dose-dependent increases in the incidences of forestomach squamous hyperplasia, inflammation (statistically significant in high dose males and females) and ulceration (for high dose males only).

Repeat-dose toxicity

The available data suggest that isoeugenol has low repeated dose toxicity, based on results from animal tests following oral exposure.

Pre-meeting public submissions

One (1) public submission was received what supported lowering the cut-off concentration to 1% or less for cosmetic use only. For other products with no intended skin contact, the lowering of the exemption concentration cut-off was not supported.

The public submission is available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that the Schedule 5 and 6 entries in the SUSMP for isoeugenol be amended as follows:

Schedule 6 – Amend Entry

ISOEUGENOL **except:**

a) when included in Schedule 5; or

b) in *preparations intended for contact with skin* containing ~~10~~ *0.5* per cent or less of isoeugenol.

Schedule 5 – Amend Entry

ISOEUGENOL in preparations *not intended for skin contact* containing 25 per cent or less of isoeugenol **except** in preparations *intended for contact with skin* containing ~~10~~ *0.5* per cent or less of isoeugenol.

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

The ACCS advised an implementation date of **1 June 2017**.

The reasons for the advice included:

- Isoeugenol is a chemical fragrance with widespread use in cosmetic and household products;
- Acute oral and dermal toxicity and irritancy classifies isoeugenol as a Schedule 6 substance;
- Skin sensitisation recorded at 1% v/v isoeugenol; and
- Isoeugenol is identified as carcinogenic although the evidence is limited.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Public submissions received;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling Policy Framework (SPF 2015); and
- Other relevant information.

Delegate's interim decision

The delegate notes and accepts the advice of the ACCS to amend the Schedule 5 and Schedule 6 entries for isoeugenol. The delegate notes that this advice is based primarily on the acute oral and dermal toxicity and irritancy for isoeugenol, including the skin sensitisation data recorded at 1 per cent. Evidence is limited regarding the classification of isoeugenol as a carcinogen. The use profile of isoeugenol as a chemical fragrance is widespread in cosmetic and household products.

A late implementation date of **1 June 2017** is proposed to allow for the re-labelling of isoeugenol-containing products already on the market.

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

Schedule 6 – Amend Entry

ISOEUGENOL **except:**

a) when included in Schedule 5; or

b) in preparations intended for contact with skin containing 0.5 per cent or less of isoeugenol.

Schedule 5 – Amend Entry

ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol **except** in preparations intended for contact with skin containing 0.5 per cent or less of isoeugenol.