Australian Government
Department of Health
Therapeutic Goods Administration

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

17 May 2017

(ACMS and ACCS meetings – March 2017)

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

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

The delegate's interim decisions and reasons related to:

- scheduling proposals initially referred to the March 2017 meeting of the Advisory Committee on Medicines Scheduling (ACMS#20);
- scheduling proposals initially referred to the March 2017 Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS#15); and
- scheduling proposals initially referred to the March 2017 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#19).

Pre-meeting public notices

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

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

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

Interim decisions

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

Further submissions must be relevant to the proposed amendment, must address a matter mentioned in section 52E of the *Therapeutic Goods Act 1989* and be received by the closing date, 31 May 2017.

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

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

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

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

The closing date for further submissions is 31 May 2017.

Privacy and your personal information

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

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

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

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

The Department's privacy policy is available on the Department of Health website.

Alternatively, you may contact the Department by telephone on 02 6289 1555 or 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
CAS	Chemical Abstract Service

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

Abbreviation	Name
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
OCM	Office of Complementary Medicines

Abbreviation	Name
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
SCCP	Scientific Committee on Consumer Products

Abbreviation	Name
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

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Interim decisions on matters referred to an expert advisory committee (March 2017)

1. Advisory Committee on Medicines Scheduling (ACMS #20)

Summary of delegate's interim decisions

Substance	Interim decision
Dihydrocodeine	**Schedule 8 – Amend Entry** DIHYDROCODEINE **except** when included in Schedule 3 or 4. **Schedule 4 – Amend Entry** DIHYDROCODEINE when compounded with one or more other therapeutically active substances: a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or b) in undivided preparations with a concentration of not more than 2.5 per cent of dihydrocodeine, **except** when included in Schedule 3. **Schedule 3 – Amend Entry** DIHYDROCODEINE when indicated for cough suppression and compounded with one or more other therapeutically active substances: a) in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or b) in undivided preparations containing 0.25 per cent or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine. **Schedule 2 – Delete Entry** *The proposed implementation date is **1 October 2017**.*
1,3-Dimethylbutylamine (DMBA) and other aliphatic alkylamines including 1,5-dimethylhexylamine (DMHA)	**Schedule 10 – New Entries** 1,3-DIMETHYLBUTYLAMINE (DMBA) **except** when separately specified in these schedules. 1,5-DIMETHYLHEXYLAMINE (DMHA) **except** when separately specified in these schedules. ALKYLAMINES WITH STIMULANT PROPERTIES **except** when separately specified in these schedules.

	Index – New Entries **1,3-DIMETHYLBUTYLAMINE (DMBA)** cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate) Schedule 10 **1,5-DIMETHYLHEXYLAMINE (DMHA)** cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate) Schedule 10 **ALKYLAMINES WITH STIMULANT PROPERTIES** cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate) Schedule 10 *The proposed implementation date is **1 October 2017**.*
Ulipristal	**Schedule 3** ULIPRISTAL for emergency post-coital contraception. **Appendix H – New Entry** ULIPRISTAL for emergency post-coital contraception. **Index – Amend Entry** ULIPRISTAL Schedule 4 Schedule 3 Appendix H *The proposed implementation date is **1 February 2018**.*
Ibuprofen	**Schedule 3 – Amend Entry** IBUPROFEN: a) in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units, when labelled: i) with a recommended daily dose of 1200 mg or less of ibuprofen; and ii) not for the treatment of children under 12 years of age; or

	b) in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32 dosage units, when labelled: i) with a recommended daily dose of 1200 mg or less of ibuprofen; and ii) not for the treatment of children under 12 years of age, **except** when included in or expressly excluded from Schedule 2. **Appendix H – New Entry** IBUPROFEN *The proposed implementation date is **1 October 2017**.*
Flurbiprofen	The delegate's interim decision is that the current scheduling of flurbiprofen remains appropriate.
Penciclovir	**Schedule 4 – Amend Entry** PENCICLOVIR **except** in preparations containing 1 per cent or less of penciclovir for the treatment of *herpes labialis* in packs containing 10 g or less. **Schedule 2 – Delete Entry** **Index – Amend Entry** **PENCICLOVIR** Schedule 4 *The proposed implementation date is **1 October 2017**.*
Loratadine	**Schedule 4 – Amend Entry** LORATADINE **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 6 years of age and over-when: i) in a primary pack containing 10 dosage units or less; and ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine. **Schedule 2 – Amend Entry** LORATADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis when: a) in a primary pack containing 10 dosage units or less when

	labelled for children 6 years and over; and b) labelled with a recommended daily dose not exceeding 10 mg of loratadine. *The proposed implementation date is **1 October 2017**.*

1.1. Dihydrocodeine

Referred scheduling proposal

A delegate from the TGA has referred the substance dihydrocodeine for consideration for the appropriateness of the Schedule 2 and Schedule 3 entries, noting the recent up-scheduling of codeine.

Current scheduling status

Dihydrocodeine is currently listed in Schedules 8, 4, 3 and 2 of the Poisons Standard as follows:

Schedule 8

DIHYDROCODEINE **except** when included in Schedule 2, 3 or 4.

Schedule 4

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or

b) in undivided preparations with a concentration of not more than 2.5 per cent of dihydrocodeine,

except when included in Schedule 2 or 3.

Schedule 3

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

a) in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or

b) in undivided preparations containing 0.25 per cent or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine,

except when included in Schedule 2.

Schedule 2

DIHYDROCODEINE when compounded with aspirin and no other therapeutically active substance in divided preparations:

a) containing 5 mg or less of dihydrocodeine per dosage unit;

b) packed in blister or strip packaging or in a container with a child-resistant closure;

c) enclosed in primary packs containing 25 or less dosage units; and

d) labelled with a recommended dose not exceeding 10 mg of dihydrocodeine.

The related substance acetyldihydrocodeine is in Schedule 8.

Scheduling history

In December 2016, the delegate made a decision to up-schedule codeine from Schedules 2 and 3 to Schedule 4. The decision and reasons are on the TGA website at: Scheduling delegate's final decision: codeine, December 2016.

In November 1979 - June 1980, the Poisons Schedule Committee (PSC) reviewed the scheduling of dihydrocodeine in certain preparations following evidence of abuse. The committee discussed the desirability of placing uncompounded preparations containing less than 1% dihydrocodeine in Schedule 4, and considered that uncompounded preparations currently available in Schedule 2 should be classified in Schedule 8. Two manufacturers sought the committee's concurrence that inclusion of sorbitol (40 g/100 mL) in their products would remove the need for Schedule 2 status of their products. Members agreed to take no further action.

Between August 1985 and July 1987, the PSC and Drugs and Poisons Schedule Committee (DPSC) reviewed the scheduling of dihydrocodeine, following potency concerns raised by WA regarding the inclusion of dihydrocodeine tartrate in Schedule 2 as this allowed a higher limit than codeine, which was reported to be equipotent. At the November 1986 meeting the Committee foreshadowed a recommendation to alter the Schedule 2 entries for opiates (except dihydrocodeine) and other substances with regard to a specific quantity per dosage unit in divided preparations, a percentage limit for undivided preparations and an upper dose limit recommended for both divided and undivided preparations. Members agreed to delete dihydrocodeine from Schedule 2 and enter it into Schedule 3 in February 1987. Following this, the committee received further information about the decision to delete Schedule 2 and create a new Schedule 3 entry. The committee noted a potency equivalence of 5 mg dihydrocodeine to 10 mg of codeine and agreed to a new Schedule 2 entry for dihydrocodeine. A new Schedule 2 entry was also made for dihydrocodeine when in combination with aspirin.

In April 1994, the National Drugs and Poisons Scheduling Committee (NDPSC) considered a request from the Australian Pharmaceutical Advisory Council (APAC) to review the scheduling of dihydrocodeine combined with paracetamol, in view of the fact that dihydrocodeine with aspirin is Schedule 2. Members were not aware of a registered OTC product containing paracetamol and dihydrocodeine or of a detailed technical submission supporting such a change, or was there any response to the Gazettal invitation for public comment. Accordingly the Committee was unable to accede to the request.

In June 2010 - September 2011, the NDPSC and ACMS, considered a TGA request to reschedule several medicines, following a TGA review of the safety, efficacy, availability and packaging of all OTC cough and cold medicines. The review concluded that there was a lack of evidence of efficacy and potential safety concerns associated with use in children, especially those aged less than 6 years, and stated that the current scheduling of codeine, dihydrocodeine and pseudoephedrine was appropriate. Members noted that, of the 22 substances identified in the TGA review, a number were recommended for exemption from the proposed cascade as it was considered that either existing controls were sufficient (codeine, dihydrocodeine and pseudoephedrine) or that scheduling was not necessary (ammonia). Members noted that for some substances the current scheduling may in fact be more restrictive than the proposed cascade (e.g., pseudoephedrine) as this was the basis for the TGA Panel recommending that existing controls were sufficient for codeine, dihydrocodeine and pseudoephedrine and did not need to be rescheduled. The committee agreed that the use of certain substances in preparations for treating cough and cold be rescheduled to:

- Schedule 4 for use in children less than 2 years of age.
- Schedule 3 for use in children aged from 2 to 6 years of age.
- Schedule 2 for use in adults and children above 6 years of age.

However, the delegate decided that the scheduling of dihydrocodeine and another 14 substances (including codeine) in cough and cold preparations remained appropriate.

Scheduling application

This was a delegate initiated application made in response to the scheduling changes of codeine where from 1 February 2018, the Schedule 2 and 3 entries for codeine will be deleted.

Australian regulatory information

There are currently 7 ARTG products containing dihydrocodeine tartrate that are included on the ARTG.

International regulations

Japan

In Japan, dihydrocodeine is available without a prescription; used in cough medicines. Medicines in Japan containing dihydrocodeine are combined with caffeine to offset the sedative effects and discourage recreational use. Sale is limited by quantity and restricted by age.

UK

In the UK and other countries, 30 mg tablets containing only dihydrocodeine as the active ingredient are available; 40 mg dihydrocodeine tablets are also available in the UK. Dihydrocodeine is considered to be a Class B drug in the UK, but is available OTC in small amounts (less than 8 mg), when combined with paracetamol.

Dihydrocodeine is listed in Schedule 5 of the Misuse of Drugs Regulations 2001, exempting it from prohibition of possession provided that it is in the form of a single preparation not designed for injection and less than 100 mg (as free base) or with a total concentration less than 2.5% (as free base).

New Zealand

The NZ database of Medicine Classifications states that dihydrocodeine (or drocode) is a prescription medicine.[1] It is also conditionally classed as a C2 and C6 Controlled drug (drugs that pose a moderate risk of harm to individuals, or to society, by its misuse).[2]

Acetyldihydrocodeine is also a Class C2 controlled drug in NZ.

United States of America

In the USA, dihydrocodeine is a Schedule II controlled substance.

Preparations containing small amounts of dihydrocodeine are classified as Schedule III or V, depending on the concentration of dihydrocodeine relative to other active constituents, such as paracetamol (acetaminophen). The USA currently has 2 combination products registered and available as prescription medicines containing paracetamol (acetaminophen) or aspirin with caffeine and dihydrocodeine tartrate (dihydrocodeine bitartrate).[3]

Substance summary

Dihydrocodeine (CAS number 125-28-0) is a semi-synthetic phenanthrene opioid receptor agonist analgesic with a molecular weight of 301.4, $C_{18}H_{23}NO_3$ (molecular weight for the tartrate is 451.5, molecular formula $C_{22}H_{29}NO_9$, CAS number for the tartrate is 5965-13-9). Dihydrocodeine is a chemical derivative of codeine and is an opioid pain reliever that produces similar effects to codeine, prepared by codeine or neopine (Merck Index). The chemical name for dihydrocodeine is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol. Dihydrocodeine is a white or almost white, crystalline powder, freely

[1] Database of Medicine Classifications
[2] Misuse of Drugs Act 1975: Schedule 3 Class C controlled drugs
[3] Drugs@FDA: FDA Approved Drug Products

soluble in water, sparingly soluble in alcohol and practically insoluble in cyclohexane. Martindale[4], indicates that dihydrocodeine is available as both tartrate and phosphate salts.

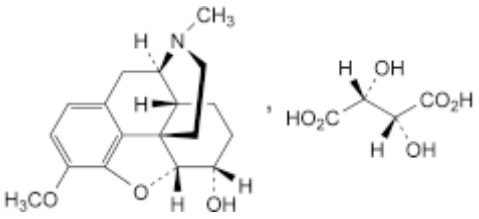


Figure 1.1: Structure of dihydrocodeine tartrate

Abuse

As with other opioids, tolerance and physical and psychological dependence develop with repeated use of dihydrocodeine. Martindale indicates that dihydrocodeine has been reported to be widely abused by opiate addicts.[5]

Pharmacokinetics

Dihydrocodeine is converted by cytochrome P450 isoenzyme CYP2D6 in the liver to the primary active metabolite dihydromorphine[6]. Oral bioavailability is approximately 20%. Dihydromorphine has potent analgesic activity, although the analgesic effect of dihydrocodeine appears to be mainly due to the parent compound. Dihydrocodeine is excreted in urine as unchanged drug and metabolites, including glucuronide conjugates. Elimination half-life ranges from 3.5 - 5 h. Martindale reports that the peak plasma concentration for dihydrocodeine is delayed and the area under the plasma concentration-time curve is greater in subjects with renal impairment compared with healthy subjects.

Pre-meeting public submissions

Five (5) public submissions were received.

Three (3) submissions supported the scheduling proposal. The main points were:

- Cases of misuse/abuse of dihydrocodeine reported to the NSW Poisons Information Centre have increased in recent years.
- Acknowledge no reason to have different scheduling compared with codeine, but also supports deleting Schedule 2 and amending Schedule 3 and Schedule 4 pack sizes.

Two (2) submissions did not support the scheduling proposal. The main points were:

- Schedule 3 is appropriate for dihydrocodeine in low doses when indicated as a cough suppressant. There have been no reported events related to abuse or dependence of OTC dihydrocodeine products on the ARTG in the past 6 years. Undivided preparations of dihydrocodeine in conjunction with sorbitol are not seen as candidates for abuse or misuse.
- An additional safety measure of a mandatory warning label about the potential for addiction was proposed as an alternative.

[4] Dihydrocodeine
[5] Swadi H, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **300:** 1313; Robertson JR, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119; Strang J, *et al.* Misuse of dihydrocodeine tartrate (DF 118) among opiate addicts. *BMJ* 1990; **301:** 119; Seymour A, *et al.* The role of dihydrocodeine in causing death among drug users in the west of Scotland. *Scott Med J* 2001; **46:** 143–6
[6] Pharmacokinetics of dihydrocodeine and its active metabolite after single and multiple oral dosing Wilder-Smith CH, *et al.* The visceral and somatic antinociceptive effects of dihydrocodeine and its metabolite, dihydromorphine: a cross-over study with extensive and quinidine-induced poor metabolizers. *Br J Clin Pharmacol* 1998; **45:** 575–81

- As there are no products on the ARTG containing any aspirin or other analgesic preparation co-formulated with dihydrocodeine for the treatment of pain, there is no opposition to the removal of dihydrocodeine from Schedule 2 of the SUSMP.
- There are already control measures in place in the pharmacy for dispensing Schedule 3 medicines. There is also a longstanding status of Schedule 3 medicines for the treatment of cough. Removal of dihydrocodeine from Schedule 3 would limit the availability of treatment options for stubborn cough available without a prescription. This would necessitate the consumer visiting the doctor for a prescription. This provides an added cost to the consumer.
- Dihydrocodeine is an efficacious cough-suppressant.
- There are minimal side effects with dihydrocodeine.

The public submissions will be made available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the Schedule 2 entry for dihydrocodeine be deleted and the Schedule 8, 4 and 3 entries be amended as follows:

Schedule 8 – Amend Entry

DIHYDROCODEINE **except** when included in Schedule ~~2,~~ 3 or 4.

Schedule 4 – Amend Entry

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or

b) in undivided preparations with a concentration of not more than 2.5 per cent of dihydrocodeine,

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

Schedule 3 – Amend Entry

DIHYDROCODEINE when indicated for cough suppression and compounded with one or more other therapeutically active substances:

a) in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or

b) in undivided preparations containing 0.25 per cent or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine,

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

Schedule 2 – Delete Entry

~~DIHYDROCODEINE when compounded with aspirin and no other therapeutically active substance in divided preparations:~~

a) ~~containing 5 mg or less of dihydrocodeine per dosage unit;~~

b) ~~packed in blister or strip packaging or in a container with a child-resistant closure;~~

c) ~~enclosed in primary packs containing 25 or less dosage units; and~~

d) ~~labelled with a recommended dose not exceeding 10 mg of dihydrocodeine.~~

The Committee also recommended an implementation date of **1 October 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; (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:

- Dihydrocodeine is effective for stubborn, unproductive cough.
- Dihydrocodeine has a known potential for abuse, but misuse is uncommon with the current formulation, and overdose, although possible, doesn't appear to be common.
- There is a single product available which is indicated for stubborn, unproductive cough.
- There is limited evidence of respiratory depression in overdose, and potential toxicity in high doses. Reports of overdose were largely from the UK where dihydrocodeine is used in the context of addiction treatment, and the product used is in tablet form.
- Dihydrocodeine can produce euphoria and has a known potential for abuse. The potential for abuse is limited by the formulation, indication, Poisons Schedule and potential cost.
- Consideration should be given to monitoring adverse events and additional safeguards to prevent misuse in light of the changed access to non-prescription codeine from February 2018.
- There is a lack of evidence of abuse of the current product to justify removing it from Schedule 3, however the Schedule 3 entry should be limited to products used for cough suppression.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is to delete the Schedule 2 entry for dihydrocodeine and amend the Schedule 8, 4 and 3 entries. The proposed Schedule entry is as follows:

Schedule 8 – Amend Entry

DIHYDROCODEINE **except** when included in Schedule 3 or 4.

Schedule 4 – Amend Entry

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or

b) in undivided preparations with a concentration of not more than 2.5 per cent of dihydrocodeine,

except when included in Schedule 3.

Schedule 3 – Amend Entry

DIHYDROCODEINE when indicated for cough suppression and compounded with one or more other therapeutically active substances:

a) in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or

b) in undivided preparations containing 0.25 per cent or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine.

Schedule 2 – Delete Entry

The proposed implementation date is **1 October 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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- There is data indicating dihydrocodeine is an efficacious cough suppressant.
- There are lower blood levels of its metabolites compared to codeine.
- Dihydrocodeine has a known potential for abuse, but misuse is uncommon with the current formulation, and overdose, although possible, doesn't appear to be common.
- There is a single Schedule 3 product available which is indicated for stubborn, unproductive cough.
- There is limited evidence of respiratory depression in overdose, and potential toxicity in high doses. Reports of overdose were largely from the UK where dihydrocodeine is used in the context of addiction treatment, and the product used is in tablet form.
- Dihydrocodeine can produce euphoria and has a known potential for abuse. The potential for abuse is limited by the formulation, indication, Poisons Schedule and potential cost.
- Consideration should be given to monitoring adverse events and additional safeguards to prevent misuse in light of the changed access to non-prescription codeine from February 2018.
- There is a lack of evidence of abuse of the current product to justify removing it from Schedule 3, however the Schedule 3 entry should be limited to products used for cough suppression. Restricting its Schedule 3 indication to cough suppression only will restrict products and use.
- There needs to be consideration on whether a 200mL Schedule 3 product is appropriate.
- There are no Schedule 2 products on the ARTG.

1.2. 1,3-Dimethylbutylamine (DMBA) and other aliphatic alkylamines including 1,5-dimethylhexylamine (DMHA)

Referred scheduling proposal

An application was submitted to include entries for 1,3-dimethylbutylamine (DMBA) and other aliphatic alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA) in Schedule 10.

Current scheduling status

DMBA and DMHA are currently not specifically scheduled. However, the related substances, 1,3-dimethylamylamine (DMAA), propylhexedrine and tuaminoheptane are in the Poisons Standard as follows:

Schedule 10

1,3-DIMETHYLAMYLAMINE (DMAA)

Schedule 4

PROPYLHEXEDRINE.

Schedule 2

TUAMINOHEPTANE.

Scheduling history

DMBA and DMHA have not been previously considered for scheduling; therefore a scheduling history is not available.

DMAA

In August 2012, the ACMS considered a delegate-initiated proposal to list DMAA in Schedule 9 of the Poisons Standard, following New Zealand's temporary Class Drug Notice of 8 March 2012 advising that DMAA would be classified as a temporary class drug (equivalent to Schedule 9). New Zealand's temporary prohibition of DMAA came into effect on 9 April 2012.

Members noted that: there was inadequate evidence to suggest DMAA's toxicological and pharmacological properties warrant a Schedule 9 listing. DMAA is not listed in either Schedule IV to the *United Nations Convention on Narcotic Drugs, 1961* or in Schedule 1 to the *United Nations Convention on Psychotropic Substances, 1971*. There was a lack of supporting evidence to reach the conclusion that DMAA needs the same level of control as amphetamine. DMAA's toxicological properties meet the Appendix C (now Schedule 10) scheduling criteria. In the absence of a current accepted therapeutic use, the stimulant effect that can induce a psychoactive effect, its active promotion as a party drug as well as a sports supplement, the lack of evidence of dependence, the significant number of adverse events including cardiac, nervous and psychiatric disorders that have been reported with use of DMAA including cerebral haemorrhage and heart attacks and the high potential for misuse and abuse, the committee recommended that the substance be placed in Appendix C (now Schedule 10). Based on DMAA's toxicity, lack of data supporting long-term safety, wide variability in potency of different doses of DMAA and the high risk of use, misuse and illicit use, the delegate placed DMAA in Schedule 10 effective on 8 August 2012[7]. Reasons for the substance ban were published on the TGA website at: The TGA decision to ban DMAA.

[7] Scheduling delegate's final decisions: DMAA, August 2012

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 10 – Proposed New Entry

1,3-DIMETHYLBUTYLAMINE (DMBA) AND OTHER ALIPHATIC ALKYLAMINES WITH STIMULANT PROPERTIES INCLUDING 1,5-DIMETHYLHEXYLAMINE (DMHA) **except** when separately specified in these schedules.

Index – Proposed New Entry

1,3-DIMETHYLBUTYLAMINE (DMBA) AND OTHER ALIPHATIC ALKYLAMINES WITH STIMULANT PROPERTIES INCLUDING 1,5-DIMETHYLHEXYLAMINE (DMHA)
cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5—dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA

Schedule 10

The applicant's reasons for the request are:

- 1,3-Dimethylbutylamine (DMBA) is a structural analogue of 1,3-Dimethylamylamine (DMAA) which was previously included in Schedule 10 of the Poisons Standard. It is proposed DMBA be added to the same schedule as DMAA due their structural and pharmacological similarity and potential for misuse and potential to result in harm. DMBA is a stimulant with no known therapeutic use.
- 1,3-Dimethylbutylamine (DMBA) has structural and likely pharmacological similarity with 1,3Dimethylamylamine (DMAA). DMAA has been banned by regulatory agencies in United States of America (USA), United Kingdom, the Netherlands and Brazil because of its links to negative health events including as strokes, heart failure and sudden death. In 2012, Australia listed DMAA Appendix C (now Schedule 10). In New Zealand, DMAA was classified as a prescription medicine and it was noted that that it did not meet the definition of a dietary supplement. The applicant questions the classification of DMAA, given the deaths linked to DMAA internationally.
- DMBA is prohibited from sport under the World Anti-Doping Agency (WADA) List of Prohibited Substances and Methods, due to its structural similarity to DMAA under category 'S6. Stimulants'.
- DMBA appears to have become increasingly prevalent in supplements following the removal of DMAA from dietary supplements due to the intervention of food regulators in several countries. The effects of DMBA in humans have not been fully studied or clinically evaluated, and as such its efficacy and safety is unknown. Cohen, *et al.*, (2014), called for regulatory agencies to act expeditiously to warn consumers and remove DMBA from supplements.
- A review of reports in online forums states that users had a strong stimulant effect. Anecdotal side effects reported by users of DMBA included 'jitteriness (sic), rapid heartbeat, dizziness, headache, and a crash after it has worn off'. There were also reports of depression and anxiety.
- Despite the lack of proof of the efficacy and safety of products containing DMBA they are readily available for purchase in Australian supplement stores and through online suppliers in Australia and overseas. Distributors are promoting products containing DMBA as supplement that improves athletic performance, increases weight loss and enhances brain function.
- Supplement products containing DMBA have promoted or implied that DMBA, is a 'naturally occurring' botanical substance derived from Pouchong tea (Camellia sinensis). This claim has been proven to be false, an analysis of 25 authentic and commercial samples of Camellia sinensis tea leaves failed to detect DMBA.

- DMBA is prohibited from sport under the World Anti-Doping Agency (WADA) List of Prohibited Substances and Methods, due to its structural similarity to DMAA under category 'S6. Stimulants'.

- Since DMBA is a synthetically produced compound, the United States Food and Drug Administration (FDA) issued a warning in April 2015 that DMBA is not an approved dietary ingredient. The FDA determined products containing DMBA would not meet the definition of a "dietary supplement" and supplements containing DMBA are considered to be adulterated. The FDA has issued warnings, requiring manufacturers to immediately cease distribution and recover products containing DMBA already in the marketplace.

- Supplement manufacturers appear responsive to regulatory initiatives to restrict the supply of substances by converting to analogues or substances of similar effects. When regulatory agencies banned DMAA from all dietary supplements, alternative pressor amines such as DMBA appeared on the market replacing DMAA supplements. This demonstrates the need to regulate to prevent other compounds of this class from being added as ingredients to supplements.

- There are reports by supplement distributors online of plans to replace DMBA in supplements should DMBA be regulated in a similar way to DMAA. One of the suggested replacement substances is DMHA. Websites such as Herb Nutritionals and Mr Supplement have called DMHA a replacement for DMAA and DMBA. The websites also note that although there are unverified claims of the botanical nature of the compound, DMHA is likely to be synthetically produced.

- Given its structural similarity to DMAA, the application seeks to list DMBA on Schedule 10. Should this not be considered appropriate, the application seeks to list DMBA in Schedule 4.

- Given the evidence that more advanced analogues of DMBA, such as DMHA, and other aliphatic alkylamines with similar stimulant properties are reaching the market, the applicant also propose the scheduling apply to the class of substances. Scheduling of DMBA and its alkyl-analogues will protect public health from the potential adverse impacts of these unapproved substances. The adaptability of the supplements industry in developing chemically similar substances with similar stimulant like properties further underlines the need to be proactive and consider including an analogues clause that thereby schedules this class appropriately.

Australian regulatory information

DMBA and DMHA are not currently scheduled in Australia.

A search of the ARTG found no products containing DMBA or DMHA.

The Australian Sports Anti-Doping Authority (ASADA) has issued a warning to athletes, asserting that the presence of DMBA in a bodily sample collected during the competition period is an anti-doping rule violation and may attract a range of penalties including a 2-year ban from sport. If an anti-doping organisation can however demonstrate that the athlete intentionally took DMBA, the ban could be as high as 4 years.

International regulations

1,3-Dimethylbutylamine (DMBA)

DMBA is prohibited from sport under the World Anti-Doping Agency (WADA) List of Prohibited Substances and Methods, due to its structural similarity to DMAA under category 'S6. Stimulants'. WADA, noted that novel psychoactive substances (DMBA and DMHA) are derived from stimulants and marketed for these effects. The substances arrive on the market with little pharmacological data and the use of non-approved drugs in humans poses risks for health. Under the World Anti-Doping Code, use of these substances by athletes may result in ineligibility to compete in sport for up to 4 years. WADA confirmed DMBA is deemed to be a health risk given it is a non-approved drug with little pharmacological data regarding its effect on humans.

The US FDA issued a statement in relation to the inclusion of DMBA in dietary supplements[8] following warning letters to 14 companies sent in April 2015, where DMBA was considered an adulterant in 17 products. The US FDA considers any dietary supplement containing DMBA to be "adulterated".

In New Zealand, DMBA is classified as a psychoactive substance and its sale and supply are prohibited under the Psychoactive Substances Act.

1,5-Dimethylhexylamine (DMHA)

No information could be found regarding the status of DMHA in the USA. However, the US FDA website includes warnings regarding DMAA, DMBA and BMPEA (β-methylphenylethylamine, reportedly sourced from *Acacia rigidula*) in Dietary Supplements[9]. None of these substances have been determined to meet the statutory definition of a dietary ingredient. The US FDA issued warning letters to 5 companies sent in April 2015 regarding BMPEA and *Acacia rigidula*[10].

No information could be found regarding the status of DMHA in New Zealand.

In Canada, DMHA is known as 'octodrine and its salts' and is listed as prohibited on the Health Canada Cosmetic Ingredient list.[11]

Substance summary

1,3-Dimethylbutylamine (DMBA)

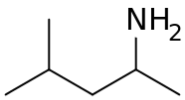


Figure 1.2A: Structure of DMBA

DMBA, is an aliphatic amine stimulant that is structurally related to DMAA, where a butyl group replaces the amyl group. DMBA is commonly found in OTC supplements commonly described as 'pre-workouts' and 'fat burners'. DMBA has a molecular weight 101.2, and molecular formula $C_6H_{15}N$.

Some products market DMBA on labels as a compound extracted from Pouchong tea and infer that it is a natural product, rather than synthetic. This may imply safety for consumption. A similar marketing approach was used for DMAA as a geranium extract. However, Cohen, *et al.,* (2014) noted 'we are unaware of any scientific evidence that DMBA has ever been extracted from any plant, while synthetic DMBA is easy to synthesise and widely available'.

DMBA belongs to the family of pressor-amines including DMAA, tuamine and propylhexedrine. The concentrations found in the supplements analysed strongly suggest DMBA is synthetically mass-produced to create pharmaceutical effects.

DMAA was listed in Schedule 10 in 2012. The use of DMBA and structurally related stimulants has generated concern in medical circles due to their amphetamine-like effect and possible health consequences. It appears manufacturers are intentionally including DMBA in sports supplements to restore, and possibly surpass, the effect generated by DMAA before its prohibition.

In the scheduling of DMAA in August 2012 the ACMS noted:

- there are risks due to DMAA's toxicity
- DMAA has no current accepted therapeutic use

[8] DMBA in Dietary Supplements
[9] DMBA in Dietary Supplements
[10] BMPEA in Dietary Supplements
[11] Cosmetic Ingredient Hotlist

- DMAA has a stimulant effect which can induce a psychoactive effect
- there are a number of significant adverse events including cardiac, nervous and psychiatric disorders that have been reported with use of DMAA including cerebral haemorrhage (stroke) and heart attacks
- there is a wide variability in the potency of the different doses of DMAA

As DMBA is a new ingredient there do not appear to be any peer-reviewed studies assessing the pharmacology, toxicology, and safety of the compound.

1,5-Dimethylhexylamine (DMHA)

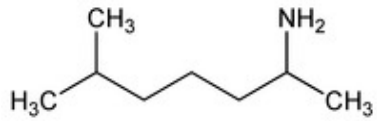


Figure 1.2B: Structure of DMHA

DMHA, also referred to as Octodrine, 6-methyl-2-heptanamine, molecular weight 129.3, has the following molecular formula $C_8H_{19}N$. DMHA is an α-adrenergic agonist and decongestant. The hydrochloride salt is crystalline and soluble in water, and the Merck Index reports LD_{50} in mice, rats (mg/kg): 59, 41.5 i.p. Websites report that DMHA is found in sufficient doses in nature, in particular in the *Kigelia africana* fruit and state that this allows it to be considered a dietary supplement and get approval from the relevant authorities[12]. Website product names that contain DMHA include *Giant Sports Giant Rush*.

There has been limited research regarding the harms and possible therapeutic benefits associated with the use of the substances proposed for scheduling. The potential side effects of this class of stimulants are wide ranging. Significant adverse events include cardiac, nervous and psychiatric disorders that have been reported with use of DMAA. As an analogue of this Schedule 10 substance, DMBA is believed to pose similar health risks.

The health risks from DMBA in pharmacological doses are unknown. DMBA has never been studied in humans. DMBA has pressor effects and DMBA should be considered an active pharmaceutical ingredient that requires rigorous clinical testing and evaluation prior to marketing.

These substances are being used by athletes and the broader community as a stimulant before physical activity. Supplements containing DMBA have been marketed to improve athletic performance, increase weight loss and enhance brain function.

Available information on pre-workouts and thermogenics suggest that this part of the supplement industry is expanding considerably in Australia.

DMBA can be included in sports supplements as part of a proprietary blend and as such product labelling usually does not specify the exact dosage per serving.

The study conducted by Cohen et al (2015) tested the relative concentrations of DMBA in a range of sports supplements sold in the USA ranging from 13 mg to 120 mg per serving. Based on the maximum daily number of servings some products allowed for a daily intake of up to 320 mg. As there has been no testing on the safety or efficacy of this compound it is unknown what level of intake (if any) would be safe. Australian supplement websites and internet forums report taking three to five times the recommended daily dose in one serving in order to experience the full psychoactive effect.

An analysis of numerous supplements on the Australian market produced data showed two products from the pre-workout and weight management category contained DMBA and DMAA at high

[12] Is this the new DMAA? and The New DMAA (DMHA / 2-Aminoisoheptane / Octodrine)

concentrations and other products with low-level cross-contamination in complex botanical ingredients.

Due to the purported psychoactive properties of DMBA, it is used primarily as a stimulant to increase focus during workouts. It also has the potential to be used for other purposes and has been promoted as a study aid as its stimulant properties are reported to increase mental focus.

Pre-meeting public submissions

No submissions were received.

Summary of ACMS advice to the delegate

The committee advised that a new entry be created for 1,3-dimethylbutylamine (DMBA) and other alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA) in Schedule 10, **except** when separately specified in these schedules, as follows:

Schedule 10 – New Entries

1,3-DIMETHYLBUTYLAMINE (DMBA) **except** when separately specified in these schedules.

1,5-DIMETHYLHEXYLAMINE (DMHA) **except** when separately specified in these schedules.

ALKYLAMINES WITH STIMULANT PROPERTIES **except** when separately specified in these schedules.

Index – New Entries

1,3-DIMETHYLBUTYLAMINE (DMBA)
cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

1,5-DIMETHYLHEXYLAMINE (DMHA)
cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

ALKYLAMINES WITH STIMULANT PROPERTIES
cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate)

Schedule 10

The committee also recommended an implementation date of **1 October 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; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance.

The reasons for the advice comprised the following:

- There is a significant health risk.
- DMBA is readily available in Australia despite lack of proof of efficacy and safety, and there is no current accepted therapeutic use.

- DMBA is listed by ASADA and WADA in anti-doping rules. WADA considers DMBA to be a health risk due to little pharmacological data of its effects in humans and is a non-approved drug.
- The potential for misuse and abuse is high.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is to create new entries for 1,3-dimethylbutylamine (DMBA) and other alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA) in Schedule 10, except when separately specified in these schedules. The proposed Schedule entry is as follows:

Schedule 10 – New Entries

1,3-DIMETHYLBUTYLAMINE (DMBA) **except** when separately specified in these schedules.

1,5-DIMETHYLHEXYLAMINE (DMHA) **except** when separately specified in these schedules.

ALKYLAMINES WITH STIMULANT PROPERTIES **except** when separately specified in these schedules.

Index – New Entries

1,3-DIMETHYLBUTYLAMINE (DMBA)
cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

1,5-DIMETHYLHEXYLAMINE (DMHA)
cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

ALKYLAMINES WITH STIMULANT PROPERTIES
cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisoheptane, DMHA, 1,5-dimethylhexylamine , 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate)

Schedule 10

The proposed implementation date is **1 October 2017**, since this is the earliest possible implementation date.

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; (e) the potential for abuse of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- There is a significant health risk.
- DMBA is a structural analogue of DMAA which was previously included in Schedule 10 of the Poisons Standard. DMBA is readily available in Australia despite lack of proof of efficacy and safety, and there is no current accepted therapeutic use.
- DMBA is listed by ASADA and WADA in anti-doping rules. WADA considers DMBA to be a health risk due to little pharmacological data of its effects in humans and is a non-approved drug.
- The potential for misuse and abuse is high.

1.3. Ulipristal

Referred scheduling proposal

An application was submitted to amend the Schedule 3 entry for ulipristal by including 'ulipristal for emergency post-coital contraception' in Appendix H.

Current scheduling status and relevant scheduling history

Ulipristal is currently listed in Schedules 3 and 4 of the Poisons Standard.

Schedule 4

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

Schedule 3

ULIPRISTAL for emergency post-coital contraception.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Appendix H – Proposed New Entry

ULIPRISTAL for emergency post-coital contraception

Index – Proposed Amendment

ULIPRISTAL

Schedule 4
Schedule 3
Appendix H

The applicant's reasons for the request are:

- Emergency contraception (EC) gives women a simple, safe and convenient option to avoid an unintended pregnancy if used within a few days of UPSI. However, while sales of EC in Australia

are approaching 650,000 units per year (IMS October 2015 - September 2016), knowledge about the availability and use of EC remains low.

- The applicant refers to a 2011 study surveying 632 Australian women aged 16 - 35 that concluded that although Australian women have a high level of awareness of EC, their inadequate knowledge limits its potential to assist in reducing unintended pregnancy and abortion rates: "A media campaign could be an effective means of disseminating information about the pharmacy availability, time frame for effective use and safety of EC".

- The applicant refers to a 2008 study surveying 627 Australian university students regarding knowledge and attitudes about emergency contraception and their understanding of the risk for pregnancy that concluded that "EC needs to be better understood by all members of the community as a back-up contraceptive method after unprotected sexual intercourse to reduce the number of terminations of pregnancy after unprotected sexual intercourse to reduce the number of terminations of pregnancy and unwanted pregnancies" and "Allowing EC to be advertised via the mass media has the greatest potential to improve general community knowledge about EC".

- The applicant also refers to US and UK European studies that found media campaigns increased community awareness and education about this method of contraception and increased contact with EC hotlines and did not invoke any special controversy.

- The applicant estimates approximately 200 000 unplanned pregnancies and 80 000 terminations in Australia a year in 2005. Two thirds of women presenting for abortions in Australia reported contraception use at time of conception. The applicant's data shows the number of abortions decreased slightly since EC became available, but its availability has not had a significant impact.

- The applicant states that under the TG Act, 'Unless a substance is included in Appendix H, members of the community cannot be given any product-specific information including via company websites, display material in pharmacies or even via training material for pharmacy assistants.'

- The applicant proposes to determine the media used by women of reproductive age to obtain information on contraception options, including EC and identify the sources of information for the different age groups and how women in each age group prefer to receive this information. This will be used to develop appropriate, targeted and responsible direct-to-consumer advertising and informational material specific to ulipristal that supports and complements the role of pharmacists in assisting women facing the possibility of unintended pregnancy. This could include a dedicated web site, consumer leaflets for distribution through pharmacies, doctors' surgeries, family planning centres etc. and social media as well as the more traditional print and broadcast media.

- The applicant proposes involving professional pharmacy bodies in campaigns to educate women on the use of EC in general and ulipristal in particular with the aim of reducing the number of unwanted pregnancies and abortions (with education and training material covering the condition, the role and benefit of the product as EC, pharmacist involvement). The applicant requests a 12 month delay for implementation from the Schedule 3 implementation date to allow pharmacists to become familiar with the use of ulipristal as Schedule 3.

- Ulipristal is advertised in 25 EU countries. Branded advertising is allowed in 13 of those countries with 'category' (emergency contraception) advertising in the other 12 countries.

- Consumer surveys have shown that knowledge of the availability, safety and effects of EC is poor among Australian women and that this may act as a barrier to its use (Hobbs 2011, Calabretto 2008). Specific, targeted, responsible advertising that reinforces the important role of pharmacists has considerable potential to reverse this situation with a significant reduction in unwanted pregnancies and consequent abortions. This would have important direct and indirect benefits for public health and in avoiding the social and economic costs of abortions.

- The advertising of ulipristal is unlikely to lead to inappropriate patterns of medication use: as pharmacists are involved in every sale, the pack contains a single tablet to be taken as soon as possible after UPSI, so potential for inappropriate or incorrect use is low and all forms of advertising will emphasize the important role of pharmacists in advising women on the correct and appropriate use of ulipristal.
- The sponsor for ulipristal will lodge an application to change the label to the TGA to amend the label for the existing ulipristal acetate 30 mg tablet blister pack to match the requirements for schedule 3 medicines (adding a 'pharmacist only medicine' signal heading plus indications & directions for use) and in line with this proposes to comply with advertising of therapeutic goods in Australia must comply with the Therapeutic Goods Advertising Code (TGAC). Section 6(3)(e) of the Code requires the inclusion of words to the effect of: "YOUR PHARMACIST'S ADVICE IS REQUIRED" in all advertisements for schedule 3 medicines. This message will be a key feature in all advertising material.
- Pharmacists remain involved in sale of Schedule 3 medicines and the CMI will reflect the involvement of pharmacists in counselling consumers.
- Experience with the non-prescription use of levonorgestrel EC since 2003 provides reassuring evidence that pharmacy access has not created any particular indirect risk. Studies that have examined the use of EC when provided directly at the pharmacy or given in advance of need, have shown that, compared to prescription provision, direct access:
  - Does not increase sexual risk taking behaviour in adolescents (Ekstrand 2008, Harper 2008, Raine 2012).
  - Does not lead to increased frequency of unprotected intercourse (Marston 2005, Moreau 2006).
  - Does not lead to decreased use of effective methods of contraception (Marston 2005, Raine 2005, Ziebland 2005, Moreau 2006, Ekstrand 2008, Moreau 2008) and women's EC experience is actually described as a motivating factor leading to more consistent use of regular contraception (Gainer 2003).
  - Does not lead to increased rates of sexually transmitted infections (Raymond 2006, Raine 2005).
- The applicant states that ulipristal does not have an abortifacient action.
- The applicant proposes to work with pharmacy organisations to provide pharmacists educational materials in relation to ulipristal to meet legal and professional obligations and supports them in that role.
- The applicant proposes to discuss parameters for advertising with pharmacy organisations to ensure advertising and educational material will be framed to increase awareness of the availability of EC through pharmacists and to complement the pharmacist's role in ensuring the 'quality use' of ulipristal.
- While nearly 70 per cent of Australian women of reproductive age are using some form of contraception (Richters 2003), the uptake of the most effective forms of contraception, long-acting reversible contraception, remains low (Garrett 2015), leaving many women at an increased risk of an unplanned pregnancy.
- Women have expressed that the availability of emergency contraceptive pills over the counter is advantageous because it gives them more control over their contraception (Hobbs 2009).
- The need for more information about fertility and contraception, particularly emergency contraception, has been highlighted by both women and healthcare professionals across a number of studies. Young women have expressed the need for more information and education about emergency contraception, as there is little information available to them (Hobbs 2009). Not only is there a need for more information, but both women and healthcare professionals have expressed

the need for more inclusive and easier to access contraceptive information, including easy-to-understand wording, and information in audio and video formats (Garrett 2015).

- Women may be receiving conflicting, out-dated, inaccurate and anecdotal information, rather than evidence-based, current information.
- Women have reported frustration that healthcare providers had not informed them of alternatives to the contraceptive pill and many felt that they were unable to make informed choices about contraception because of limited understanding of their available options and how they work (Garrett 2015).
- Poor knowledge about emergency contraception has been linked to its non-use.
- When women take responsibility for their healthcare and seek EC from a pharmacy, they report being concerned about a lack of privacy within the pharmacy, resulting in feelings of awkwardness and embarrassment (Hobbs 2011). These women reported that they want the pharmacists' role to be limited and their experience at the pharmacy to be as short as possible (Hobbs 2009).
- Consumers want to exercise more control in the management of their own health, particularly in this personal and sensitive areas. Responsible, targeted advertising could start to address this issue while increasing community knowledge of the availability of this simple, safe and effective option for preventing unwanted pregnancy and at the same time supporting and enhancing the role of pharmacists in helping women through this difficult time.
- Ulipristal is a safe and effective medicine for the prevention of unwanted pregnancy.
- The ability to advertise ulipristal and make educational information available to consumers will significantly improve public awareness and knowledge of this simple, safe, effective and convenient option for Australian women to prevent unwanted pregnancies. This increased awareness has the potential to significantly reduce the number of abortions with consequent benefits for public health.

Australian regulatory information

Ulipristal acetate was included in the ARTG on 6 March 2015.

International regulations

Ulipristal was first approved in the EU in May 2009, where it is not subject to medical prescription and has marketing authorisation with the requirement of periodic safety update reports.

Ulipristal is approved as prescription emergency contraception in New Zealand, Canada and the USA. It was approved in the USA in August 2010. In Canada, ulipristal is marketed by two companies, XXXX in 30 mg tablet form and XXXX in 5 mg tablet form.

Substance summary

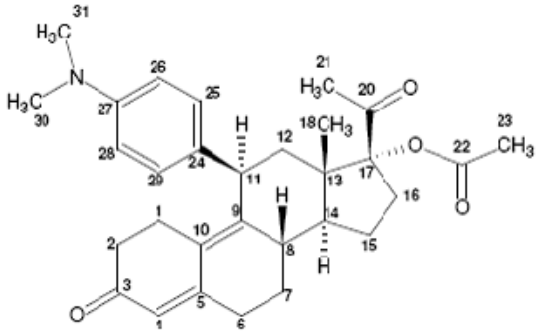


Figure 1.3: Structure of ulipristal acetate

Ulipristal acetate (chemical name: 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione) 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 luteinizing hormone surge.

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

Pre-meeting public submissions

Fourteen (14) submissions were received.

Thirteen (13) submissions supported the scheduling proposal. Main points:

- Ulipristal acetate provides increased efficacy and a longer window of opportunity to prevent unwanted pregnancy compared to other available emergency contraception.
- An increased uptake of emergency contraception has the potential to prevent unplanned pregnancies, contributing to the reduction of direct and indirect costs to the health care system.
- There would be a direct reproductive health benefit for women by enabling them to avoid unplanned pregnancies.
- Some women have misconceptions about its use, especially the time period of its effective use. It is also not widely understood by pharmacists and other practitioners.
- The likelihood of "inappropriate use" would be minimised with comprehensive training with the pharmacy sector and education with women.
- EC is extremely safe, even when used repeatedly. Compared with the potential health risks of pregnancy, taking ECPs to prevent unintended pregnancy is much safer.
- The pack contains a single tablet so the potential for inappropriate or incorrect use is very low.
- Ulipristal will remain in Schedule 3 meaning a pharmacist must be personally involved in every sale.
- There should also be an expansion of the list of health professionals to include remote area nurses, midwives and nurse practitioners to supply the ulipristal acetate to women in remote and isolated areas.
- Direct to consumer marketing will not only promote UPA, but importantly it will also serve to raise awareness of emergency contraception more generally in the community.
- All forms of advertising will emphasise the important role of pharmacists in advising women on the correct and appropriate use.
- A UK advertising campaign on emergency ulipristal was shown to be worthwhile.

Two (2) submissions did not support the scheduling proposal. Main points:

- There may be an increase in requests for the medicine from third parties with advertising.
- An Appendix H listing would not be in the public interest.
- Short period of experience as Schedule 3 medicine.

The public submissions will be made available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the Schedule 3 entry for ulipristal be amended by including 'ulipristal for emergency post-coital contraception' in Appendix H, as follows:

Schedule 3

ULIPRISTAL for emergency post-coital contraception.

Appendix H – New Entry

ULIPRISTAL for emergency post-coital contraception.

Index – Amend Entry

ULIPRISTAL

Schedule 4
Schedule 3
Appendix H

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

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

- Public health is likely to be improved, since increased community knowledge may improve access to this product, which will likely reduce the incidence of unplanned pregnancies.
- Low toxicity and low potential for abuse, since only available as single dose tablet.
- Risk of misuse may be mitigated through need for pharmacist counselling and supply. Ulipristal is not an abortifacient therefore risk of 'abuse' is minimal.
- Listing in Appendix H is supported by the majority of clinical stakeholders. Concerns raised by pharmacists may be mitigated through.
- A delayed start date will give some lead time for pharmacists to gain experience with the relatively new Schedule 3 listing.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 3 entry for ulipristal by including 'ulipristal for emergency post-coital contraception' in Appendix H. The proposed Schedule entry is as follows:

Schedule 3

ULIPRISTAL for emergency post-coital contraception.

Appendix H – New Entry

ULIPRISTAL for emergency post-coital contraception.

Index – Amend Entry

ULIPRISTAL

Schedule 4
Schedule 3
Appendix H

The proposed implementation date is **1 February 2018** to allow sufficient time for experience to be gained with the relatively new Schedule 3 listing prior to advertising.

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

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Public health is likely to be improved, since increased community knowledge may improve access to this product, which will likely reduce the incidence of unplanned pregnancies.
- Low toxicity and low potential for abuse, since only available as single dose tablet.
- Risk of misuse may be mitigated through need for pharmacist counselling and supply. Ulipristal is not an abortifacient therefore risk of 'abuse' is minimal.
- Listing in Appendix H is supported by the majority of clinical stakeholders. Concerns raised by pharmacists may be mitigated through.
- A delayed start date will give some lead time for pharmacists to gain experience with the relatively new Schedule 3 listing.

1.4. Ibuprofen

Referred scheduling proposal

An application was submitted with the following proposal to amend the Schedule 3 entry for ibuprofen to include a modified release dosage form of 600 mg of ibuprofen per dosage unit in packs of 32 or less dosage units when labelled:

a) with a recommended daily dose of 1200 mg or less of ibuprofen and

b) not for the treatment of children under 12 years of age.

and include in Appendix H ibuprofen 600 mg in modified release dosage form.

Current scheduling status

In monotherapy preparations, ibuprofen is included in Schedules 4, 3 and 2 as follows:

Schedule 4

IBUPROFEN **except**:

a) when included in or expressly excluded from Schedule 2 or 3; or

b) in preparations for dermal use.

Schedule 3

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

a) with a recommended daily dose of 1200 mg or less of ibuprofen; and

b) not for the treatment of children under 12 years of age;

except when included in or expressly excluded from Schedule 2.

Schedule 2

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

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

b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:

i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent);

ii) packed in blister or strip packaging or in a container with a child-resistant closure;

iii) in a primary pack containing not more than 25 dosage units;

iv) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

v) not labelled for the treatment of children 6 years of age or less; and

vi) not labelled for the treatment of children under 12 years of age when combined with phenylephrine.

It is also included in **Appendix F, Part 3** under the entry:

IBUPROFEN:

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

If you have a stomach ulcer.

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

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

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

For more than a few days at a time.

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

If you have asthma.

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

- Ibuprofen is listed in Schedule 4 when in compounded products with paracetamol, in a primary pack containing more than 30 dosage units.
- Ibuprofen is listed in Schedule 3 when in compounded products with paracetamol in a primary pack containing 30 dosage units or less **except** when included in Schedule 2.
- Ibuprofen is also listed in Schedule 2 when compounded in products with paracetamol in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack.

Scheduling history

In November 1985, the National Health and Medical Research Council (NHMRC) considered a request to change to Schedule 2 (currently in schedule 4 of UPS) as Ibuprofen was not scheduled in Victoria. It was agreed there were anaphylactic problems with people sensitive to aspirin. It was decided not to alter the scheduling.

In November 1987 the NHMRC considered a request to move ibuprofen from Schedule 4 to Schedule 2 with pack size restrictions. The committee was of the opinion that there was a place for ibuprofen outside Schedule 4. Recommendation for a new Schedule 3 entry with pack size restrictions of less than 50 tablets or capsules (200 mg).

In May 1995, the NDPSC considered proposal for a new Schedule 2 entry for ibuprofen and agreed to a new entry. Schedule 4 entry amended. New Schedule 2 for ibuprofen in divided preparations for oral use containing 200mg or less with a recommended dose of 1200mg or less.

In November 1998, the NDPSC considered an application for ibuprofen liquid suspension 100 mg/5 mL to be rescheduled from Schedule 4 to Schedule 2. Overall, the committee considered that a Schedule 3 classification was more appropriate for this formulation, and agreed that the Poisons Standard be amended accordingly. The committee agreed that a maximum daily dose should be stipulated, but because the proposed pack size was 200 mL (maximum of 4 g ibuprofen) a restriction on total content was not required for this classification. A new entry for Schedule 3 was agreed in undivided preparations for oral use when labelled with a recommended daily dose of not more than 1200 mg of ibuprofen.

In May 2000, the NDPSC considered a proposal to amend the Schedule 2 entry for ibuprofen to include oral liquid preparations containing more than 20 mg/1 mL. The committee considered the safety profile of ibuprofen and that Schedule 2 is appropriate when used in analgesic dose for minor and temporary ailments for short periods. The committee was seeking consistency with divided dose formulations.

In June 2003, the NDPSC considered a proposal to exempt ibuprofen from scheduling in divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 24 or less dosage units when labelled with a maximum recommended daily dose of 1200 mg of ibuprofen. The NDPSC decided to exempt ibuprofen from scheduling as requested, but with an amended maximum pack size (25 dosage units) and additional restrictions as follows: ibuprofen as the only therapeutically active constituent other than an effervescent agent; and requirements for label warnings (consistent with Appendix F warnings for Schedule 2 ibuprofen). The minutes note that the NDPSC had agreed

that the schedule wording should be comparable with that of the current aspirin and paracetamol entries.

In October 2003, following consideration of further public submissions, the NDPSC made some amendments to the label warning statements required for ibuprofen when exempted from scheduling, in particular, by adding warnings not to use the product unless advised by a doctor in children ages 6 years or less, or by people aged 65 years or over.

The NDPSC subsequently made some editorial amendments to the Schedule 2 exemption in June 2004 and February 2005.

In August 2010 the NDPSC considered the scheduling of paracetamol in combination with ibuprofen in June 2010. At that time, divided dose combinations containing up to 200 mg ibuprofen + 500 mg paracetamol were included in Schedule 2 (when labelled with a maximum daily dose of 1200 mg ibuprofen, and in packs of up to 100 dosage units). The NDPSC recommended, and the delegate confirmed, that the scheduling of ibuprofen and paracetamol that was current at that time remained appropriate.

In June 2011 the ACMS considered a proposal from the Advisory Committee on Non-prescription Medicines (ACNM) that the delegate/ACMS consider up-scheduling paracetamol/ibuprofen combinations (containing up to 500 mg paracetamol/200 mg ibuprofen) from Schedule 2 to Schedule 3. The ACNM had also recommended consideration of a maximum pack size for Schedule 3 paracetamol/ibuprofen combinations. The ACNM, in an assessment of an application to register a combination paracetamol/ibuprofen product, had raised concerns that the sponsor had not satisfactorily established the safety of the product, and considered that pharmacist intervention was needed to assist consumers with safe use of the combination.

The ACMS recommended that the combination paracetamol/ibuprofen products that were in Schedule 2 should be rescheduled to Schedule 3, when in packs containing 30 dosage units or less, with larger packs to be included in Schedule 4. The delegate agreed with the ACMS advice.

In February 2013 the ACMS considered proposals to reschedule paracetamol 500 mg when combined with ibuprofen 200 mg from Schedule 3 to Schedule 2 in packs containing 12 dosage units or less, and to also include Schedule 3 paracetamol when combined with ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol in combination with ibuprofen remained appropriate, and that paracetamol in combination with ibuprofen should not be included in Appendix H. The reasons for opposing rescheduling to Schedule 2 included insufficient data to disprove the safety concerns with the combination, lack of evidence to support rescheduling, lack of long-term evidence of safety of the combination, potential for additive gastrointestinal side effects, potential for inadvertent misuse and no experience with use of paracetamol/ibuprofen combination products in Australia. The ACMS also considered that there were no public health benefits with inclusion of the combination in Appendix H, and that advertising could lead to inappropriate use. The delegate agreed with the ACMS advice.

In June 2012, the ACMS considered a submission to reschedule ibuprofen from Schedule 2 to unscheduled when in divided preparations containing 200 mg or less of ibuprofen in fixed dose combination with 5 mg or less of phenylephrine, in packs containing not more than 25 tablets. ACMS advised the delegate that ibuprofen in combination with phenylephrine should be exempt from scheduling, as requested. The delegate decided to also restrict the scheduling exemption to use for the treatment of adults and children aged 12 years of age and over.

In November 2015, the ACMS considered a submission to amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less. The ACMS advised that paracetamol should be included in Schedule 2 when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a pack of not more than 3 day supply. The delegate agreed with the ACMS and made an interim decision based on the ACMS advice. After deferring their final decision to give consideration to a late submission received during the interim decision consultation period, the

delegate decided to vary their decision. In view of the dosage levels of paracetamol and ibuprofen the delegate considers it is more appropriate to limit the Schedule 2 part a) entry to 12 dosage units per pack rather than 3 days' supply packs as this would ensure the total paracetamol available in the pack would not be excessive.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 3 - Proposed Amendment

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

a) with a recommended daily dose of 1200 mg or less of ibuprofen; and

b) not for the treatment of children under 12 years of age;

IBUPROFEN in a modified release dosage form containing 600 mg of ibuprofen per dosage unit in packs of 32 or less dosage units when labelled:

a) with recommended daily dose of 1200 mg or less; and

b) not for the treatment of children under 12 years of age.

except when included in or expressly excluded from Schedule 2.

Appendix H – Proposed New Entry

Ibuprofen 600 mg in a modified release dosage form.

The applicant's reasons for the request are:

- The total daily dose of ibuprofen 600 mg IR/ER does not exceed 1200 mg and is therefore identical with that already approved for non-prescription ibuprofen 200 mg and 400 mg IR products.
- Ibuprofen 600 mg IR/ER is bioequivalent to ibuprofen 200 mg IR tablets after single and multiple doses in terms of AUCL, AUCI, AUC0-12h, and overall Cmax.
- The human safety profile for ibuprofen 600 mg IR/ER tablet is favourable and similar to that observed for ibuprofen 200 mg IR.
- The new formulation approximates the immediate release characteristics of an ibuprofen 200 mg tablet, combined with extended release properties to maintain plasma concentrations adequate to provide up to 12 hours of pain relief with less frequent dosing.
- Ibuprofen 600 mg IR/ER is efficacious for up to 12 hours in a model of dental pain, and this efficacy is sustained over multiple doses.
- The non-prescription availability of ibuprofen 600 mg IR/ER as Schedule 3 provides an alternative option not only to the limited range of non-prescription modified release analgesics available in the market for short-term use but also to existing immediate release analgesic products that fall short of providing longer lasting relief from persistent pain conditions likely to last for more than 6 hours.
- Creating a Schedule 3 and Appendix H entry of ibuprofen 600 mg IR/ER is consistent with the current scheduling status of comparable non-prescription analgesics namely, naproxen 600 mg modified release, diclofenac 25 mg immediate release and paracetamol 665 mg sustained release

that are permitted to be advertised as a result of inclusion in Appendix H or in the case of paracetamol, inclusion in Schedule 2.

- Ibuprofen 400 mg IR is currently included in Schedule 3, however, the information in this application is specific and relevant only to ibuprofen 600 mg IR/ER and does not translate to ibuprofen 400 mg IR. Hence, the proposal to include ibuprofen in Appendix H with specific conditions by stipulating the dosage strength and form, i.e. ibuprofen 600 mg in a modified release dosage form. This approach is consistent with the dimenhydrinate inclusion in Appendix H, which has specific conditions applied stipulating the indication of use that the product can only be advertised for.
- The non-prescription availability and advertising of ibuprofen 600 mg IR/ER as a Schedule 3 medicine provides significant benefits are listed below:
  - The non-prescription approval of ibuprofen 600 mg IR/ER would provide an alternative option to a limited range of modified release analgesics available in the market for short term use and existing immediate release analgesics that fall short of providing sustained effect for longer lasting (more than 6 hours) pain conditions.
  - Improved access to a treatment option that provides rapid and extended analgesic relief over 12 hours reducing the frequency of dosing for those consumers who cannot optimally manage their persistent pain lasting for more than 6 hours with existing immediate release analgesics.
  - Breakthrough pain that can occur with short-acting analgesics in addition to the need to wake during the night to take a medication can be avoided with the use of ibuprofen 600 mg IR/ER.
  - Quality Use of Medicines principles will be supported by advertising and consumer programmes which are effective communication tools to educate consumers on this new dosage form, drive familiarity of appropriate use and encourage consumers to consult a pharmacist.
  - Consultation with a pharmacist will ensure appropriate and quality use of the product and improved clinical outcomes for consumers including those currently accessing analgesics for self-selection from grocery and pharmacy channels who may not be optimally managing their pain condition.
  - Cost savings associated with the use of ibuprofen 600 mg IR/ER over immediate release formulations and economic benefits resulting from self-care and use of professional pharmacy resources.
- Suggested measures to manage potential risks associated with Schedule 3 entry and advertising ibuprofen 600 mg IR/ER (i.e. misuse, overdose, accidental ingestion, drug interactions, delay in treatment of an underlying condition, prolonged use) include:
  - Mandatory requirement for pharmacist intervention at the point of sale ensures that only consumers who have pain lasting for more than 6 hours have access to and use ibuprofen 600 mg IR/ER for the shortest period of time and inappropriate use for transient pain does not occur.
  - Consumer labelling contains necessary information to ensure correct and safe use of the medicine. The front/ main panel includes dosing-related statements, an entirely unique feature that differentiates the product from other non-prescription analgesics to emphasise correct dosing ensuring safe use of the product).
  - Implementation of education programs, resources and promotional materials (facilitated by inclusion in Appendix H) to educate consumers on the difference between persistent and transient pain ensuring appropriate and quality use of ibuprofen 600 mg IR/ER.

– Education programs for pharmacists to supplement current resources to help increase their awareness of a new dosage form of ibuprofen and ensure that request for the product by consumers is managed appropriately.

Australian regulatory information

A search of the ARTG[13] returned 240 entries for ibuprofen containing products. The ibuprofen products are approved for treatment of infants to adults and come in multiple dosage strengths and forms. Dosage strength and forms include 200 mg and 400 mg capsules, gel capsule, liquid capsule, 200 mg and 400 mg tablets and film coated tablets, 20 mg/1 ml, 40 mg/1 ml, 100 mg/5 ml oral liquids, 200 mg and 400 mg effervescent granules, 100 mg chewable tablets.

In addition to the oral forms there are 50 mg/g topical gels and 400 mg and 800 mg vials for injection.

Combination products include ibuprofen with codeine, ibuprofen with paracetamol and ibuprofen with pseudoephedrine. The ARTG also included entries for ibuprofen lysine 324 mg tablets and capsules as well as ibuprofen sodium dihydrate 256 mg capsule and tablet.

A search of the Database for Adverse Events Notifications (DAEN) between January 1985 and August 2016 resulted in 1229 cases related to ibuprofen with 819 cases with a single suspected medicine. Of these 36 cases were reported to have resulted in death.[14]

International regulations

There is no modified-release OTC ibuprofen product in NZ. Medsafe[15] regulates ibuprofen up to 200 mg for external use and oral use with pack size restrictions for general sale and/or pharmacy only depending on dose unit number or total ibuprofen amount. Up to 400 mg in single dose form in packs of less than 50 dose units are restricted without consent of the Minister or the Director-General. Dosages over 400 mg are considered prescription medicines. An 800 mg ibuprofen sustained release tablet is prescription-only in New Zealand.

In February 2016, Health Canada[16] switched a modified release oral dosage form that provides 600 mg or less per dosage unit of ibuprofen to non-prescription status. This is available as 'Advil 12 Hour', containing 'ibuprofen extended release tablets BP, 600 mg'. This appears to be the formulation proposed in the current scheduling request.[17]

February 2016: Health Canada updated its Summary Safety Review of prescription ibuprofen to investigate the link between ibuprofen at high doses and serious heart and stroke events[18].

The UK has 200 mg ibuprofen modified release products available OTC, and an 800 mg sustained release tablet available by prescription.

In the USA, 800 mg ibuprofen prolonged release tablets are available by prescription.

Substance summary

Ibuprofen is a white or almost white, crystalline powder or colourless crystals. It is practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates. The molecular weight of ibuprofen is 206.3, molecular formula $C_{13}H_{18}O_2$.

[13] Therapeutic Goods Administration Search results
[14] Database of Adverse Event Notifications - medicines
[15] Database of Medicine Classifications
[16] Notice - Prescription Drug List (PDL): Ibuprofen
[17] Advil Frequently Asked Questions
[18] Summary Safety Review - Prescription Oral Ibuprofen (Non-Steroidal Anti-inflammatory Drug) - Risk of Serious Heart and Stroke Adverse Events at High Doses

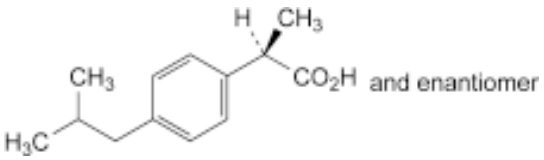


Figure 1.4: Structure of ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used as an analgesic, antipyretic, and anti-inflammatory. It decreases synthesis of pain- and inflammation-promoting prostaglandins via non-selective inhibition of both cyclo-oxygenase (COX), COX-1 and COX-2 enzymes. It has been extensively studied, and its efficacy and safety profile in humans following oral administration is well-established.

Numerous oral non-prescription ibuprofen formulations are now available (including tablets, capsules, liquigels, and oral suspension), with various dosage strengths. These 'immediate release' (IR) non-prescription dose forms are indicated for the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders and soft-tissue disorders such as sprains and strains. It is also used to reduce fever. The currently recommended non-prescription ibuprofen oral dose for pain and/or fever in adults is 200 - 400 mg every 4 to 6 hours as needed, with a maximum daily dose of 1200 mg.

Pre-meeting public submissions

Two (2) submissions were received. Both supported the scheduling proposal. Main points:

- Ibuprofen has well-characterised safety profile. The rescheduling would be consistent with other comparable analgesic substances and risks are mitigated via the intervention of a pharmacist (i.e. Schedule 3 criteria).
- This proposal aligns with other recent NSAID rescheduling decisions.
- Permitting advertising would have benefits for both consumers and pharmacists with increasing awareness of Schedule 3 medicines in general.

The public submissions will be made available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the Schedule 3 entry for ibuprofen be amended as follows:

Schedule 3 – Amend Entry

IBUPROFEN:

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

   i) with a recommended daily dose of 1200 mg or less of ibuprofen; and

   ii) not for the treatment of children under 12 years of age; or

b) in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32 dosage units, when labelled:

   i) with a recommended daily dose of 1200 mg or less of ibuprofen; and

   ii) not for the treatment of children under 12 years of age,

except when included in or expressly excluded from Schedule 2.

Appendix H – New Entry

IBUPROFEN

The committee also recommended an implementation date of **1 October 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; (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:

- This will give consumers access to a product for pain relief that is longer-lasting than currently available products.
- The potential for abuse and toxicity are low and in line with existing ibuprofen products.
- Pharmacist intervention, CMI and TGA mandated RASML warning statements will assist consumers with managing any risks.
- There is a public health interest to inform consumers about pain relief options through advertising.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 3 entry for ibuprofen. The proposed Schedule entry is as follows:

Schedule 3 – Amend Entry

IBUPROFEN:

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

   i) with a recommended daily dose of 1200 mg or less of ibuprofen; and

   ii) not for the treatment of children under 12 years of age; or

b) in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32 dosage units, when labelled:

   i) with a recommended daily dose of 1200 mg or less of ibuprofen; and

ii) not for the treatment of children under 12 years of age,

except when included in or expressly excluded from Schedule 2.

Appendix H – New Entry

IBUPROFEN

The proposed implementation date is **1 October 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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- This will give consumers access to a product for pain relief that is longer-lasting than currently available products.
- The potential for abuse and toxicity are low and in line with existing ibuprofen products.
- Pharmacist intervention, CMI and TGA mandated RASML warning statements will assist consumers with managing any risks.
- There is a public health interest to inform consumers about pain relief options through advertising.

1.5. Flurbiprofen

Referred scheduling proposal

An application was submitted to down-schedule flurbiprofen from Schedule 2 to unscheduled containing 0.25 per cent or less of flurbiprofen or containing 10 mg or less per dose of flurbiprofen when in undivided dosage forms.

Current scheduling status

Flurbiprofen is currently listed in Schedules 4 and 2 as follows:

Schedule 4

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

Schedule 2

FLURBIPROFEN in preparations for topical oral use when:

a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit; or

b) in undivided preparations containing 0.25 per cent or less, or 10 mg or less per dose, of flurbiprofen.

Scheduling history

Flurbiprofen was first included in Schedule 4 in November 1993. The committee decided to reschedule flurbiprofen in divided preparations for topical oral use containing 10 mg or less of flurbiprofen per dosage unit from Schedule 4 to Schedule 3 in February 2000. Subsequent rescheduling to Schedule 2

for this type of preparation followed in October 2002. The committee's decision was based on post-marketing safety data demonstrating that the preparation had a very low potential for causing adverse effects and no evidence of abuse or misuse.

In February and June 2010, the NDPSC considered an application to reclassify flurbiprofen to unscheduled in lozenges and liquid preparations for topical oral use. Members generally felt that the case for unscheduled access to topical oral flurbiprofen had not been made. Members agreed that there was only a small risk, but this needed to be balanced against little benefit. The committee agreed that preparations of flurbiprofen for topical oral use (10 mg or less) should remain in Schedule 2. The discussion on whether to include undivided preparations in Schedule 2 (and not unscheduled) included: a lack of experience with the use of undivided preparations in Australia; flurbiprofen had been classified as a Category C pregnancy risk and this was not appropriate for an unscheduled product; while there was only a small risk, there was little demonstrated benefit; the risk of idiosyncratic reactions to flurbiprofen. The committee confirmed the February 2010 decision to broaden the Schedule 2 flurbiprofen entry to include undivided preparations containing 0.25 per cent or less or 10 mg or less per dose of flurbiprofen.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 4 – Proposed Amendment

FLURBIPROFEN **except** when included or expressly excluded from Schedule 2.

Schedule 2 – Proposed Amendment

FLURBIPROFEN in preparations for topical oral use when:

a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit; or

b) in undivided preparations ~~containing 0.25 per cent or less, or 10 mg or less per dose, of flurbiprofen~~ **except**:

i) in preparations containing 0.25 per cent or less of flurbiprofen; or

ii) in preparations containing 10 mg or less per dose of flurbiprofen.

The applicant's reasons for the request are:

- The proposed rescheduling would allow the sale of throat sprays containing flurbiprofen in retail outlets other than pharmacy.
- Although there are no 'factors' for an 'unscheduled' classification, XXXXX meets or exceeds all of the factors for Schedule 2.
- The dose of NSAID in XXXX is low, at around 15% of the maximum recommended oral dose of flurbiprofen. Systemic exposure is further reduced by relatively low absorption from the oral mucosa of around 10% of the equivalent dose when swallowed.
- NDPSC in February 2010, in relation to a proposal for unscheduled status for flurbiprofen products for topical oral use, "agreed that there was only a small risk, but this needed to be balanced against little benefit".
- The NDPSC's conclusion on risk has been confirmed by the low number of adverse events reported in TGA's Database of Adverse Event Notifications since 2001 and the low incidence of adverse events in relation to cumulative exposure worldwide since 1976.

- In terms of benefit, XXXXX containing flurbiprofen 8.75 mg per 0.54 mL actuation was registered in September 2015 following evaluation by TGA. The approved indications are: "For relief of pain, swelling and inflammation associated with severe sore throats".
- Efficacy was further confirmed in a recent well-conducted study investigating the use of XXXX in adults with sore throat due to upper respiratory tract infection. This study concluded: "Flurbiprofen spray provides rapid and long-lasting relief from sore throat symptoms, and is well-tolerated over three days".
- The currently marketed XXXX products include the standard label warning statements that are required for all NSAIDS, including the small packs of ibuprofen that are available for sale in supermarkets.
- Given the low level of risk associated with flurbiprofen for topical oral use, the mitigation of that risk by appropriate labelling, the accepted efficacy of XXXX for the symptomatic treatment of sore throat and the long-standing acceptance of this condition as being suitable for self-treatment by consumers in a non-pharmacy environment, an 'unscheduled' classification is warranted.

Australian regulatory information

Currently, in Australia, flurbiprofen products are available as lozenges for the treatment of sore throats (Schedule 2) and eye drops for the treatment of intraoperative meiosis (Schedule 4).

The ARTG has flurbiprofen or its sodium hydrate salt, flurbiprofen sodium dehydrate, as the active ingredient included in 5 registered products associated with two different sponsors. The registered formulations include: 8.5 mg granules; 8.75 mg/0.54 mL throat spray solution pump metered dose aerosol; 0.03% eye drops and 300 microgram/mL eye drops; and 8.75 mg lozenge blister pack.

The current application is referring to 8.75 mg/0.54 mL throat spray solution pump metered dose aerosol.

International regulations

In the USA, flurbiprofen in eye drops and tablets are prescription medicines[19]. It was first entered as a prescription drug in 1985. No information could be found regarding flurbiprofen as an OTC product in the USA.

In Canada, flurbiprofen or its salts was entered on the Prescriptions Drugs List in December 2013 as a product for human use[20].

In New Zealand, flurbiprofen is a prescription product except in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit, which have been pharmacy-only medicines since 2010[21].

Flurbiprofen lozenges are also marketed in countries including, New Zealand, Italy, Thailand, Poland, Australia, United Kingdom and Ireland as non-prescription medicines. In addition they are also available in several European countries as prescription medicines[22].

Substance summary

Flurbiprofen is a non-selective COX inhibitor. It inhibits human recombinant COX-1 and COX-2 with IC_{50} values of 0.04 and 0.51 µM, respectively[23]. Flurbiprofen is a white crystalline solid, molecular

[19] Drugs@FDA: FDA Approved Drug Products
[20] Prescription Drug List
[21] Database of Medicine Classifications
[22] Application to the Medicines Classification Committee for Reclassification of a Medicine Proposal for reclassification of flurbiprofen 8.75mg lozenges from pharmacist only medicine to pharmacy medicine
[23] J. Barnett, J., *et al*. Purification, characterization and selective inhibition of human prostaglandin G/H synthase 1 and 2 expressed in the baculovirus system. *Biochimica et Biophysica Acta* **1209** 130-139 (1994)

weight 244.3, molecular formula $C_{15}H_{13}FO_2$. Flurbiprofen is a member of the phenylalkanoic acid derivative family of NSAIDs. It is used in ophthalmic solutions, throat lozenges and throat sprays. Other reported uses include orally for arthritis and dental pain. Pharmacokinetic data indicate greater than 99% protein binding, hepatic metabolism (CYP2C9), with an elimination half-life of 4.7 - 5.7 h and renal excretion.

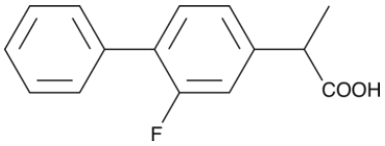


Figure 1.5: Structure of flurbiprofen (anhydrous free acid)

Flurbiprofen is a weak, monoprotic carboxylic acid (pKa 4.2), structurally related to ibuprofen. It has an anti-inflammatory effect when applied directly to the throat (de Looze 2016). Buccal absorption of flurbiprofen is low, with blood levels around 10% of those obtained from the same dose taken orally and swallowed (Gonzales-Younes 1991).

The recommended maximum daily dose of 43.75 mg (5 doses) in the throat spray is less than 15% of the 300 mg maximum recommended daily dose of flurbiprofen for oral ingestion (Martindale November 2016).

Pre-meeting public submissions

One (1) submission was received and this opposed the scheduling proposal. Main points:

- Schedule 2 is appropriate as it gives consumers access to professional advice to enable the determination of the nature and cause of the condition being treated.
- Unsupervised sales of flurbiprofen would pose unnecessary and preventable risk to consumers, particularly for use in pregnancy, use in children, pre-existing health conditions and interactions with other medications.
- A sore throat may be an indication of a more serious complication and those from demographics at higher risk of developing such complications may require referral to a doctor.

The public submission will be made available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the current scheduling of flurbiprofen remains appropriate.

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

The reasons for the advice comprised the following:

- there has been a fatal hypersensitivity reaction
- although other unscheduled substances are also pregnancy Category C, there is limited experience with this product
- no public health benefit from availability as unscheduled

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

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

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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice:
- There has been a fatal hypersensitivity reaction.
- Although other unscheduled substances are also pregnancy Category C, there is limited experience with this product.
- Unsupervised sales of flurbiprofen would pose unnecessary and preventable risk to consumers, particularly for use in pregnancy, use in children, pre-existing health conditions and interactions with other medications.
- No public health benefit from availability as unscheduled.

1.6. Penciclovir

Referred scheduling proposal

An application was submitted to exempt penciclovir from scheduling in preparations containing 1 per cent or less of penciclovir for the treatment of herpes labialis in packs containing 10 g or less.

Current scheduling status

Penciclovir is currently included in Schedules 4 and 2 of the Poisons Standard as follows:

Schedule 4

PENCICLOVIR except when included in Schedule 2.

Schedule 2

PENCICLOVIR for external use for the treatment of herpes labialis.

Scheduling history

In August 1996, the NDPSC considered a proposal to include penciclovir in Schedule 3 after registration approval was granted. It was noted that while penciclovir and aciclovir were related drugs and few adverse effects would be expected to be associated with the use of penciclovir, there was no data on adverse effects resulting from the widespread use of penciclovir in topical form. In addition, it did not appear to be more efficacious than aciclovir and a public need for this particular product had not been demonstrated. The committee considered that Schedule 4 for penciclovir was appropriate, in view of the lack of post-marketing experience with the topical preparation in Australia and the availability of other preparations of similar efficacy and well documented post-marketing history.

In May 1998, the NDPSC considered proposal to reschedule penciclovir from Schedule 4 to Schedule 2 in preparations for the treatment of cold sores (herpes labialis) in preparations containing 1% of penciclovir. The committee agreed that on the basis of market history, another product for treatment of herpes labialis already being in Schedule 2 and the low concern for possible unknown side effects of penciclovir (the active metabolite of famciclovir) that Schedule 2 was appropriate.

In August 1998, the NDPSC agreed that Schedule 2 was appropriate for dermal preparations containing penciclovir. The committee did not consider that there was sufficient justification to require Warning Statement 64 on either aciclovir or penciclovir cold sore creams. Warning statement 64 was recommended to be removed from Appendix F, part 3 for penciclovir and aciclovir at the February 1999 NDPSC meeting.

Relevant scheduling history for related substance, aciclovir

Current scheduling of aciclovir: Schedule 4 **except** in preparations containing 5 per cent or less of aciclovir for the treatment of herpes labialis in packs containing 10 g or less.

When compounded with hydrocortisone, aciclovir is Schedule 3 at 5% w/w or less in adults and adolescents (12 years of age and older).

In August 1984, the Poisons Scheduling Standing Committee agreed to place aciclovir in Schedule 4.

In May 1993, the committee considered a request for a change of topical aciclovir scheduling from Schedule 4 to Schedule 3, for an OTC indication, without the product or indication having already been approved by the TGA. The committee declined to consider the application for a drug product which it believed should be evaluated through the appropriate channels.

In May 1996, the NDPSC considered a submission in support of a change from Schedule 4 to Schedule 2 for aciclovir cold sore cream (5% w/w, 2g). The committee noted that when the sponsor had applied for ADEC approval for the indication for "the treatment of herpes simplex viral infection of the lips" that committee had agreed to the indication. The committee agreed to waive the "2 year rule" in view of the fact that aciclovir has been used for many years as an eye ointment in Australia and had been available overseas for many years as a cold sore non-prescription preparation, without giving rise to public health concerns.

In August 1997, the NDPSC noted the Australian Approved Name (AAN) change from acyclovir to aciclovir.

In February 1999, the NDPSC endorsed amendment of the Schedule 2 entry to read: 'ACICLOVIR FOR EXTERNAL USE FOR THE TREATMENT OF HERPES LABIALIS'.

In 2001 - February 2002, the NDPSC considered the proposal to exempt preparations containing 5% or less of aciclovir for dermal use from the requirements of scheduling. The committee agreed to exempt dermal preparations containing aciclovir for use in the treatment of cold sores from the requirements of scheduling with appropriate pack size restriction which accommodated existing Schedule 2 products.

In November 2001, the NDPSC agreed to exempt preparations containing 5 per cent or less of aciclovir for the treatment of herpes labialis in packs containing 10 g or less, on the grounds that herpes labialis was a short-term and self-limiting condition, appropriate for self-diagnosis and management by consumers. In addition, the product was simple to use and increased access to such a product would be beneficial to public health.

In October 2002, the NDPSC considered the NZ MCC recommendations to harmonise aciclovir and decided that it should remain unharmonised and be placed on the 2-year review list of unharmonised substances.

In March 2015, the ACMS reconsidered the scheduling of hydrocortisone when compounded with aciclovir, in relation to a proposed Schedule 3 amendment and Appendix H listing. The committee recommended that it was not necessary to include aciclovir in Appendix H as topical aciclovir has been exempt from scheduling for over a decade without signals indicating significant risk at this scheduling level. The Schedule 3 entry for hydrocortisone and hydrocortisone acetate was amended in October 2015 for human therapeutic use containing 1 per cent of hydrocortisone for dermal use in packs containing 2 g or less of such preparations, containing no therapeutically active constituent other than aciclovir (5% w/w or less) in adults and adolescents (12 years of age and older).

Relevant scheduling history for related substance, famciclovir

The current scheduling of famciclovir in the Poisons Standard is 'Schedule 4 **except** when included in Schedule 3', and 'Schedule 3: FAMCICLOVIR for oral use, in divided preparations containing a total dose of 1500 mg or less of famciclovir for the treatment of herpes labialis (cold sores)'.

The related substance famciclovir is an oral pro-drug that is converted to penciclovir *in vivo*. In June 1994, ADEC recommended approval for the registration of famciclovir for the treatment of herpes zoster [shingles] infection. In May 1995, the NDPSC agreed to include famciclovir in Schedule 4.

The TGA approved famciclovir for the treatment of recurrent herpes labialis (cold sores) in January 2007. The approved dosage was 1500 mg administered orally either as a single dose or 750 mg twice daily at 12 hourly intervals (to a total dose of 1500 mg per episode). Famciclovir is also indicated in immune compromised patients for the treatment of uncomplicated herpes zoster (shingles), and treatment and prophylaxis of herpes labialis.

In February 2009, the NDPSC considered a submission to down-schedule famciclovir (oral use, single dose) for the treatment of herpes labialis in immunocompetent patients from Schedule 4 to Schedule 3 and inclusion in Appendix H. The NDPSC noted the potential risk of generating resistance in the community and thus putting immunocompetent patients at risk. Also noted that in immunocompetent patients, the condition was self-resolving and the benefit of oral treatment over topical therapy was not significant. Overall, the NDPSC was of the opinion that the risks associated with down-scheduling outweighed the benefits, and agreed that the current scheduling remained appropriate.

The same rescheduling proposal was considered at the October 2009 NDPSC meeting. The applicant provided additional data that showed absence of evidence of resistance developed by immune compromised patients. The application also provided a draft pharmacist treatment algorithm and discussed some educational initiatives. The NDPSC noted that a lack of evidence of resistance was not the same as evidence proving that over the- counter (OTC) use of famciclovir orally would not lead to resistance. The NDPSC decided that the current Schedule 4 remained appropriate.

In May 2009, the New Zealand MCC rejected a submission to reclassify famciclovir 500 mg tablets from prescription medicine to restricted (pharmacist only) medicine. Subsequently, at its November 2009 meeting, the MCC reconsidered the submission with further information on warnings and training material relating to use in immunocompromised patients. The MCC agreed to reclassify famciclovir 500 mg tablets to restricted (pharmacist only) medicine in packs of 3 tablets for the treatment of recurrent herpes labialis.

In February 2010, the NDPSC considered whether to harmonise with the MCC's November 2009 decision in reclassifying famciclovir to restricted (pharmacist only) medicine. The NDPSC contended that the MCC's decision to reclassify famciclovir was dependent on a number of NZ specific requirements, and argued that Australian jurisdictions may not be able to enforce these requirements to a similar degree. The NDPSC recommended to not harmonise with NZ.

In October 2011 the ACMS again considered a proposal to down-schedule famciclovir to Schedule 3. The committee noted that the potential for development of resistance had been sufficiently addressed, since famciclovir is not activated into penciclovir until taken into cells infected with the virus. The proposed single (divided) oral dose was considered acceptable and would be beneficial when the use of topical formulation would not be appropriate (i.e. around the eyes). The committee agreed to down-schedule famciclovir to Schedule 3 for oral use, in divided preparations, containing a total dose of 1500 mg or less of famciclovir for the treatment of herpes labialis (cold sores). This was implemented in 2012.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 4 – Proposed Amendment

PENCICLOVIR **except** ~~included in Schedule 2~~ in preparations containing 1 per cent or less of penciclovir for the treatment of herpes labialis in packs containing 10 g or less.

Schedule 2 – Delete entry

~~PENCICLOVIR for external use for the treatment of herpes labialis.~~

Index – Proposed Amendment

PENCICLOVIR

Schedule 4
~~Schedule 2~~

The applicant's reasons for the request are:

- It is estimated that up to a third of the world's population are affected by herpes simplex at some stage in their life, with the majority of infections presenting as repeated vesicular eruptions, herpes labialis within the general community. While herpes labialis is self-limiting and will generally resolve within 7-8 days, it can significantly decrease quality of life of those with active or recurrent infections as it can be painful, emotionally distressing and highly contagious. Historically, penciclovir has been used to treat herpes labialis topically, successfully promoting faster resolutions and a reduction in pain.

- Topical cold sore treatments are commonly used by consumers after self-diagnoses of their condition, as already occurs with topical aciclovir. Penciclovir, an alternate option for recurrent cold sore sufferers, is in many respects similar to aciclovir, with benefits in improved healing time and associated pain. As a major difference with aciclovir, available as a 5% topical formulation, penciclovir topical products are formulated at 1%, and although less concentrated they still retain an effective therapeutic outcome due to their greater activity, exclusive towards infected cells.

- Penciclovir is indicated only for short term topical use. The product is intended to be applied at two hourly intervals, at least six times a day for up to four days as stated on labelling and packaging. The nature of the product indication is self-limiting. The mean duration of recurrences is 7-8 days, but individual episodes of up to 15 days have been reported. As for aciclovir, it has a low risk of masking a serious disease, compromising the medical management of a disease, or resulting in a consumer mistaking a cold sore for a more serious condition. With an indicated time frame for product use of 4 days, any misdiagnosis would not significantly delay any referral to a

healthcare professional. In addition to an excellent well-defined safety profile, penciclovir is a topical application with no known risk of misuse and abuse; it has high selectivity to viral cells; and low bioavailability / toxicity to human cells, making this medicine a good candidate for reclassification in line with aciclovir topical products.

- Reclassification of penciclovir topical would increase the availability of the product to the general community, and act as an alternative to aciclovir topical allowing consumers a greater freedom of choice. Reclassification would also be beneficial for immediate and early access to treatment, since penciclovir is effective at every stage of herpes labialis cycle, from tingle, to blister, to providing potential for early symptom relief regardless of the stage of the condition. With greater access and quicker healing, the virus will be less likely to be transmitted to others, potentially reducing spread and minimising frequency of occurrence.
- Aciclovir, a similar anti-viral agent indicated for the same condition, was reclassified in 2002 from Schedule 2 to Unscheduled, on the basis that the product was safe, simple to use and increased access would be beneficial to the general public. Since aciclovir is no longer a scheduled product when used topically for herpes labialis, it would be logical for both penciclovir and aciclovir to be similarly scheduled and equally accessible to the consumer.

Australian regulatory information

There is one registered product in Australia that contains penciclovir which is indicated for the treatment of recurrent cold sores (herpes labialis) in adults and children aged 12 years and over.

International regulations

In New Zealand penciclovir is considered Prescription, except for external use for the treatment of herpes labialis, and it is a pharmacy only medicine for external use for the treatment of herpes labialis[24]. The NDPSC was advised in November 1996 that penciclovir cream was given a Schedule 2 classification in New Zealand.

In the USA, penciclovir is marketed as a prescription 1% topical cream.[25]

In Canada, penciclovir was marketed as a prescription 1% topical cream;[26] however the product was cancelled post market.

No reference to penciclovir has been provided for in S26BB, as penciclovir is a scheduled ingredient and not eligible for use in listed medicines.[27]

Substance summary

Penciclovir is a synthetic guanine derivative, chemically designated as 9-[4-hydroxy-3-(hydroxymethyl)butyl] guanine. It is a white to pale yellow crystalline solid with a molecular weight of 253.3.

[24] Database of Medicine Classifications
[25] Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
[26] Denavir - Product information
[27] Therapeutic Goods (Permissible Ingredients) Determination No. 2 of 2016

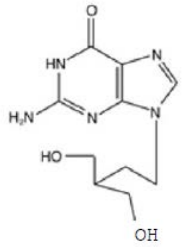


Figure 1.6: Structure of penciclovir

Penciclovir has inhibitory activity against herpes simplex virus (HSV) types 1 and 2. It targets virus-infected cells where it is rapidly converted into penciclovir-triphosphate (mediated via virus-induced thymidine kinase), which inhibits viral DNA polymerase by competition with deoxyguanosine triphosphate and is incorporated into the extending DNA chain, preventing significant chain elongation. Consequently, viral DNA synthesis and therefore viral replication are inhibited.

Penciclovir is only readily phosphorylated in virus-infected cells. In uninfected cells treated with penciclovir, concentrations of penciclovir-triphosphate are only barely detectable.

The active penciclovir triphosphate has a half-life of up to 10-20 hours, remaining active in infected cells for up to 12 hours.

Toxicity

Both penciclovir and aciclovir have a similar mechanism of action and a long history of use. Penciclovir has minimal side effects with the majority of adverse effects being at the site of application including, erythema, itching and contact dermatitis.

The applicant noted that the safety profile of aciclovir and penciclovir are fundamentally similar and for more than 20 years aciclovir use has been considered safe and well tolerated regardless of the administration route. A good safety profile of penciclovir cream has been reported in two large clinical trials. Penciclovir is poorly absorbed following oral administration. Systemic absorption is negligible and adverse effects are similar to those observed with placebo.

In the event of accidental oral ingestion or over-dosage, no untoward effects would be expected if the entire contents (2 g) of penciclovir 1% cream were ingested and no specific treatment is necessary. Some irritation of the mouth could occur.

Pre-meeting public submissions

One (1) submission was received, which opposed the scheduling proposal. Main points:

- The current scheduling remains appropriate due to best practice being a certain level of professional intervention.
- Broader access to immunocompromised individuals may contribute to drug resistance.

The public submission will be made available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that the Schedule 2 entry for PENCICLOVIR be deleted and that the Schedule 4 entry be amended as follows:

Schedule 4 –Amend Entry

PENCICLOVIR **except** ~~when included in Schedule 2~~ in preparations containing 1 per cent or less of penciclovir for the treatment of *herpes labialis* in packs containing 10 g or less.

Schedule 2 – Delete Entry

~~PENCICLOVIR for external use for the treatment of herpes labialis~~.

Index – Amend Entry

PENCICLOVIR

Schedule 4
~~Schedule 2~~

The committee also recommended an implementation date of **1 October 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; (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice comprised the following:

- Low toxicity
- Sufficient data available to demonstrate use of the product in its current presentation
- Public health benefit of increased access
- Penciclovir has a similar safety profile and precautions as unscheduled topical aciclovir

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is to delete the Schedule 2 entry and amend the Schedule 4 entry for penciclovir. The proposed Schedule entry is as follows:

Schedule 4 –Amend Entry

PENCICLOVIR **except** in preparations containing 1 per cent or less of penciclovir for the treatment of *herpes labialis* in packs containing 10 g or less.

Schedule 2 – Delete Entry

Index – Amend Entry

PENCICLOVIR

Schedule 4

The proposed implementation date to amend the Schedule 4 entry is **1 October 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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Low toxicity.
- Sufficient data available to demonstrate use of the product in its current presentation.
- Public health benefit of increased access.
- Penciclovir has a similar safety profile and precautions as unscheduled topical acyclovir.

1.7. Loratadine

Referred scheduling proposal

An application was submitted to exempt loratadine from scheduling when10 mg or less in divided preparations for oral use in packs containing not more than 5 dosage units when used in children 6 - 12 years of age for the treatment of seasonal allergic rhinitis.

Current scheduling status

Loratadine is in Schedules 4 and 2, and in Appendix F, Part 3 of the Poisons Standard as follows:

Schedule 4

LORATADINE **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

ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

Schedule 2

LORATADINE 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

b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

Appendix F, Part 3

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.

Warning statements: 39 (This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol) or 40 (This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a motor vehicle or operate machinery).

Scheduling history

At the May 1992 NDPSC meeting, the Committee recommended Loratadine be included in Schedule 4.

In November 1992 the NDPSC declined to down schedule loratadine to Schedule 3 due to concerns about cardiac side effects.

In April 1994, the NDPSC rescheduled loratadine tablets to Schedule 3.

In November 1995, the NDPSC rescheduled loratadine syrup to Schedule 3.

In May 1997, the NDPSC deferred a down-scheduling application for loratadine from Schedule 3 to Schedule 2, due to an article that was published in the Lancet, raising concerns of cardiovascular safety.

In August 1997 meeting, the NDPSC confirmed the current Schedule 3 entry.

Loratadine, cetirizine and fexofenadine were included in Appendix H in August 1998.

In February 1999, the NDPSC considered the rescheduling of loratadine from Schedule 3 to Schedule 2. The NDPSC agreed that loratadine in preparations for oral use should be rescheduled, and that the restriction to *'only therapeutically active ingredient'* should no longer apply.

In November 1999, the NDPSC supported a recommendation from the Trans-Tasman Harmonisation Working Party (TTHWP) that on the grounds of harmonisation cetirizine in preparations for oral use be rescheduled from Schedule 3 to Schedule 2. As a consequence of the deletion of the Schedule 3 entry was the deletion of the Appendix H (Schedule 3 Poisons permitted to be advertised) entry.

In October 2005, the NDPSC agreed to alter the wording of Appendix F Part 3 and remove cetirizine for oral use (except when included in Schedule 2) from Appendix K of the Poisons Standard. As the balance of current evidence indicates that cetirizine is no more sedating than loratadine.

In February 2012, the Advisory Committee of Medicines Scheduling recommended exempting from scheduling oral preparations containing 10 mg or less of loratadine in packs containing not more than five dosage units for the treatment of seasonal allergic rhinitis in adults and children over the age of 12 years. The scheduling delegate agreed with the ACMS advice, and implemented this decision on 22 November 2012.

In July 2013, the ACMS considered a proposal to reschedule loratadine from Schedule 2 to unscheduled in oral preparations containing 10 mg or less in packs containing not more than 5 daily doses for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and over, with a warning label recommending a daily dose not exceeding 10 mg loratadine for adults and children with body weight over 30 kg, or recommended daily dose not exceeding 5 mg loratadine for children with body weight 30 kg and under. The Committee recommended that the current scheduling of loratadine remained appropriate, due to the risk of inappropriate use and delay in correct diagnosis, the lack of data on adverse effects/experiences/poisoning in Australia, no substantial public health benefit in exempting from schedules and a complicated dosage regimen with risk of inappropriate dosing.

In March 2016, the ACMS considered the proposal to amend the schedule entries to increase the pack size of exempted loratadine from five dosage units to 10 dosage units. The scheduling delegate agreed with the advice from the ACMS and set an implementation date of 1 October 2016.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

LORATADINE **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~~ for children 12 years and over; or

~~ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.~~

c) in a primary pack containing 5 dosage units or less when labelled for children 6-12 years; and

i) labelled with a recommended daily dose not exceeding 10 mg loratadine for adults and children over 9 years of age, and

ii) labelled with a recommended daily dose not exceeding 5 mg

Schedule 2 – Proposed Amendment

LORATADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis when:

a) in a primary pack containing 10 dosage units or less when labelled for children 12 years and over; ~~and~~ or

b) ~~labelled with a recommended daily dose not exceeding 10 mg of loratadine~~ in a primary pack containing 5 dosage units or less when labelled for children 6-12 years; and

i) labelled with a recommended daily dose not exceeding 10 mg of loratadine for adults and children over 9 years of age, and

ii) labelled with a recommended daily dose not exceeding 5 mg loratadine for children 6-9 years of age.

The applicant's reasons for the request are:

- Allergic rhinitis is a symptomatic disorder of the nose induced by inflammation, with symptoms of nasal drainage, nasal congestion, sneezing and/or nasal itching. Allergic rhinitis is a common condition affecting children. In Australia, about 12-20% of children aged 6-14 years are affected and the prevalence could be up to 35-47% in some areas. Allergic rhinitis significantly impacts the health and quality of life in children and their carers. It reduces school attendance, impairs cognitive functioning and reduces learning ability and represents a large public health burden associated with significant healthcare costs.

- Allergic rhinitis is readily self-diagnosed by consumers and can be seasonal or perennial. SAR is caused by an IgE-mediated reaction to seasonal aeroallergens such as pollens. This reaction leads to typical symptoms such as sneezing and nasal congestion and is readily able to be identified. Most Australian adults now self-medicate for allergic rhinitis. The diagnosis and treatment of allergic rhinitis in children follows essentially the same pattern as that in adults other than in children younger than 2 years who may be referred to an allergist/immunologist for diagnosis and subsequent management. An April 2015 XXXX consumer study shows that Australian consumers purchase loratadine products for self-treatment including parents and carers who buy products for children.

- Second generation non-sedating antihistamines including loratadine, fexofenadine and cetirizine have been proven efficacious and safe for the control of SAR and are recommended as first line treatment for mild to moderate allergic rhinitis in both adults and children. To date in Australia, second generation non-sedating antihistamines are only available for children 12 years and over outside of pharmacies. This leaves an entire class of efficacious and safe medications unavailable for children under 12 years of age other than via pharmacy. This is in contrast to similar countries such as the UK and the USA where these medications have been freely accessible outside of pharmacies for children 2 years and over for more than 10 years.

- Loratadine is one of the leading second generation non-sedating antihistamines and is widely regarded as a safe and efficacious treatment for the symptoms of allergic rhinitis in children 12 months of age and over. Loratadine as an effective first line treatment for the symptoms of seasonal allergic rhinitis has been available for children 12 months and over in Australia since 1992, and it has been available as an unscheduled medicine in small packs of 5 tablets and capsules for children 12 years and over since 2012. With a long history of use in young children in Australia, access to loratadine only via pharmacy for children under 12 years of age presents a gap in access for affected children and their carers.

- Access to medicines can be restricted in terms of location and opening hours of community pharmacies in Australia. Non-pharmacy outlets such as supermarkets and local convenience stores are generally more accessible as there are many more outlets available, and they generally operate over longer trading hours. It is convenient for consumers to purchase a product suitable for their minor health condition from supermarkets or other convenience stores rather than only in pharmacies, especially for fast relief of symptoms. Increased access of a second generation non-sedating antihistamine like loratadine for children under 12 years of age outside of pharmacies will assist parents and carers and improve public health outcomes.

- The symptoms of SAR typically appear during the hayfever season when aeroallergens are abundant. The length of seasonal exposure to these aeroallergens is dependent on geographic location and climatic conditions, and can last for several months of the year in Australia. The flexibility of the antihistamine treatment loratadine which is used on an 'as needed' basis provides convenient self-medication during the hayfever season, especially for those with episodic or intermittent symptoms which may be triggered by the aeroallergens at any time during the season and last for weeks. Loratadine, with minimal toxicity compared to other medications, is an ideal candidate for rescheduling to an unscheduled medicine in a small pack of 5 dosage units for episodic treatment of symptoms in younger children during the hayfever season.

- The symptoms of SAR are easily recognised because of the rapid and reproducible onset and offset in association with pollen exposure, which are not likely to be indicative of a more serious underlying diagnosis. The seasonal nature of the symptoms leads to easy recognition by sufferers and carers, largely negating the need for professional advice. The rescheduling of loratadine from Schedule 2 to unscheduled in 2012 has shown that the risks of misdiagnosis or masking of underlying diseases are minimal. The proposed unscheduled loratadine products for children 6-12 years of age will retain the same label statements as the existing loratadine unscheduled product for use in children 12 years and over and will contain the same medical and safety information to ensure the safe use of the medication outside of pharmacies is continued in this age group. XXXX also proposes to include an additional label statement to the effect of 'Do not use this product when experiencing first-time hayfever symptoms without advice from a healthcare professional' to minimise any potential risk of misdiagnosis or delay in diagnosis in this particular age group.

- Loratadine is considered to be a ‘second generation non-sedating antihistamine’ with an excellent safety profile. The toxicity and safety of loratadine has been well established with over more than 20 years of use in Australia and internationally including use in children as young as 12 months of age.

- Loratadine has a safety profile similar to that of placebo, does not potentiate the CNS effects of alcohol or diazepam and there have been no reports of clinically significant interactions between

loratadine and drugs such as erythromycin, cimetidine and ketoconazole. Loratadine has a similar safety profile in children; the incidence of loratadine associated adverse effects in children appears to be similar to placebo.

- Loratadine has a wide therapeutic index with no unusual neurological symptoms or signs of toxicity in cases of accidental overdose. In volunteer studies, single doses of loratadine up to 160 mg were administered without any untoward effects. Loratadine is not associated with cardiovascular toxicity. Children who accidentally ingest large quantities of loratadine (up to 40 mg) have tolerated this well and can be adequately managed at home.

- Loratadine is generally safe for use in children 12 months of age and older. The types and frequencies of adverse events reported in children are consistent with those reported in adults with no increased risks identified in children. Only a few adverse events in children have been reported in Australia. The availability of unscheduled loratadine products in Australia since 2012 has not resulted in any safety concerns, providing confidence that the quality use of loratadine for children 6-12 years purchased in non-pharmacy outlets in small packs can be achieved by appropriate labelling and packaging.

- A simple age-based dosing instruction for children is proposed to ensure easy administration to children without healthcare professional advice. Current Schedule 2 loratadine medicines marketed for children in the age group of 6-12 years has an age and body weight based dosing instruction (10 mg for children 2 years and over with a body weight over 30 kg, and 5 mg for children 2-12 years of age with a body weight up to 30 kg). In a previous submission to the ACMS in July 2013, this age and body weight dosing regime was deemed too complicated for self-medication without healthcare professional assistance. Age-only dosing instructions, which are based on the evidence that the average Australian child with a body weight of 30 kg is around 9.5 years of age is proposed to ensure that the dosing is effective and safe and dosing instructions are clear and can be followed by parents and carers easily without professional advice. Proposed dosage instructions are as follows: Children 6-9 years: 1 tablet once daily as necessary Children 9-12 years and Adults: 2 tablets once daily as necessary. The proposed labelling will also state "Do not use more than the recommended dose".

- Given the evidence that loratadine has a well-established safety profile, and the risk of misuse and inappropriate use is rare, it is considered that an unscheduled pack size containing 5 dosage units of loratadine for children 6-12 years of age presents minimal risk to children while increasing the availability of an efficacious second generation non-sedating antihistamine.

- In countries with a similar regulatory system to Australia such as the UK and the USA, loratadine has been available for many years for children as an unscheduled medicine at a much younger age (2 years and over) with wider therapeutic indications SAR, perennial allergic rhinitis and chronic urticaria) with either no pack size restrictions or in larger pack sizes than in Australia. In the USA, loratadine in both solid and liquid forms is approved in OTC medications (equivalent to unscheduled medicines in Australia) for children 2 years and over without any pack size limitations. In the UK both solid and liquid forms of loratadine have been approved for children 2 years and over in large pack sizes (tablets 30 packs; liquids 70 mg) since 2012.

Australian regulatory information

The Australian Register of Therapeutic Goods (ARTG[28]) has fifty (50) entries for products containing loratadine listed. The products are marketed towards both adults and children's use and come in a range of dosage forms including, 1 mg/1 mL liquid (flavoured), 10 mg tablets and capsules, 5 mg chewable tablets, 10 mg orally disintegrating tablet and 10 mg liquid capsules. In addition there are combination products such as loratadine 5 mg with 120 mg pseudoephedrine sulphate.

[28] Therapeutic Goods Administration Search results

A search on the Database of Adverse Event Notifications list (DAEN) for dates between January 1992 and August 2016 returned 815 reported cases of adverse events related to loratadine. 710 of the cases were from a single suspected medicine. Four (4) cases were reported to have resulted in death from cardiac arrest (1), hypoxia (1), haematuria (1), and electrocardiogram abnormal (1)[29].

No reference to loratadine has been provided for in S26BB, as loratadine is a scheduled ingredient and not eligible for use in listed medicines.[30]

International regulations

Globally, loratadine-containing products are marketed in over 110 countries as a safe and effective non-sedating antihistamine for the treatment of allergic rhinitis and allergic skin disorders for adults and children.

Loratadine is available OTC in many countries. In 2 countries (Italy and Czech Republic) there is a pack size limit of 7 days' supply while in others the pack size limit is 10, 14, 30, 70 or unlimited.

In the UK, loratadine tablets have been available as an unscheduled medicine since 2002 in packs containing 7 dosage units for the symptomatic relief and treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children. The current unscheduled pack size limit for loratadine tablets is 30 dosage units when used for the symptomatic relief and treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria in adults and children 2 years and over and weighing more than 30 kg. Liquid dosage forms are also available unscheduled for children 2 years and over with a pack size limit of 70 mg.

In the USA, loratadine was first approved for OTC use (equivalent to unscheduled in Australia) in 2002 in tablet (including orally disintegrating tablets) and syrup forms for children 2 years and over for hayfever or other upper respiratory allergies without pack size limitations. In 2006, loratadine in chewable tablets and orally disintegrating tablets (5 mg) was further approved for OTC use for when used in children 2 years and over for the symptoms of hayfever or other upper respiratory allergies without pack size limitation.

Health Canada list 17 loratadine products in various dose rapid dissolve 5mg, 10 mg liquid capsule, tablets, capsules and 0.5 mg / mL oral syrup[31].

The New Zealand Medicines Classification Committee (MCC) at its November 2011 meeting recommended that loratadine be reclassified as a general sale (exempt from scheduling). Medsafe New Zealand regulates loratadine[32] in 10 mg oral divided solid dosage forms as general sale in pack sizes under 10 day supply, other oral dose forms are pharmacy medicines containing not more than 10 day supply. Products outside these restrictions are prescription products.

Substance summary

Loratadine is a white to off-white crystalline powder. It is freely soluble in methanol, ethanol and chloroform, soluble in ether and practically insoluble in water. The molecular weight of loratadine is 352.9, molecular formula $C_{22}H_{23}ClN_2O_2$.

[29] Database of Adverse Event Notifications - medicines
[30] Therapeutic Goods (Permissible Ingredients) Determination No. 2 of 2016
[31] Details for: ACTIVELLE LD
[32] Database of Medicine Classifications

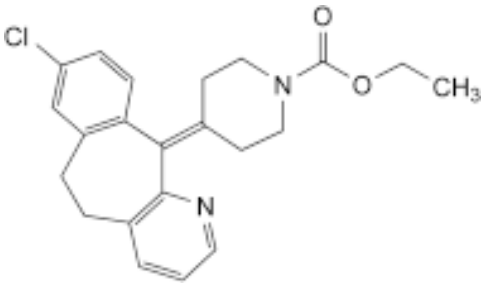


Figure 1.7: Structure of loratadine

Loratadine is a potent, long-acting tricyclic antihistamine with selective peripheral H1-receptor antagonistic activity. Its efficacy as a first line treatment for the symptomatic treatment of allergic rhinitis and allergic skin conditions such as urticaria (hives) has long been established. This once a day treatment for effective control of allergic rhinitis has been available in Australia and globally for more than 20 years. Loratadine has a rapid onset of action after oral administration, usually within one hour. Loratadine is well absorbed with peak plasma levels occurring at approximately 1-2 hours after dosing, and undergoes extensive first-pass metabolism to the active metabolite desloratadine and is then excreted in urine (~40%) and faeces (42%) in a 10 day period. Renal impairment has no significant effect on loratadine clearance.

Loratadine exhibits greater affinity for peripheral H1-receptors than for central H1-receptors, and loratadine and its metabolites do not readily cross the blood-brain barrier. These properties account for its lack of sedation compared to first generation antihistamines.

Once daily administration of loratadine at therapeutic doses, with or without erythromycin, does not induce adverse cardiac effects in children 5-12 years. No regulatory action has been taken world-wide since the launch of loratadine due to safety concerns. Safety data contained in Periodic Safety Update Reports (PSURs) demonstrates the overall benefit-risk balance for loratadine in children continues to be positive.

Pre-meeting public submissions

Three (3) submissions were received.

One (1) supported the scheduling proposal. Main points:

- Loratadine has safety profile consistent with other similar substances on the market.

Two (2) did not support the scheduling proposal. Main points:

- The proposition is not in the public interest for loratadine to be used in children under general retail availability.
- Loratadine can have sedative-like effects. With the use of higher-than-recommended doses, there is an increased risk of impaired acuity and drowsiness, particularly in young children. Inappropriate use may result without professional advice.
- The availability of different pack sizes based on age may cause confusion to consumers.

The public submissions will be made available on the TGA website.

Summary of ACMS advice to the delegate

The committee advised that loratadine be exempt from scheduling in preparations containing loratadine 10 mg or less in divided preparations for oral use in packs containing not more than 10 dosage units when used in children 6 years of age for the treatment of seasonal allergic rhinitis.

Schedule 4 – Amend Entry

LORATADINE **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 6~~12~~ years of age and over-when:

i) in a primary pack containing 10 dosage units or less; and

ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

Schedule 2 – Amend Entry

LORATADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis when:

a) in a primary pack containing 10 dosage units or less when labelled for children 6~~12~~ years and over; and

b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

The committee also recommended an implementation date of **1 October 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; (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 comprised the following:

- Loratadine for children has been available at the general sales level in both UK and USA since 2002, without increased adverse events.
- Adults should be able to identify seasonal allergic rhinitis based on symptoms. Symptoms in children are no different to symptoms in adolescents or adults, for whom loratadine is already exempt from scheduling.
- There are risks of delay in correct diagnosis in the younger age group, however risk of adverse outcomes as a result are relatively low, and there is a public health benefit in wider availability of a first line treatment for allergic rhinitis in children.
- The risks can be limited by placing restrictions on the number of days of supply or number of units to an appropriate pack size and appropriate labelling.

Delegate's considerations

The delegate considered the following in regards to this proposal:

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

Delegate's interim decision

The delegate's interim decision is to exempt loratadine from scheduling in preparations containing loratadine 10 mg or less in divided preparations for oral use in packs containing not more than 10 dosage units when used in children 6 years of age and over for the treatment of seasonal allergic rhinitis.

The proposed Schedule entry is as follows:

Schedule 4 – Amend Entry

LORATADINE **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 6 years of age and over-when:

i) in a primary pack containing 10 dosage units or less; and

ii) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

Schedule 2 – Amend Entry

LORATADINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis when:

a) in a primary pack containing 10 dosage units or less when labelled for children 6 years and over; and

b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

The proposed implementation date is **1 October 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; 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 interim decision are the following:

- The delegate acknowledges the committee's advice.
- Loratadine for children has been available at the general sales level in both UK and USA since 2002, without increased adverse events.
- Adults should be able to identify seasonal allergic rhinitis based on symptoms. Symptoms in children are no different to symptoms in adolescents or adults, for whom loratadine is already exempt from scheduling.
- There are risks of delay in correct diagnosis in the younger age group, however risk of adverse outcomes as a result are relatively low, and there is a public health benefit in wider availability of a first line treatment for allergic rhinitis in children.
- The risks can be limited by placing restrictions on the number of days of supply or number of units to an appropriate pack size and appropriate labelling.

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

Summary of delegate's interim decisions

Substance	Interim decision
N-(alkylamino) cyclohexylbenzamides (opioids)	**Schedule 9 – New Entries** *N,N*-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES **except** when separately specified in these Schedules. *N,N*-DIALKYLAMINOCYCLOHEXYLMETHYL ALKYL BENZAMIDES **except** when separately specified in these Schedules. 3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE (U-47700). **Index – Proposed New Entries** ***N,N*-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES** cross reference: 3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE *(U-47700) Schedule 9 ***N,N*-DIALKYLAMINOCYCLOHEXYLMETHYL ALKYL BENZAMIDES** Cross reference: 3,4-DICHLORO-*N*-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYL}BENZAMIDE *(AH-7921) Schedule 9 **3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE (U-47700)** cross reference: *N,N*-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES Schedule 9 *The proposed implementation date is **1 October 2017**.*
In Vitro Diagnostic and Analytical Preparations	The delegate's interim decision is that the current inclusion in Appendix A (General Exemptions) of 'IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS containing 0.001 per cent or less of a poison included in Schedules 1 to 8' remains appropriate.
Anise Alcohol	The delegate has decided to defer the interim decision for anise alcohol to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a

	new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.
Trans-anethole	The delegate has decided to defer the interim decision for trans-anethole to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.
Cinnamaldehyde	The delegate has decided to defer the interim decision for cinnemaldehyde to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.
Benzyl salicylate	The delegate has decided to defer the interim decision for benzyl salicylate to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.
Sodium α-olefin sulfonates	The delegate's interim decision is that no scheduling entry be created for sodium α-olefin sulfonate and sodium alkyl sulfate.
Resorcinol	The delegate has decided to defer the interim decision for resorcinol to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new schedule 6 entry with low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to therapeutic products when applied topically.

2.1 *N*-(alkylamino) cyclohexylbenzamides (opioids)

Referred scheduling proposal

An application was initiated by the delegate to seek advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) to include a new class entry for *N*-(alkylamino)cyclohexylbenzamides in Schedule 9, except when separately specified in these schedules.

Current scheduling status and relevant scheduling history

3,4-Dichloro-*N*-[2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide, **U-47700**, is not currently scheduled and there is currently no class entry for *N*-(alkylamino)cyclohexylbenzamides.

A scheduling history is not available for U-47700 or for *N*-(alkylamino)cyclohexylbenzamides as a class since these have not been previously considered for scheduling.

The **related structural isomer** 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide, ***AH-7921,** is currently listed in Schedule 9 under the entry:

Schedule 9

3,4-DICHLORO-*N*-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYLBENZAMIDE *(AH-7921).

It was placed in Schedule 9 in June 2014 following reported deaths in Sweden and increased use of the substance in Australia through monitoring of Australian internet forums, as well as claims that the substance has no legitimate therapeutic use. The final scheduling decision for AH-7921 was published on the TGA website in May 2014 at: Scheduling delegate's final decisions: May 2014.

Scheduling application

Delegate-initiated application.

The delegate's proposed amendment to the Poisons Standard is as follows:

Schedule 9 – Proposed New Entry

N-(ALKYLAMINO)CYCLOHEXYLBENZAMIDES except when separately specified in these Schedules.

Index – Proposed New Entries

3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE *(U-47700)
cross reference: *N*-(ALKYLAMINO)CYCLOBENZAMIDES

Schedule 9

***N*-(ALKYLAMINO)CYCLOBENZAMIDES**
cross reference: 3,4-DICHLORO-*N*-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYL}BENZAMIDE *(AH-7921)

Schedule 9

The delegate's reasons for the scheduling proposal are:

- Safety concerns have been raised that *N*-(alkylamino)cyclohexylbenzamides (such as 3,4-dichloro-*N*-[(*1R,2R*)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide, **U-47700)** are being abused overseas, and pose a public health risk, requiring restrictions on their use. U-47700 is a novel synthetic opioid that was recently placed in Schedule 1 by the US Drug Enforcement Administration (DEA), following association with morbidity (46 confirmed deaths in the USA) and abuse parallels with that of heroin, prescription opioids and other novel opioids. US enforcement agencies have found these substances in counterfeit tablets mimicking pharmaceutical opioids.
- These substances are opiates and appear to have no legitimate therapeutic use.
- The opioid analgesic substance 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methylbenzamide (**AH-7921**), a structural isomer of U-47700, is already included in Schedule 9.

Australian regulatory information

U-47700 does not have legitimate medical use in Australia and is not in any registered medicines. No legitimate industrial uses have been identified.

AH-7921 does not have legitimate medical use in Australia.

NICNAS could not locate any AICS-listed chemicals meeting this description. The National Chemical Inventories program includes one chemical, 116174-38-0 (benzamide, *N*-(cyanomethyl)-*N*-[(*1R,2R*)-2-[[(methylsulfonyl)oxy]methyl]cyclohexyl]-), with presumed industrial use, but this was not considered to fall within the relevant class description *N*-(alkylamino)cyclohexylbenzamides. This has been pre-registered under REACH, but it is not on any chemicals inventory.

International regulations

The US DEA and FDA in 2016 placed U-47700 and its isomers, esters, ethers, salts and salts of isomers, esters and ethers, in Schedule 1, effective from 14 November 2016, following confirmed deaths and inclusion of the powder form in counterfeit pharmaceuticals.

In the U.K. U-47700 is controlled under the Psychoactive Substances Act 2016. In Sweden, following sale in 2016 as a designer drug, U-47700 was made illegal in January 2016. Finland labelled U-47700 a controlled substance in September 2015.

U-47700 was reviewed at the World Health Organization (WHO) Expert Committee on Drug Dependence summit in November 2016 - see UNODC critical review report for U-47700 attached.

U-47700 is not controlled under the 1961, 1971 or 1988 United Nation Conventions.

No information is available on related scheduling in New Zealand.

Substance summary

N-(alkylamino)cyclohexylbenzamides are synthetic opioid analgesics, and include 3,4-dichloro-*N*-[(*1R,2R*)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide, U-47700, which is unscheduled, and 3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide, AH-7921, which has been in Schedule 9 since 2014. U-47700 is a structural isomer of AH-7921. In both isomers, the benzamide moiety is dichlorinated at the 3 and 4 ring positions and the aminocyclohexane moiety is *N,N*-dimethylated.

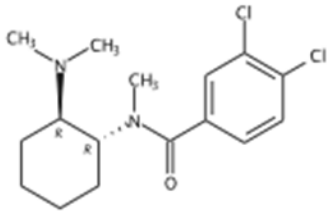


Figure 2.1A: Chemical structure of U-47700 (free base, trans stereochemistry)

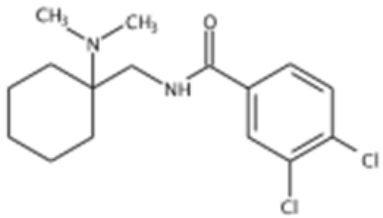


Figure 2.1B: Chemical structure of AH-7921 (free base, trans stereochemistry)

Table 2.1: General information

	U-47700	AH-7921
CAS No.	82657-23-6 (free base, trans); 121348-98-9 (form not specified)	55154-30-8 (free base); 41804-96-0 (hydrochloride salt)
IUPAC name	3,4-dichloro-*N*-[(1R,2R)-2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide	3,4-dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide
Synonyms	U4, fake morphine, pinky, pink[33]	1-(3,4-dichlorobenzamidomethyl)cyclohexyldimethylamine; doxylam
Molecular formula	$C_{16}H_{22}Cl_2N_2O$	$C_{16}H_{22}Cl_2N_2O$
Molecular weight	329.3 g/mol	329.3 g/mol
Scheduling status	unscheduled	Schedule 9

U-47700

U-47700 is a white powder. Chemical properties of U-47700 include: melting point: 97-98.5°C, boiling point 465°C, solubility is sparingly soluble in water (0.49 g/L), at pH 10.36 very soluble (527 g/L). U-47700 contains 2 chiral centres at the bonds to the 2 nitrogens off the ring resulting in 4 isomers; *cis* and *trans* each have 2 enantiomers [*cis*: are (*1R,2R*), and (*1S,2S*); *trans* are (*1R,2S*) and (*1S,2R*)]. The absolute configuration of the μ-agonist enantiomer was originally reported as *R,R.*

Identified risks of U-47700 include developing substance abuse, overdose, and death similar to that of other opioid analgesics (e.g., fentanyl, morphine, etc.). Since 2015, abuse of U-47700 has been reported as the single substance and in combination with other substances, including heroin, fentanyl, and furanyl fentanyl. The population likely to abuse U-47700 appears to overlap with the populations abusing prescription opioid analgesics, other "designer opioids", and heroin, as evidenced by drug use history documented in U-47700 fatal overdose cases.

U-47700 became the lead compound of several selective kappa-opioid receptor ligands such as U—50488, U-51754 (with a single methylene spacer difference) and U-69,593, with similar structures[34]. It has no medical use[35]. Research use has been reported[36].

[33] U-47700: Everything You Need to Know About Deadly New Drug

[34] Loew, G.; Lawson, J.; Toll, L.; Frenking, G.; Berzetei-Gurske, I.; Polgar, W. (1988). Structure activity studies of two classes of β-amino-amides: the search for kappa-selective opioids (pdf,4,26Mb). *NIDA Research Monograph*. **90**: 144-151. ISSN 1046-9516. PMID 2855852

Szmuszkovicz, Jacob; Zhao, Shikai; Totleben, Michael J.; Mizsak, Stephen A.; Freeman, Jeremiah P. *"Phenanthridone Analogs of the Opiate Agonist U-47,700 in the trans-1,2-Diaminocyclohexane Benzamide Series". Heterocycles.* **52** (1): 325-332. doi:10.3987/com-99-s27.

[35] U-47700 Critical Review Report Agenda Item 4.1

[36] Szmuszkovicz, Jacob (1999). U-50,488 and the κ receptor: A personalized account covering the period 1973 to 1990. *Progress in Drug Research*. Progress in Drug Research. Birkhäuser Basel. pp. 167–195.doi:10.1007/978-3-0348-8730-4_4. ISBN 9783034887304

Tsibulnikov, S. Yu; Maslov, L. N.; Mukhomedzyanov, A. V.; Krylatov, A. V.; Tsibulnikova, M. R.; Lishmanov, Yu B. (October 2015). Prospects of Using of κ-Opioid Receptor Agonists U-50,488 and ICI 199,441 for Improving Heart Resistance to

Media reports that U-47700 can be taken by injection, inhalation, and oral administration. An internet search indicates that U-47700 is available via the internet for up to $US35/gram[37].

The DEA placement of U-47700 in Schedule 1 raises concerns that, since this is obtained through illicit sources, the identity, purity, and quantity are uncertain and inconsistent, thus posing significant adverse health risks to the end user.

The DEA placement of U-47700 in Schedule 1 states:

- Evidence suggests that the pattern of abuse of U-47700 parallels that of heroin, prescription opioid analgesics, and other novel opioids. Seizures of U-47700 have been encountered in powder form and in counterfeit tablets that mimic pharmaceutical opioids.
- U-47700 is available over the Internet and is marketed as a “research chemical”.
- U-47700 exhibits pharmacological profiles similar to that of morphine and other μ-opioid receptor agonists. Cases of intoxication are reported in the literature with morbidity and mortality associated with U-47700 use. The toxic effects of U-47700 in humans are demonstrated by overdoses and overdose fatalities associated with this substance, as reported in the scientific literature.

Adverse reactions reported in humans are described in the WHO UNODC report. This report details misuse, abuse and dependence by humans and indicates significant abuse potential and that there are no marketing authorizations as a medicinal product for U-47700 and it has no legitimate industrial use. Seizures have been reported relating to use in Europe and the USA with reports of opiate-like adverse effects and associated fatalities.

AH-7921

AH-7921 is an opioid analgesic substance selective for the μ-opioid receptor, having around 80% the potency of morphine when administered orally. It was discovered in the 1970's by a team at Allan and Hanburys Ltd, a British pharmaceutical manufacturer. A trivial name, doxylam, has been proposed for this compound, but it has never been sold commercially for medical use. In 2013, AH-7921 was discovered to have been used as an active ingredient in "synthetic cannabis" products in Japan.

The free base form of AH-7921 is a solid; its melting point is not known. The hydrochloride salt, also a solid, has been documented to have a melting point of 215-216°C (see ECMDDA Europol Joint Report, attached). This refers to a 1974 study by Harper *et al.,* which details that the LD_{50} of AH-7921 is higher than 10 mg/kg upon intravenous administration in the rat. No studies were identified examining toxicity in humans and insufficient information was available to determine its acute toxicity.

Pre-meeting public submissions

One (1) submission was received. The submission indicated that there were no known non-medical uses of the substances. Further information may be required to assess the impact of the regulation proposal.

The public submission will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee advised that a new Schedule 9 entry be created for *N*─(alkylamino)cyclohexylbenzamides.

Ischemia/Reperfusion. *Bulletin of Experimental Biology and Medicine*. **159** (6): 718-721. doi:10.1007/s10517-015-3057-8. ISSN 1573-8221. PMID 26519268

[37] Buy Online U-47700 USA, EU, AU @ $35-$9 per g : ChingLabs; U-47700 buy U-47700 for sale online - $35.50 - Best-Feel.com.

Schedule 9 - Proposed New Entries

N-(ALKYLAMINO)CYCLOHEXYLBENZAMIDES **except** when separately specified in these Schedules.

N-(ALKYLAMINO)CYCLOHEXYLMETHYLENEBENZAMIDES **except** when separately specified in these Schedules.

3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE (U-47700).

Index – Proposed New Entries

***N*-(ALKYLAMINO)CYCLOHEXYLBENZAMIDES**
cross reference: 3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE *(U-47700)

Schedule 9

N-(ALKYLAMINO)CYCLOHEXYLMETHYLENEBENZAMIDES except when separately specified in these Schedules.
cross reference: 3,4-DICHLORO-*N*-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYL}BENZAMIDE *(AH-7921)

Schedule 9

3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE (U-47700)
cross reference: *N*-(ALKYLAMINO)CYCLOHEXYLBENZAMIDES

Schedule 9

The committee also recommended an implementation date of **1 October 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; (c) the toxicity 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:

- There is a significant public health risk similar to other opioid analgesics, such as morphine and fentanyl, including abuse potential, dependence, toxicity and overdose. Furthermore, *N*—(alkylamino)cyclohexylbenzamides poses a risk of overdose.
- There are no registered products, and there are no benefits from therapeutic use for *N*—(alkylamino)cyclohexylbenzamides.
- Toxicity reports for *N*-(alkylamino)cyclohexylbenzamides are similar to other opioid analgesics such as fentanyl and morphine, which includes fatal overdose cases. There is also a significant potential for abuse similar to heroin and other illicit prescription and novel opioids.
- There have been reports of illicit use. *N*-(alkylamino)cyclohexylbenzamides are also likely to have significant abuse liability given pharmacological profile. Although no animal studies are available to confirm this, the WHO report describes 'user reports' of tolerance and craving.
- Since *N*-(alkylamino)cyclohexylbenzamides are obtained through illicit sources, the identity, purity, and quantity are uncertain, are inconsistent and therefore pose significant risks to the end-user.
- There are no known medical or industrial uses.

- Significant mortality has been noted internationally. They may be sold as heroin, or mixed with heroin, and this contributes to overdoses.

Delegate's 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

Delegate's interim decision

The delegate's interim decision is to create new Schedule 9 entries for *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides. The proposed Schedule entry is as follows:

Schedule 9 – New Entries

N,N-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES **except** when separately specified in these Schedules.

N,N-DIALKYLAMINOCYCLOHEXYLMETHYL ALKYL BENZAMIDES **except** when separately specified in these Schedules.

3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE (U-47700).

Index – Proposed New Entries

***N,N*-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES**
cross reference: 3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE *(U-47700)

Schedule 9

***N,N*-DIALKYLAMINOCYCLOHEXYLMETHYL ALKYL BENZAMIDES**
cross reference: 3,4-DICHLORO-*N*-{[1-(DIMETHYLAMINO)CYCLOHEXYL]METHYL}BENZAMIDE *(AH-7921)

Schedule 9

3,4-DICHLORO-*N*-[(1R,2R)-2-(DIMETHYLAMINO)CYCLOHEXYL]-*N*-METHYLBENZAMIDE (U-47700)
cross reference: *N,N*-DIALKYLAMINOCYCLOHEXYL ALKYL BENZAMIDES

Schedule 9

The proposed implementation date is **1 October 2017**, as this is the earliest possible implementation date.

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

The reasons for the recommendation comprised the following:

- Independent expert advice regarding the appropriate naming of the group entries was received and is reflected in the proposed wording of the schedule entries.
- The delegate acknowledges and agrees with the committee's advice:
  - There is a significant public health risk similar to other opioid analgesics, such as morphine and fentanyl, including abuse potential, dependence, toxicity and overdose. Furthermore, *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides pose a risk of overdose.
  - There are no registered products, and there are no benefits from therapeutic use for *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides.
  - Toxicity reports for *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides are similar to other opioid analgesics such as fentanyl and morphine, which includes fatal overdose cases. There is also a significant potential for abuse similar to heroin and other illicit prescription and novel opioids.
  - There have been reports of illicit use. *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides are also likely to have significant abuse liability given pharmacological profile. Although no animal studies are available to confirm this, the WHO report describes 'user reports' of tolerance and craving.
  - Since *N,N*-dialkylaminocyclohexyl alkyl benzamides and *N,N*-dialkylaminocyclohexylmethyl alkyl benzamides are obtained through illicit sources, the identity, purity, and quantity are uncertain, are inconsistent and therefore pose significant risks to the end-user.
  - There are no known medical or industrial uses.
  - Significant mortality has been noted internationally. They may be sold as heroin, or mixed with heroin, and this contributes to overdoses.

2.2 *In Vitro* Diagnostic and Analytical Preparations

Referred scheduling proposal

An application was submitted for consideration by the delegate to seek advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on a proposal to amend 'Part 5, Appendix A General Exemptions of the Poisons Standard' to include Schedule 9 poisons at 0.001 per cent or less as exemptions for *in vitro* diagnostic and analytical preparations.

Current scheduling status

In Australia, poisons in Schedules 1 to 8 at concentrations of up to 0.001 per cent in *in vitro* diagnostic and analytical preparations are included in Appendix A as follows:

> **Appendix A – General Exemptions**
>
> IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS containing 0.001 per cent or less of a poison included in Schedules 1 to 8.

Scheduling history

In 1987, the Drugs and Poisons Scheduling Committee (DPSC) rejected a proposal that a general exemption for all scheduled substances when incorporated into an *in vitro* diagnostic test kit be included in the Poisons standard. The Committee felt that each case needs to be considered on its merits so that substances contained in these kits can be properly assessed and the correct labelling, storage and clinical advice given.

Scheduling application

This is a general application. The applicant's proposed amendment to the Poisons Standard is as follows:

Appendix A – Amend Entry

IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS containing 0.001 per cent or less of a poison included in Schedules 1 to ~~8~~ 9.

The applicant's reasons for the request are:

- This amendment is requested to allow in vitro diagnostic medical device (IVD) companies to legally import, store and supply IVDs containing very small amounts of substances included in Schedule 9.
- These IVDs items are positive controls used for screening clinical specimens for the detection of drugs of abuse. The amount of drugs included in the controls is very small (≤ 300 ng/mL) well below the amount specified in the standard. The range of drugs which are screened for varies but the most common drugs are MDMA, LSD, phencyclidine (PCP) and methaqualone.

Australian regulatory information

In Australia, all *in vitro* diagnostic medical devices (IVD medical devices or IVDs) that are intended to be used for a therapeutic purpose are subject to regulation under the *Therapeutic Goods Act 1989*. A new regulatory framework for IVDs was implemented on 1 July 2010, following amendments made to the *Therapeutic Goods (Medical Devices) Regulations 2002* (the Regulations) to include IVDs as a subset of medical devices.

The changes made to the legislation apply to all IVDs, and require that all manufacturers of IVDs certify that their products are safe, perform appropriately for their intended purpose, and are manufactured to a high standard of quality by complying with a set of Essential Principles (EPs) to identify performance levels required, hazards to be addressed, or issues to be considered. The EPs for safety and performance form the basis of the IVD regulatory framework and are set out in Schedule 1 of the Regulations.

In vitro diagnostic medical devices (IVDs) are defined as:

a) a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination with another diagnostic product for in vitro use; and

b) intended by the manufacturer to be used in vitro for the examination of a specimen derived from the human body, solely or principally for:

   i) giving information about a physiological or pathological state or a congenital abnormality; or

   ii) determining safety and compatibility with a potential recipient; or

   iii) monitoring therapeutic measures; and

c) not a product that is:

i) intended for general laboratory use; and

ii) not manufactured, sold or presented for use as an IVD medical device.

International regulations

New Zealand

In New Zealand, in IVDs are currently exempt from mandatory notification to WAND (web assisted notification of devices) database but must still comply with the requirements of the Medicines Act 1981 and its Regulations.[38]

USA

An overview of IVD Regulation is available on the FDA website.[39]

- 21 CFR 864.4010(a) is applied to general purpose reagents (GPRs). A GPR is a chemical reagent that has general laboratory application, is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and is not labelled or otherwise intended for a specific diagnostic application. GPRs do not include laboratory machinery, automated or powered systems).
- 21 CFR 864.4020(a) is used to classify analyte specific reagents (ASRs). ASRs are antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens) used in IVDs.

Also on the FDA website is a review on Drugs of Abuse Tests.[40]

Canada

In Canada,[41] reagents, instruments, apparatus, equipment or systems not manufactured, sold or represented by manufacturers for use in *in vitro* diagnostic applications are not considered to be *in vitro* diagnostic devices (IVDDs). This includes products used in general laboratory applications, even if they are used by laboratories to develop their own diagnostic assays for the laboratory's own use.

IVDDs labelled "For Research Use Only" (not otherwise labelled or otherwise represented by a manufacturer for a specific diagnostic application, or labelled with specific performance characteristics, or a bibliography listing articles referring to the use of the marker for a specific application) are exempt from the *Medical Devices Regulations*.

In accordance with subparagraph 3(2) of the Regulations, all *in vitro* diagnostic products that are a drug or contain a drug listed in Schedule E or F to the *Food and Drugs Act*, in the Schedule to Part G or Part J of the *Food and Drug Regulations,* in the Schedules to the *Controlled Drugs and Substances Act*, or in the Schedule to the *Narcotic Control Regulations*, are not subject to the *Medical Devices Regulations.* The following is a short description of these schedules.

Section 15 of the *Act* prohibits the sale of a drug mentioned in Schedule F. Therefore, if an *in vitro* diagnostic product was a drug or contained a drug listed on Schedule F to the Act, its sale would be prohibited. In the case of *in vitro* diagnostic products that was a drug or contained a drug listed on Schedule E to the *Act*, it would be subject to the provisions of the *Food and Drug Regulations.*

[38] NZ: Medical Devices: In-Vitro Diagnostic (IVD) Devices
[39] USA, IVD Regulation: Overview of IVD Regulation
[40] USA, review on Drugs of Abuse Tests
[41] Canada: Guidance Document: Guidance for the Risk-based Classification System for In Vitro Diagnostic Devices (IVDDs)

In vitro diagnostic products listed on the Schedule to Part G or the Schedule to Part J of the *Food and Drug Regulations* are subject to the provisions of the *Controlled Drugs and Substances Act* (CDSA) and the *Food and Drug Regulations.* The Schedule to Part G lists controlled drugs, such as barbiturates and anabolic steroids. The Schedule to Part J lists restricted drugs, such as some amphetamines and lysergic acid diethylamide. All drugs listed in Schedules G and J of the *F&D Regulations* are also listed on the Schedules to the CDSA.

In addition to the products listed on Schedules G and J of the *Food and Drug Regulations* and on the Schedule to the *Narcotic Controlled Regulations*, there are other products listed on the schedules to the CDSA that are also not subject to the *Medical Devices Regulations*.

In vitro diagnostic products listed on the Schedule to the *Narcotic Controlled Regulations* are subject to the provisions of the CDSA (also listed in its schedules) and of the *Narcotic Controlled Regulations.*

Europe

There is guidance document regarding IVD and medical devices in the EU.[42] In the EU, devices intended to be used only in the course of law enforcement or other non-medical purposes, for example paternity tests or tests for detecting drugs of abuse/alcohol, are not IVD's. If however, the *in vitro* examination of human specimens with a medical purpose is one of the intended uses of a specific product, the IVD Directive will apply.[43] A list of substances used in IVDs in the EU is given in the IDV directive and includes Drugs of Abuse/Toxicology such as amphetamines, barbiturates, benzodiazepines, cannabinoids THC, cocaine, codeine, morphines and other.[43]

Examples of test kits are available at the following websites:

- ThermoFisher Scientific – CEDIA Cocaine OFT Assay
- Agilent – LSD Analysis in Urine by LC-MS
- Roche – LSD Assay

Substance summary

An *in vitro* diagnostic medical device (IVD):

- is any medical device which is a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination (with other diagnostic goods for *in vitro* use); and
- intended by the manufacturer to be used *in vitro* for the examination of specimens derived from the human body, solely or principally for the purpose of giving information about a physiological or pathological state, a congenital abnormality or to determine safety and compatibility with a potential recipient or to monitor therapeutic measures.

The range of drugs tested varies but currently the most common are MDMA, LSD, phencyclidine (PCP) and methaqualone. *In vitro* diagnostic preparations for the screening of drugs of abuse are not therapeutic goods and therefore do not require approval by the TGA. However, the controls and calibrators for the IVDs are therapeutic goods and do require TGA approval. Therefore, the products related to this application are all evaluated and approved by the TGA before supply.

The products involved are controls or calibrators, i.e. urine or serum samples, that contain specified amounts of a range of commonly used drugs of abuse. The products are used exclusively in pathology laboratories, which are secure premises from which diversion is unlikely. Also the amount of drug

[42] EU, IVD medical devices review: MEDDEV. 2.14/1 rev. 1 Guidelines on Medical Devices: IVD Guidances: Borderline issues - A Guide for Manufacturers and Notified Bodies (pdf,94kb)
[43] IVD directive: In Vitro Diagnostic Product Classification - Revision 5 (pdf,141kb)

present in the products is very small (≤ 300 ng /mL) and therefore the risk of diversion or abuse is considered to be low.

Pre-meeting public submissions

No submissions were received.

Summary of ACCS-ACMS advice to the delegate

On the basis of the information contained in the application, the committee recommended that the current inclusion in Appendix A (General Exemptions) of 'IN VITRO DIAGNOSTIC AND ANALYTICAL PREPARATIONS containing 0.001 per cent or less of a poison included in Schedules 1 to 8' remains appropriate.

The committee suggested that additional information may be available regarding the scope of use from IVD Australia, MTAA and workplace testing facilities, and requested the Secretariat to engage with these bodies to gain further information to support reconsideration by the committee/delegate.

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

The reasons for the advice comprised the following:

- Consideration of Schedule 9 substances proposed for inclusion in Appendix A should be considered on a case-by-case basis.
- Some Schedule 9 poisons are very potent and the potential diversion of small amounts of specific chemicals may be problematic.
- The toxicity of the Schedule 9 poisons varies according to the class of substance (opioid, hallucinogen, stimulant) and is dose related. Schedule 9 poisons can lead to serious health risks if diverted due to their toxicity and potency.
- The committee noted the risk of diversion from an IVD is low from authorised diagnostic laboratories however external to these, the risks outweighed the benefit.
- The potential for abuse of *in vitro* diagnostic substances would be significantly increased when provided in analytical solutions, however is likely to be very minimal if limited to the well-plate of IVD kits when supplied to NATA accredited laboratories and hospitals, and given the very small quantities (less than or equal to 500 nanograms per mL) in test kits regulated under the Therapeutic Goods (Medical Devices) Regulations 2002, and the matrix in which the Schedule 9 poisons exist (i.e. urine).
- There is a growing area of workplace testing, as well as testing that is undertaken in laboratories and universities, and limiting supply to forensic laboratories, hospitals and workplaces is an important consideration.
- An exemption under Appendix A for Schedule 9 poisons at a concentration of 0.001 per cent or less for in vitro diagnostic and analytical preparations may not automatically apply in all jurisdictions.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS-ACMS advice

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

Delegate's interim decision

The delegate's interim decision is that the current inclusion in appendix a (general exemptions) of 'in vitro diagnostic and analytical preparations containing 0.001 per cent or less of a poison included in schedules 1 to 8' remains appropriate.

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

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Consideration of Schedule 9 substances proposed for inclusion in Appendix A should be considered on a case-by-case basis.
- Some Schedule 9 poisons are very potent and the potential diversion of small amounts of specific chemicals may be problematic.
- The toxicity of the Schedule 9 poisons varies according to the class of substance (opioid, hallucinogen, stimulant) and is dose related. Schedule 9 poisons can lead to serious health risks if diverted due to their toxicity and potency.
- The committee noted the risk of diversion from an IVD is low from authorised diagnostic laboratories however external to these, the risks outweighed the benefit.
- The potential for abuse of *in vitro* diagnostic substances would be significantly increased when provided in analytical solutions, however is likely to be very minimal if limited to the well-plate of IVD kits when supplied to NATA accredited laboratories and hospitals, and given the very small quantities (less than or equal to 500 nanograms per mL) in test kits regulated under the Therapeutic Goods (Medical Devices) Regulations 2002, and the matrix in which the Schedule 9 poisons exist (i.e. urine).
- There is a growing area of workplace testing, as well as testing that is undertaken in laboratories and universities, and limiting supply to forensic laboratories, hospitals and workplaces is an important consideration.
- An exemption under Appendix A for Schedule 9 poisons at a concentration of 0.001 per cent or less for *in vitro* diagnostic and analytical preparations may not automatically apply in all jurisdictions.
- The current entry remains appropriate, but further information may be available, and will be sought from the applicant, IVD Australia, MTAA and workplace testing facilities to assist reconsideration by the committee/delegate.

2.3 Anise alcohol

Referred scheduling proposal

The scheduling delegate is seeking advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on an application submitted by the National Industrial Chemicals

Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new Schedule 6 entry for anise alcohol for use in cosmetic and domestic products with appropriate concentration exemption cut-offs in alignment with international regulations.

Current scheduling status and relevant scheduling history

Anise alcohol is not currently listed in the Poisons Standard and has not been previously considered for scheduling; therefore a scheduling history is not available.

Benzyl alcohol (read across in eye irritation study) is not currently scheduled; however similar substances, anise oil and star anise oil, are currently scheduled.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

ANISE ALCOHOL in cosmetic and domestic products **except**:

a) in leave-on preparations containing 0.001 per cent or less of anise alcohol when labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals; or

b) in wash-off preparations containing 0.01 per cent or less of anise alcohol when labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

Appendix E – New Entry

ANISE ALCOHOL

Standard statements: E1 (If in eyes wash out immediately with water).

Appendix F – New Entry

ANISE ALCOHOL

Warning statements: 28 [(Over) (Repeated) exposure may cause sensitisation].

The applicant's reasons for the request are:

- Anise alcohol is a skin sensitiser;
- Anise alcohol has moderate acute oral toxicity;
- Anise alcohol is expected to be an eye irritant;
- There is reported to be widespread use of anise alcohol in cosmetic and domestic products overseas at concentrations up to 2.5%; this is assumed to be representative of its use in Australia;
- There are overseas restrictions for use of anise alcohol (the International Fragrance Association (IFRA) standard, 2015; and
- As a sensitiser, when applied directly to skin in cosmetic and domestic products, the risk can only be mitigated by concentration limits and warning statements.

Australian regulatory information

Anise alcohol is included as an excipient in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017, where it has the following restrictions:

- Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.
- If used in a flavour the total flavour concentration in a medicine must be no more than 5%.
- If used in a fragrance the total fragrance concentration in a medicine must be no more than 1%.

Anise alcohol is included as an excipient in 98 formulations on the ARTG, including listed and registered medicines. These products include topical and oral preparations such as sunscreen, children preparations for cold and pain relief, anti-nausea preparations, anti-depressants and oral probiotics. The listed products are therapeutic goods that are not evaluated prior to being released for sale.

International regulations

EU

Anise alcohol is listed in the EU Cosmetic Regulation EC No. 1223/2009, Annex III: List of substances which cosmetic products must not contain except subject to the restrictions laid down. Anise alcohol may be used in cosmetics and personal care products, but must be specified in the list of ingredients referred to in article 19(1)g in 0.001% leave-on and 0.01% in rinse-off products.

Additionally, IFRA has restricted the use of Anise alcohol in finished products at concentrations of 0.04-2.5% depending on the product category.

USA

Anise alcohol (listed as anisyl alcohol) is a food additive in the USA.

Canada

Anise alcohol is a flavour enhancer and fragrance ingredient in Canada.

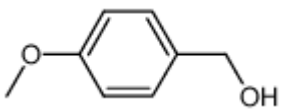
New Zealand

Anise alcohol is not regulated in New Zealand.

Substance summary

Anise alcohol is a colourless to slightly yellow liquid having a pleasant floral odour.

Table 2.3A: General information

Property	Anise alcohol
CAS No.	105-13-5
Chemical structure	
Molecular formula	$C_8H_{10}O_2$

Molecular weight	138.16 g/mol
IUPAC and/or common and/or other names	Anise alcohol (INCI and AAN); benzenemethanol, 4-methoxy- (CAS); anisyl alcohol; 4-methoxybenzyl alcohol; anisic alcohol; p-methoxybenzyl alcohol

The following information has been extracted from the NICNAS IMAP Human Health Tier II assessment report for anise alcohol.[44]

Table 2.3B: Acute toxicity end-points for anise alcohol

Toxicity	Species	Anise alcohol	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat[45]	1200–1340	Schedule 6
	Mice[45]	1600–1784	
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits[45]	>2500 <5000	Schedule 5
	Mice[45]	>10 000	
Acute inhalational toxicity LC_{50} (mg/m^3/4h) (Predicted, QSAR studies)	Rat[45]	1019	Schedule 6
	Mice[45]	1070	
Skin irritation	Rat[45], Mice and Rabbits	Moderate irritation (erythema and oedema)	Schedule 5
Eye irritation (Read across, benzyl alcohol)	New Zealand White rabbit	Expected to be irritating	Schedule 5
Skin sensitisation	CBA/Ca mice [LLNA]	Sensitising (EC3 5.9%)	Schedule 6
	Guinea pig[45], Hartley; Epicutaneous test, Draize method	Not sensitising	N/A

Acute toxicity

Anise alcohol has moderate acute oral toxicity based on results from animal tests. Anise alcohol has low acute dermal toxicity in rabbits and mice. Acute inhalation toxicity is predicted to be moderate.

[44] Publicly available on the NICNAS website at: Human Health Tier II Assessment for Benzenemethanol, 4-methoxy-
[45] Strain/species not specified

Irritation

Based on animal studies, anise alcohol is reported to moderately irritate the skin.

- Anise alcohol (0.5 mL) was applied to albino rats (n=12, 6 with normal and 6 with abraded skin) under occlusive conditions for 24 h. Rats were monitored for 72 h. Moderate irritation including erythema and slight oedema were observed.
- In two studies conducted in mice (n=10) and rabbits (n=4), anise alcohol was administered at doses of 1250, 2500 or 5000 mg/kg bw. Moderate irritation (primary irritation score=4) was observed including moderate erythema and oedema.
- No data are available for anise alcohol for eye irritation. Based on the available data for an analogue chemical (benzyl alcohol, CAS No. 100-51-6) with similar physicochemical properties, anise alcohol is expected to be an eye irritant.
- Irritation was reported after application of the analogue chemical, benzyl alcohol, to the eyes of New Zealand White rabbits. The irritation scores were 1-2 for corneal opacity, 0.3-1 for iritis, 2-2.7 for conjunctivitis and 0.7-2.2 for chemosis.

Sensitisation

Based on the weight of evidence from the available animal and human (see Observation in humans below) studies, anise alcohol is considered to be a skin sensitiser.

- In a murine LLNA compliant with the principles of good laboratory practice (GLP), anise alcohol was diluted using 1:3 ethanol:diethyl phthalate and 25 µL was applied to the dorsal surface of each ear of CBA/Ca mice (n = 4 females/dose) at doses of 2.5, 5, 10, 25 and 50% w/v for three consecutive days. The EC3 (estimated concentration that elicits a three-fold increase in lymphocyte proliferation) value was found to be 5.9%, confirming anise alcohol as a skin sensitiser.

However, positive skin reactions[46] were not reported in several studies conducted in guinea pigs, where:

- animals were subjected to anise alcohol at 1, 3, 10, 30 or 100% in water, acetone or petrolatum for induction and challenged with anise alcohol at 5% in the same vehicle;
- animals were subjected to a modified Draize test, using anise alcohol in petrolatum at 0.625% for induction and 10% for challenge; and
- neat anise alcohol was intra-dermally injected into the animals for the induction phase, and following a two week rest period, the animals were subjected to a modified Draize test, involving an injection of 0.25% and topical exposure of 10% to anise alcohol.

Repeat-dose toxicity

No data are available for repeated oral and inhalation exposure.

Based on the limited information available, anise alcohol is not considered to cause serious damage to health from repeated dermal exposure.

Genotoxicity

Based on the limited data available, anise alcohol is not considered to be genotoxic.

[46] Secretariat note: A preliminary general search of adverse reactions database for skin sensitisation indicated that there was only one reaction linked to sunscreens, with no specific ingredient noted.

Carcinogenicity

Based on the available data in mice, anise alcohol is not expected to be carcinogenic.

Reproduction and developmental toxicity

No data are available.

Observation in humans

Irritation

Irritation was observed in a closed patch study in 11/465 (2.3%) of human subjects after application of anise alcohol (under occlusion to the forearm) at 0.05-5% in a cream base solution.

In an irritation screening study, anise alcohol did not produce skin reactions at 5% in petrolatum when applied under occlusion to the skin of human subjects (n = 7) for 48 h.

Skin sensitisation

The IFRA reported a No Expected Sensitisation Induction Level (NESIL) of 1500 μg/cm^2 based on a human maximisation test and, therefore, classified anise alcohol as a weak sensitiser.

Reports from the Scientific Committee on Consumer Safety (SCCS), 2012, list anise alcohol as an allergen.

Positive reactions were reported in the following human studies:

- A study conducted on 20 perfume allergic patients: anise alcohol at 5% in petrolatum gave a positive reaction in 5/20 of the subjects;
- Diagnostic patch studies on dermatological patients:
  - skin reactions in 4/20 patients who are sensitive to perfume treated with anise alcohol at 5% in petrolatum;
  - skin reactions in 1/2004 patients with dermatitis treated with anise alcohol at 1% in petrolatum; and
  - skin reactions in 3/167 patients sensitive to fragrance allergens and suspected of contact dermatitis treated with anise alcohol at 5% in petrolatum.

No skin reactions were reported in the following human studies:

- A maximisation study: 25 subjects were pre-treated for 24 h with 5% aqueous sodium lauryl sulfate (SLS). Following a 10-14 day rest period, subjects were applied with anise alcohol (3450 μg/cm^2, 5%) in petrolatum occlusively to the forearm/back region for five 48h periods and monitored for a further 48 h;
- Diagnostic patch studies on dermatological patients:
  - 320 patients with eczema suspected of a contact allergy to fragrances or cosmetics were treated with anise alcohol at 5%; and
  - 115 patients with contact dermatitis were treated with anise alcohol at 5% in petrolatum.

Public exposure

Considering the range of domestic, cosmetic, therapeutic and personal care products that may contain anise alcohol, the main route of public exposure is expected to be through the skin, and inhalation from products applied as aerosols, and potential oral exposure from lip and oral hygiene products.

Dermal application of products containing anise alcohol at high concentrations may give rise to allergic responses.

Pre-meeting public submissions

Three (3) public submissions were received, which were all opposed to the proposal. The main points were:

- An Appendix B entry should be considered as has been previously for other flavour/fragrance ingredients used in cosmetic and household hygiene products with low acute toxicity and low public exposure.
- Based on IFRA standards, there are restrictions on concentration depending on use pattern of the product due to the concern that anise alcohol has skin sensitisation potential. Due to IFRA standards already existing for anise alcohol, scheduling is not required.
- The EU only requires the inclusion of anise alcohol in the ingredients list if the concentration in the finished product is ≥0.001% in leave-on products, and ≥0.01% in rinse-off products.

The public submissions will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee advised that a new Schedule 6 entry and Appendix E and F entries be created for anise alcohol:

Schedule 6 - New Entry

ANISE ALCOHOL **except**:

a) in preparations intended for therapeutic use; or

b) in domestic preparations [not intended for direct skin contact] containing 5 per cent or less of anise alcohol when included in the list of ingredients; or

c) in leave-on cosmetic and personal care preparations containing 2.5 per cent or less of anise alcohol when included in the list of ingredients and labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals; or

d) in rinse-off cosmetic and personal care preparations containing 5 per cent or less of anise alcohol when included in the list of ingredients and labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

e) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of anise alcohol; or

f) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of anise alcohol.

Appendix E, Part 2 - New Entry

ANISE ALCOHOL

Standard 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)).

Appendix F, Part 3 - New Entry

ANISE ALCOHOL

Warning Statements: 28 [(Over) (Repeated) exposure may cause sensitisation].

Safety directions: 4 (avoid contact with skin).

The committee also recommended an implementation date of **1 February 2018** if no label change would be required by scheduling.

The committee also recommended an implementation date of **1 June 2018** to allow a 12 month phase in of the new label requirements.

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

The reasons for the advice comprised the following:

- Anise alcohol is a flavour and fragrance excipient used in many medicinal, cosmetic and personal care products: 98 products on ARTG include anise alcohol as an excipient. The risks of the substance at the currently used concentrations appear low.
- It is listed as a Fragrance or Flavour Excipient (under Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017).
- The EU Cosmetic Regulation states 'This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.'
- The IRFA Standard restricts use to maximum of 2.5% depending on the product use (i.e. those with skin contact). Anise alcohol is currently specified within the Permissible Ingredients List and the requirements that apply to these ingredients when contained in a medicine are that the flavour is no more than 5% and the fragrance is no more than 1%.
- In Australia, there are domestic products that contain up to 5% of anise alcohol available. Worldwide use is widespread in cosmetic and domestic products and is at concentrations of up to 2.5.
- The risks of anise alcohol include systemic risks through oral exposure, local risks of eye irritation and skin sensitisation and inhalational risk (which is a predicted risk). It is also a known allergen listed on the List of Established Contact Allergens, (whilst low importance category however identified as a known fragrance allergen (SCCNFP 1999)).
- The toxicity of anise alcohol includes a moderate acute oral toxicity (based on animal studies) and possible skin sensitisation (it is listed by SCCS).

Delegate's considerations

The delegate considered the following 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

Delegate's interim decision

The delegate has decided to defer the interim decision for anise alcohol to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.

2.4 Trans-anethole

Referred scheduling proposal

The scheduling delegate is seeking advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on an application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new entry for trans-anethole in Schedule 6 to include use in cosmetic and domestic products with an exemption concentration cut-off.

Current scheduling status and relevant scheduling history

Trans-anethole is not specifically scheduled and has not been previously considered for scheduling.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

TRANS-ANETHOLE in cosmetic and domestic products **except** in preparations containing 10 per cent or less of trans-anethole.

Appendix E, Part 2 – New Entry

TRANS-ANETHOLE

Standard statements: E1 (If in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

TRANS-ANETHOLE

Warning statements: 28 [(Over) (Repeated) exposure may cause sensitisation].

The applicant's reasons for the request are:

- Trans-anethole is a skin sensitiser;
- Trans-anethole is reported to be used in cosmetic and domestic products overseas, particularly as a fragrance ingredient at concentrations up to 10%. In the absence of specific Australian information, this is taken as being representative of its use in Australia; and
- Internationally, there is a recommendation for use of trans-anethole at concentrations up to 10%; however, the available data does not preclude skin sensitisation occurring following exposure to concentrations below 10% (Scientific Committee on Consumer Safety (SCCS), 2012.

Australian regulatory information

Trans-anethole is included in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017 for use as an excipient.

Trans-anethole is as an ingredient in 249 products on the ARTG, including disinfectants, sunscreens, dental hygiene preparations, cold and cough relief products, anti-depressants, nicotine chewing gum products and gastric reflux relief preparations.

International regulations

New Zealand

Anethole is unclassified in New Zealand.

Canada

A number of over the counter (OTC) products containing anethole have been cancelled post market in Canada. There are no approved products containing anethole currently available in Canada.

USA

Anethole has a "Generally Recognised as Safe" status in the USA.[47]

EU

Anethole is in the European Chemicals Agency (ECHA) Annex III inventory requiring REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Registration.[48]

Substance summary

Trans-anethole is a component of a number of essential oils, such as anise, fennel, anise myrtle, guarana, camphor and star anise. Trans-anethole is also present in absinthe, magnolia blossoms and liquorice and is closely related to estragole, present in tarragon and basil.

Trans-anethole is a precursor for paramethoxyamphetamine (PMA).

Anethole is used broadly in multiple sectors due to its presence in essential oils, some of which have already been scheduled. It contributes a large component of the odour and flavour of the substances listed in the table below.

Table 2.4A: Anethole-containing essential oils, herbs and plants

Anethole-containing substance	Plant genus/family	Schedule	% of Anethole
Anise (seed) oil	*Pimpinella anisum / Apiaceae*	**Part 2, Section Two Containers** **Name of the Poison:** Anise oil when included in Schedule 5. **Nominal capacity:** 200 millilitres or less	79-95%[49,50]

[47] CFR - Code of Federal Regulations Title 21
[48] Annex III inventory
[49] Neşet Arslan, Bilal Gürbüz, Ercüment O. Sarihan, Ali Bayrak, Ahmet Gümüşçü (**2004**) *Turk J Agric For,* 28, 173-177
[50] Zheljazkov, VDJ *et al.* (**2013**) *HORTSCIENCE*, 48 (11), 1393-1396.

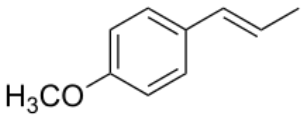
		Schedule 5 ANISE OIL **except**: a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 50 mL or less fitted with a restricted flow insert and compliant with the requirements of the Required Advisory Statements for Medicine Labels; b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 50 mL or less fitted with a restricted flow insert, and labelled with the warning: KEEP OUT OF REACH OF CHILDREN; or c) in preparations containing 50 per cent or less of anise oil. **Appendix E, Part 2** – ANISE OIL Standard Statement: A, G3.	
Fennel oil	*Foeniculum vulgare / Apiaceae*	Not currently scheduled. Considered for scheduling at November 2016 meeting of the Joint Advisory Committee on Chemicals and Medicines Scheduling.	82-88%[51,52,53,54]
Star anise	*Illicium verum / Illiciaceae*	**Schedule 5** STAR ANISE OIL **except**: a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 50 mL or less fitted with a restricted flow insert and compliant with the requirements of the Required Advisory Statements for Medicine Labels; b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of	77-92%[55,56,57]

[51] Senatore, F *et al.* (**2013**) *Fitoterapia*, 90, 214-219
[52] Dadaliogÿlu, I and Evrendilek GA (**2004**) *J. Agric. Food Chem*. 52, 8255-8260
[53] Dio, W *et al.* (**2014**) *Food Control*, 35 (1), 109-116.
[54] Piccaglia, R and Marotti, M (**1993**) *Flavour and Fragrance Journal*, 8, 115-122.
[55] Gholivand, M. B.; Rahimi-Nasrabadi, M.; Chalabi, H. (**2009**) *Analytical Letters*; 42 (10), 1382–1397.
[56] Wong, YC, Lee, PP and Wan Nurdiyana, WA (**2014**) *Oriental Journal of Chemistry*, 30 (3), 1159-1171.
[57] Gholivand, MB *et al.* (**2009**) *Analytical Letters*, 42 (10), 1382-1397.

		50 mL or less fitted with a restricted flow insert, and labelled with the warning: KEEP OUT OF REACH OF CHILDREN; or c) in preparations containing 50 per cent or less of star anise oil.	
Anise myrtle oil	*Syzygium anisatum / Myrtaceae*	Not scheduled.	90%[58],[59]
Liquorice[60]	*Glycyrrhiza glabra / Fabaceae*	**Appendix B, Part 3** LIQUORICE, DEGLYCYRRHISINISED. Date of entry: May 2009 Reason for entry: a (Low Toxicity) Area of use: 7.1 (General, Any use).	Not found
Dill	*Anethum graveolens / Apiaceae*	Not scheduled.	11%[61]
Magnolia blossoms[62]	*Magnolia salicifolia / Magnoliaceae*	Not scheduled.	6.0%[63]
Coriander	*Coriandrum sativum / Apiaceae*	Not scheduled.	Trace[64]
Cicely	*Myrrhis odorata / Apiaceae*	Not scheduled.	85%[65]
Sweet cicely	*Osmorhiza longistylis / Apiaceae*	Not scheduled.	95%[65]
Marigold pepper	*Piper marginatum / Piperaceae*	Not scheduled.	80%[65]

[58] Blewitt, M and Southwell, IA (**2000**) *J Ess Oil Res*, 12 (4), 445-454.
[59] Sultanbawa, Y (**2016**) 'Chapter 23 Anise Myrtle (Syzygium anisatum) Oils' in *Essential Oils in Food Preservation, Flavor and Safety*, Elsevier Inc.
[60] Fenwick, GR (**1990**) *Food Chemistry*, 38, 119-143.
[61] Singh, G *et al.* (**2005**) *J. Food Sci.*, 70(4)
[62] Kelm *et al.* (**2008**) *International Journal of Pharmacognosy*, 35(2), 84-90.
[63] Fujita, S-I and Fujita, Y (**1975**) *Chem. Pharm. Bull.*, 23(10), 2443-2445.
[64] Baratta, MT *et al.* (**2011**) *J. Essent. Oil Res,* 10, 618-627. M208-M215.
[65] Surana, SJ *et al.* (**2006**) *Natural Product Radiance*, 5(4), 270-278.

Table 2.4B: General information

Property	Trans-anethole
CAS No.	4180-23-8
Chemical structure	
Molecular formula	$C_{10}H_{12}O$
Molecule weight	148.21 g/mol
Alternative names	trans-anethole (INCI); anisole; anise camphor; p-propenyl-, (E)-; (E)-1-p-methoxyphenylpropene; anethole (AAN); benzene, 1-methoxy-4-(1-propenyl)-, (E)- (CAS); 1-Methoxy-4-[(1*E*)-prop-1-en-1-yl]benzene (IUPAC); *p*-Propenylanisole; Isoestragole

The following information was extracted from the NICNAS IMAP Human Health Tier II assessment report for trans-anethole.[66]

Table 2.4C: Acute toxicity end-points for trans-anethole

Toxicity	Species	Trans-anethole	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Osborne-Mendel Rats	2090-3200	Schedule 5
	CD-1 Mice	1820-5000	
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits (strain not specified)	>4900	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rats (strain not specified)	>5100	N/A
Skin irritation	New Zealand White Rabbits	Not irritating (slight erythema)	N/A
Eye irritation	New Zealand White Rabbits	Not irritating	N/A

[66] Publicly available on the NICNAS website at: Human Health Tier II Assessment for Benzene, 1-methoxy-4-(1-propenyl)-, (E)-

Toxicity	Species	Trans-anethole	SPF (2015) Classification
Skin sensitisation	CBA Mice (LLNA)	Sensitising (EC3 <25%)	Schedule 6
	Guinea pig (strain not specified) (GPMT)	Sensitising	

Acute toxicity

Trans-anethole has low acute toxicity based on results from animal tests following oral, dermal and inhalation exposure.

Irritation

Trans-anethole is not considered to be a skin or eye irritant:

- slight erythema (fully resolved after 8 h) was observed after trans-anethole was semi-occlusively applied to clipped, intact dorsal skin of New Zealand White rabbits for 4 h; and
- no signs of pain or irritation were observed after neat trans-anethole was instilled into the eyes of New Zealand White rabbits.

Sensitisation

Trans-anethole is considered to be a skin sensitiser based on the positive results seen in a mouse LLNA and GPMT:

- In a mouse LLNA conducted according to OECD TG 442B, female CBA mice (n = 4 animals/dose) were exposed to trans-anethole at 25, 50, or 100% in acetone/olive oil (4:1 v/v). The stimulation indices (SI) calculated were 3.49, 3.53 and 3.85 for the low, mid and high doses, respectively, indicating that trans-anethole was positive for skin sensitisation.
- In a GPMT conducted according to the OECD TG 406, 10 guinea pigs were induced with trans-anethole at 2% (intradermal) and 50% (topical). Trans-anethole at 10% was administered as a challenge dose and 10/10 animals tested positive for skin sensitisation. Each guinea pig was then challenged weekly, at a non-irritating concentration and 10/10 guinea pigs tested positive for skin sensitisation.

Repeat-dose toxicity

Based on the available data, repeated oral exposure to trans-anethole is not considered to cause serious damage to health. No data are available for repeated dermal and inhalation toxicity.

Genotoxicity

Based on the negative results from several *in vitro* and *in vivo* studies, trans-anethole is not considered to be genotoxic.

Carcinogenicity

Based on the data available, trans-anethole is not considered to be carcinogenic.

Reproduction and developmental toxicity

Trans-anethole does not show any signs of reproductive or developmental toxicity. Any developmental effects seen were secondary to maternal toxicity.

Public exposure

Trans-anethole has been identified to be used in cosmetic (perfumes and fragrances) and domestic products (polishes and waxes; softeners; soaps and cleaning products; and air care products) overseas at concentrations up to 10%. This use pattern is taken to be representative of its use in Australia [see Australian regulatory information].

Due to the use patterns of trans-anethole, direct dermal exposure is expected.

Pre-meeting public submissions

Two (2) public submissions were received. Both submissions opposed the scheduling proposal. The main points were:

- An Appendix B entry has been previously considered for other flavour/fragrance ingredients used in cosmetic and household hygiene products with low acute toxicity and low public exposure.
- Due to the similarity of this substance with other scheduled items, regulatory control must be consistent with other related existing schedule entries and across all current uses of the substance (both therapeutic and cosmetic/domestic).

The public submissions will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee advised that further consideration of exemption cut-offs applied to associated essential oils, such as star anise, anise oil and fennel oil, for the purposes of scheduling consistency before any advice can be provided on this application.

The committee advised that no scheduling is required at this stage, pending further advice to ensure consistency in any scheduling decision.

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

The reasons for the advice comprised the following:

- Anethole is a large and natural component of essential oils, used as a fragrance and flavour ingredient. It is found in 249 products on ARTG and these products have a wide range of uses. Anethole is also used in an unknown amount of cosmetic and household hygiene/domestic products, such as perfumes, fragrances, polishes, waxes, soaps, cleaning products, air care products and food flavourings. These products are used orally, topically and domestically with greatly varied packaging/labelling.
- The benefits of anethole were not presented for both medicinal and domestic use, however its presence in a number of essential oils and wide range of products means the substance should continue to be available and accessible. Anethole is typically found in products that are designed to be applied topically and consumed up to 10%.
- The potential for misuse or abuse is low. However, there is a risk that anethole can be synthesised to create a recreational drug, paramethoxyamphetamine (PMA), that has been known to cause death in users.
- Anethole has skin sensitising potential (EC3 <25%) and has low acute oral toxicity (LD_{50} >~2g/kg). The severity of skin sensitisation does not appear to be well established. There is no evidence of human poisoning presented.

- A new Schedule 6 entry for anethole will require a review of all scheduled essential oils of which trans-anethole is a major component of as they are currently either Schedule 5 or unscheduled (fennel oil).

Delegate's considerations

The delegate considered the following 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

Delegate's interim decision

The delegate has decided to defer the interim decision for trans-anethole to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.

2.5 Cinnamaldehyde

Referred scheduling proposal

The scheduling delegate is seeking advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on an application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new Schedule 6 entry for cinnamaldehyde for use in cosmetics and domestic preparations with appropriate warning labels and exemption cut-off concentrations in line with international standards.

Current scheduling status and relevant scheduling history

Cinnamaldehyde is not currently scheduled and has not previously been considered for scheduling.

In July 2016, the ACCS advised that structurally similar substances, hexyl and amyl cinnamaldehyde, be listed in Appendix B, PART 3 - 'Substances considered not to require control by scheduling', due to their low toxicity. The implementation date is 1 February 2017. Please see Final Decision.

Scheduling application

This was a general application. The applicant's proposed amendments to the SUSMP are as follows:

Schedule 6 – New Entry

CINNAMALDEHYDE **except** in preparations for dermal use containing 0.01/0.05 per cent or less of cinnamaldehyde.

Appendix E – New Entry

CINNAMALDEHYDE

Standard statements: E1 (If in eyes wash out immediately with water).

Appendix F – New Entry

CINNAMALDEHYDE

Warning statements: 28 [(Over) (Repeated) exposure may cause sensitisation], 79 (Will irritate eyes).

Safety directions: 4 (Avoid contact with skin).

The applicant's reasons for the request are:

- Cinnamaldehyde is an established contact allergen in humans;
- Cinnamaldehyde is a potential strong skin sensitiser, based on a local lymph node assay (LLNA)-derived EC3 (estimated concentration to produce a three-fold increase in lymphocyte proliferation) value of 0.2%;
- The existing overseas restrictions (New Zealand, EU) on the use of cinnamaldehyde in cosmetic products, where the presence of cinnamaldehyde must be indicated in the list of ingredients when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products;
- The most recent SCCS opinion on cinnamaldehyde recommends a concentration limit of 0.01% for safe use of cinnamaldehyde as a fragrance in cosmetic products; and
- The current IFRA guidelines restrict use of cinnamaldehyde to concentrations of 0.02% in lip care and deodorant/anti-perspirant products, 0.04% in intimate wipes, 0.4% in mouthwashes and 0.05% in all other personal care products including fragrances.

Australian regulatory information

Cinnamaldehyde, as well as alpha-methyl cinnamaldehyde, alpha-hexylcinnamaldehyde and alpha-amyl cinnamaldehyde, are listed as excipients in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017. The specific requirements applying to all these substances are:

- Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.
- If used in a flavour the total flavour concentration in a medicine must be no more than 5%.
- If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.

Cinnamaldehyde is included as an excipient in 215 formulations at present on the ARTG, including listed and registered medicines, both OTC and prescription-only. These products range from disinfectants, hand hygiene formulations, sunscreens, nicotine gum, children's pain relief and cold preparations, toothpaste, vitamins and mineral supplements and probiotics.

International regulations

Use of cinnamaldehyde in cosmetics in the European Union (EU) is subject to the restrictions described in EU Cosmetics Regulation 344/2013 (as an amendment to the listing under Annex III of Regulation 1223/2009). The presence of the substance must be indicated in the list of ingredients when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

Use of cinnamaldehyde in cosmetics and domestic articles in several other countries is also restricted in accordance with the following listings:

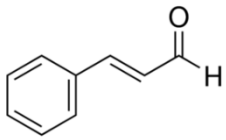
- European Commission (EC) Toy Safety Directive 2009/48/EC: Allergenic fragrances toys shall not contain; and
- the New Zealand Cosmetic Products Group Standard: Schedule 5 - Components cosmetic products must not contain except subject to the restrictions and conditions laid down. The presence of the

substance must be indicated in the list of ingredients when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

Substance summary

Cinnamaldehyde is an organic compound which occurs naturally as predominately the trans (E) isomer, it gives cinnamon its flavour and odour. This pale yellow, viscous liquid occurs in the bark of cinnamon trees and other species of the genus Cinnamomum. The essential oil of cinnamon bark is approximately 50% cinnamaldehyde.[67]

Table 2.5A: General information

Property	Cinnamaldehyde
CAS No.	104-55-2
Chemical structure	
Molecular formula	C_9H_8O
Molecular weight	132.16 g/mol
Alternative names	(2E)-3-phenylprop-2-enal (IUPAC); cinnamal; cinnamic aldehyde; 2-Propenal, 3-phenyl- (CAS)

The following information was extracted from the NICNAS New Chemical assessment report for cinnamaldehyde.[68] Further information can also be found in the SCCS (2012) opinion on fragrance allergens in cosmetic products.[69]

[67] Singh, Gurdip; Maurya, Sumitra; deLampasona, M.P.; Catalan, Cesar A.N. (2007). "A comparison of chemical, antioxidant and antimicrobial studies of cinnamon leaf and bark volatile oils, oleoresins and their constituents". *Food and Chemical Toxicology*. **45** (9): 1650–1661

[68] This report is publicly available on the NICNAS website: Human Health Tier II Assessment for 2-Propenal, 3-phenyl-.

[69] This report is publicly available at Scientific Committee on Consumer Safety: Opinion on Fragrance allergens in cosmetic products

Table 2.5B: Acute toxicity end-points for cinnamaldehyde

Toxicity	Species	Cinnamaldehyde	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	620-1260	Schedule 6
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	-
Skin irritation	Rabbit	Severe skin irritation (undiluted) Mild skin irritation (3-5% solution) No irritation (1% solution)	Schedule 6
Eye irritation	Rabbit	Mild to severe eye irritation (0.125-1%) Severe chemosis and discharge at 1.25%	Schedule 6
Skin sensitisation	Mouse (LLNA)	Moderate to strong skin sensitiser (EC3 0.2-3.1%)	Schedule 6
	Guinea pig (GPMT)	Positive reactions in 90-100% of animals tested at 0.75%. Sensitisation effects seen as low as 0.1%.	

Acute toxicity

Cinnamaldehyde has low acute oral toxicity, but moderate acute dermal toxicity based on results from animal tests.

Irritation

The available data from animal and human studies indicate that cinnamaldehyde is irritating to the skin, eyes and respiratory system, warranting hazard classification:

- Cinnamaldehyde produced severe irritation in rabbits when applied undiluted, mild irritation in mice and guinea pigs at concentrations of 3-5%, and it was non-irritating to rabbits at 1%. The US EPA considers cinnamaldehyde a strong skin irritant in guinea pigs (no study details provided).
- In New Zealand White rabbits, cinnamaldehyde produced eye irritation when applied undiluted, and effects were not completely reversed after 7 days. In three separate experiments, concentrations of 0.125%, 1% and 1.25% cinnamaldehyde were instilled in rabbit eyes. Intense to mild conjunctival irritation was observed and, at the highest concentration (1.25%), severe chemosis and considerable discharge were observed. The effects were reversible after a week at all concentrations except the highest.
- Respiratory irritation was assessed in CF-1 female mice by recording their respiratory rate following exposure to nebulised cinnamaldehyde for 1 minute, either through nose-only exposure or via a tracheal cannula. Marked respiratory depression with nose-only exposure was observed.

The ED25 (dose providing a 25% reduction in respiratory rate) was calculated to be 241 µg/L. No significant effects were observed when inhalation was via the tracheal cannula.

Sensitisation

Based on the available animal and human data, cinnamaldehyde is considered to be a moderate to strong contact skin sensitiser:

- In a study equivalent to OECD Test Guideline (TG) 429, cinnamaldehyde was reported to be positive for skin sensitisation in an *in vivo* mouse LLNA. The mice were administered 0, 0.1, 0.3, 1.0, 3.0 or 10.0% (w/v) of cinnamaldehyde in ethanol/diethyl phthalate (ratio of 3:1). Stimulation indices (SI) were not reported; however, the EC3 was determined to be 0.2%. A similar study with cinnamaldehyde, at doses of 0, 0.5, 1.0, 2.5, 5 and 10% in acetone/olive oil (ratio of 4:1), reported positive results for skin sensitisation with SI of 1, 1.4, 0.9, 1.9, 7.1 and 15.8 respectively. An EC3 of 3.1% was calculated.
- Cinnamaldehyde has also been reported as sensitising at almost all concentrations (0.1–20%) studied in various guinea pig sensitisation tests. A recent review of cinnamaldehyde by the Danish EPA reported skin sensitisation effects in 90-100% of animals tested at a concentration of 0.75% in three separate guinea pig maximisation tests (GPMTs). Strong sensitisation effects were also reported with 3% cinnamaldehyde, although further study details were not provided. In a modified Draize test, an injection challenge concentration of 0.25% cinnamaldehyde with a 20% topical application challenge dose resulted in sensitisation effects after the challenge was repeated a week later. In addition, concentrations of 0.1-1.0% cinnamaldehyde in acetone have resulted in skin sensitisation effects at all doses in a Buehler delayed hypersensitivity test.
- A 3-day application of 10% cinnamaldehyde on the ear dorsum in mice resulted in a high differentiation index (DI) of 8.7, according to OECD standards. The DI is defined as a ratio of maximum response percentages in lymph node activation and skin inflammation, where a DI >1 indicates an allergic reaction pattern.

Repeat-dose toxicity

Based on the available information, cinnamaldehyde is not considered to cause serious damage to health through repeated oral exposure. Systemic toxicity has not been demonstrated via the dermal route. No information was available for repeated dose toxicity by inhalation route.

Genotoxicity

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

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of cinnamaldehyde. Based on the available genotoxicity data, mechanistic information and history of human oral exposure, cinnamaldehyde is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available information, cinnamaldehyde is not expected to be a reproductive or developmental toxin.

Observation in humans

Irritation

Cinnamaldehyde has been shown to cause skin irritation in humans in a number of reports. Cinnamaldehyde produced irritation in 10/63 volunteers at 3% in diethyl phthalate/ethanol (ratio of 3:1). Severe skin irritation was observed in 5/5 volunteers treated with 8% cinnamaldehyde in

petrolatum. In another study, doses of 40 and 48 mg of cinnamaldehyde in petrolatum (concentrations not reported) were applied under occlusive conditions to human skin for 48 hours. Cinnamaldehyde was concluded to be severely irritating to human skin. A review carried out by the Research Institute for Fragrance Materials (RIFM) Expert Panel reported that cinnamaldehyde produced no skin irritation effects in 171 volunteers at concentrations of 0.125-1.25% in a variety of vehicles.

In a limited data eye irritation study, a solution of 8% cinnamaldehyde was instilled in human eyes. Cinnamaldehyde produced slight irritant effects. It was noted that the cornea was not affected; however, no further details were described.

Cinnamaldehyde induced coughing in all ten human subjects following inhalation of nebulised chemical (dose levels from 125-800 mM), with a distinct dose-response relationship observed - the response being the number of coughs recorded after exposure to cinnamaldehyde. Cinnamaldehyde was found to be a specific agonist of the TRPA-1 receptor, and induced cough due to chemaesthesis of the airways.

Sensitisation

Cinnamaldehyde is a well-recognised and frequently reported consumer contact allergen. It is one of eight components of the diagnostic test, the fragrance mix, used by dermatologists to determine if a patient has allergies to common chemicals used in fragrances. It is an established contact allergen in humans according to the Scientific Committee on Consumer Safety (2012), and accounts for 5-36% of the reactions to the fragrance mix.

A number of human repeat insult patch tests (HRIPTs) have been undertaken to determine the skin sensitisation potential of cinnamaldehyde in healthy volunteers, as well as groups of subjects suspected of skin allergies to fragrances. Although fewer cases of sensitisation were found when the concentration of cinnamaldehyde was less than 1%, positive allergic responses have been reported in cases where the administered concentration of cinnamaldehyde was as low as 0.2%. Skin irritation effects were generally predominant at concentrations above 3% cinnamaldehyde, and often impeded the interpretation of results from the patch testing.

Many cases of skin sensitisation have occurred following occupational and consumer exposure to cinnamaldehyde. Workers in spice manufacturing plants, hairdressing salons and bakeries have reported cases of contact dermatitis that were traced back to cinnamaldehyde. In addition, exposure of consumers to toothpaste, cosmetics and perfumes containing cinnamaldehyde as a fragrance ingredient have resulted in a number of case studies identifying cinnamaldehyde as an agent responsible for the allergic reactions.

Public exposure

Cinnamaldehyde is a very widely used and easily available fragrance ingredient. Considering the range of domestic, cosmetic and personal care products that may contain cinnamaldehyde, the main route of public (non-food) exposure is expected to be dermal. There is also possible ocular and inhalation exposure from products applied as aerosols. At the applied concentrations, the irritant effects of cinnamaldehyde are unlikely to present a risk. However, there are recorded cases of human skin sensitisation attributed to fragrance use.

The risk of skin sensitisation could be mitigated by implementing concentration limits and restricting uses to limit dermal exposure. The restrictions on the use of cinnamaldehyde in cosmetic products in New Zealand and the European Union are considered appropriate to mitigate the risk.

Pre-meeting public submissions

Three (3) public submissions were received. All three opposed the scheduling proposal. The main points were:

- An Appendix B entry as has been previously considered for other flavour/fragrance ingredients used in cosmetic and household hygiene products with low acute toxicity and low public exposure.

- The EU only requires the inclusion of cinnamaldehyde in the ingredients list, on the label of products, if the concentration in the finished product is ≥0.001% in leave-on products, and ≥0.01% in rinse-off products.
- IFRA standards already exist for cinnamaldehyde and therefore scheduling is not required. cinnamaldehyde should be considered to be included in Appendix B.
- Cinnamaldehyde does not require scheduling due to the derivatives amyl and hexyl cinnamaldehyde being included in Appendix B in September 2016.
- If there are any decisions to schedule cinnamaldehyde, then these should align with IFRA standards.

The public submissions will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee advised that a new Schedule 6 entry be created for cinnamaldehyde:

Schedule 6 - New Entry

CINNAMALDEHYDE **except**:

a) in preparations intended for therapeutic use; or

b) in domestic preparations not intended for direct skin contact containing 0.4 per cent or less of cinnamaldehyde when included in the list of ingredients; or

c) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of cinnamaldehyde; or

d) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of cinnamaldehyde.

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

The committee also recommended other actions by the delegate as follows:

- The derivatives definition to be reviewed to provide greater transparency for industry as part of the SPF review.

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

The reasons for the advice comprised the following:

- Cinnamaldehyde is a known human allergen and there is evidence of potentially strong sensitisation potential.
- Cinnamaldehyde is a naturally occurring fragrance and flavour substance used internationally in a wide range of products including in food, therapeutic goods, cosmetics and consumer products. There is therefore a potential for significant impact from any scheduling decision.
- Cinnamaldehyde is listed in the US FDA GRAS list.
- Risk and benefit profile of cinnamaldehyde is very similar to another scheduled substance, citral.
- The toxicity profile of cinnamaldehyde show that it is a skin and eye irritant, has acute dermal toxicity, is a strong skin sensitiser and is a respiratory irritant at high concentrations.

- There is a potential for significant impact from any scheduling decision due to the wide range of uses and potentially large numbers of products affected.

Delegate's considerations

The delegate considered the following 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

Delegate's interim decision

The delegate has decided to defer the interim decision for cinnemaldehyde to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.

2.6 Benzyl salicylate

Referred scheduling proposal

The scheduling delegate is seeking advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on an application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new Schedule 6 entry for benzyl salicylate.

Current scheduling status and relevant scheduling history

Benzyl salicylate is not currently scheduled.

A derivative of benzyl salicylate, salicylic acid, is in Schedule 3 of the Poisons Standard as follows:

> **Schedule 3**
>
> SALICYCLIC ACID in preparations for dermal use **except** in preparations containing 40 per cent or less of salicylic acid.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

> **Schedule 6 – New Entry**
>
> BENZYL SALICYLATE in cosmetic and domestic products **except**:
>
> a) in leave-on preparations containing 0.001 per cent or less of benzyl salicylate when labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals; or

b) in rinse-off products containing 0.01 per cent or less of benzyl salicylate when labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals

Appendix E, Part 2 – New Entry

BENZYL SALICYLATE

Standard statements: E1 (If in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

BENZYL SALICYLATE

Warning statements: 28 [(Over) (Repeated) exposure may cause sensitisation].

The applicant's reasons for the request are:

- Benzyl salicylate is a skin sensitiser;
- Benzyl salicylate is an eye irritant;
- Benzyl salicylate is reported to be used in cosmetic and domestic products overseas, in particular, as a fragrance, solvent and UV light absorber at concentrations up to 7%. In the absence of specific Australian information, this is taken as being representative of its use in Australia;
- There are overseas restrictions for the use of benzyl salicylate in cosmetics; and
- Skin sensitisation from use of benzyl salicylate in cosmetic products can only be mitigated by implementation of concentration limits.

Australian regulatory information

Benzyl salicylate is the AAN (reference Merck Index). It is in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017 for use only in combination with other permitted ingredients as a flavour at no more than 5% or a fragrance at no more than 1%. Benzyl salicylate is an excipient in 331 listed and registered products (both oral and topical) on the ARTG.

International regulations

Benzyl salicylate is in the EU Cosmetic Regulation EC No. 1223/2009, Annex III - List of substances which cosmetic products must not contain except subject to the restrictions laid down. It states that *'This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.'*

Substance summary

Benzyl salicylate is a salicylic acid benzyl ester occurring naturally in a variety of plant extracts. It is a clear, colourless to pale yellow oil with a balsamic clean herbal oily sweet scent. Benzyl salicylate is commonly used as a flavour and fragrance agent and as a UV absorber.[70]

[70] Benzyl salicylate

Table 2.6A: General information

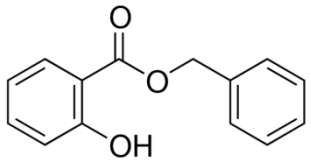
Property	Benzyl salicylate
CAS No.	118-58-1
Chemical structure	
Molecular formula	$C_{14}H_{12}O_3$
Molecular weight	228.24 g/mol
Alternative names	benzyl salicylate (INCI and AAN); benzoic acid, 2-hydroxy-, phenylmethyl ester (CAS); salicylic acid, benzyl ester; benzyl 2-hydroxybenzoate (IUPAC); phenylmethyl 2-hydroxybenzoate.

Table 2.6B: Acute toxicity end-points for benzyl salicylate

Toxicity	Species	Benzyl salicylate	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats[71]	2227	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits[71]	14150	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A
Skin irritation	New Zealand White Rabbits	Slightly irritating	Schedule 5
	Dunkin Hartley Guinea pigs	Slight erythema	
Eye irritation	Rabbit[71]	Irritating	Schedule 6
Skin sensitisation	Mice[71] (LLNA)	Sensitising (EC3 1.5-2.9%)	Schedule 6
	Dunkin Hartley Guinea pig (GPMT)	Sensitising	

[71] Strain not specified

Acute toxicity

Based on the available data, benzyl salicylate has low acute oral and dermal toxicity. No data are available for acute inhalation toxicity.

Skin irritation

Based on the available data in animals and humans (see Observation in humans section), benzyl salicylate is slightly irritating to skin:

- In two studies in female New Zealand White rabbits, slight erythema and slight oedema was reported in one study, and well defined erythema and very slight to slight oedema was reported in another study when benzyl salicylate was semi-occlusively applied to the shaved flanks.

Slight irritation was observed in Dunkin Hartley guinea pigs after benzyl salicylate was dermally administered (non-occlusively) for 24 or 48 h at 10% (1/5 animals) and 30% (5/5 animals).

Eye irritation

Based on the available data in animals, benzyl salicylate is considered to be an eye irritant:

- In an *in vivo* study (Draize method) conducted in albino rabbits (n = 3), 0.1 mL of benzyl salicylate at a 10% concentration in alcohol was instilled into the right eye and animals were observed for 10 days. Mild conjunctival irritation was observed in all rabbits and corneal opacity in one rabbit. All effects were reversed within seven days. The mean scores reported for iritis (0/4), conjunctival redness (1.89/4), chemosis (1.22/4) and corneal opacity (0.33/4) were below the cut-off for classification. However, individual average (24, 48 and 72 h) scores for two rabbits for conjunctival redness were 2/4, which is sufficient for classification by GHS criteria (but not by Approved Criteria). Considering the effects observed at this concentration, benzyl salicylate is expected to be irritating to the eyes if exposed at higher or neat concentrations.

Sensitisation

Based on the available data in mice, benzyl salicylate is considered to be a skin sensitiser.

LLNA

- Mice were topically administered 25 µL of benzyl salicylate at 10% in 4:1 acetone/olive oil to the ear lobe for three days. The estimated concentration required to produce a three-fold increase in lymphocyte proliferation (EC3) was reported to be 1.5%.

- The EC3 value was determined to be 2.9% in mice after treatment with benzyl salicylate at 2.5, 5, 10, 25 or 50% in 1:3 ethanol:diethyl phthalate.

GPMT

- Hartley guinea pigs were intra-dermally and topically induced with benzyl salicylate at 10% and 50%, respectively and challenged at 5, 10 or 20%. Positive reactions were observed at the 20% challenge (2/20) and there were some 'questionable' reactions at other concentrations (3/20 at 5%, 5/20 at 10% and 4/20 at 20%).

- Hartley albino guinea pigs were intra-dermally and topically induced at 10 and 30%, respectively. After three weeks, the animals were challenged twice at 0.003, 0.01 or 0.03%. No reactions were observed after the first challenge. After the second challenge, positive reactions were reported at 0.03% after 24 h, and at all concentrations after 48 h and 72 h.

- Female albino Dunkin Hartley guinea pigs were intra-dermally induced with benzyl salicylate at 10%. Following a seven day rest period, benzyl salicylate at 10% in acetone was topically applied to the shoulder region for 48 h. Two weeks later, challenge doses of benzyl salicylate at 5, 10 or 20% in acetone were applied to the shaved flanks of each animal and observations made at 24, 48 and 72 h. Positive reactions were observed at all challenge concentrations.

- Sensitisation was not reported in outbred Himalayan white-spotted guinea pigs when benzyl salicylate was used at 5% for intradermal induction, 25% in petrolatum for topical induction and <0.1% in petrolatum for the topical challenge.
- Similarly, no positive reactions were reported in a Magnusson-Kligman GPMT after benzyl salicylate was intra-dermally applied at 1% in ethanol and dermally at 100%; no further study details are available.

Repeat-dose toxicity

No data are available for benzyl salicylate. However, based on data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS No. 69-72-7), benzyl salicylate is not expected to cause serious health effects from repeated oral or inhalation exposure.

Genotoxicity

Limited data are available for benzyl salicylate. However, based on data for the metabolite benzyl alcohol (CAS No. 100-51-6), benzyl salicylate is not considered to be genotoxic.

Carcinogenicity

No data are available for benzyl salicylate. However, based on the data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS No. 69-72-7), benzyl salicylate is not considered to be carcinogenic.

Reproduction and developmental toxicity

No data are available for benzyl salicylate. However, based on data for the metabolites benzyl alcohol (CAS No. 100-51-6) and salicylic acid (CAS 69-72-7), benzyl salicylate is not considered to cause developmental toxicity. Any developmental effects for the metabolites were only observed secondary to maternal toxicity.

Other effects

The oestrogenic activity of benzyl salicylate has been assessed *in vitro*, using MCF7 human breast cancer cells. Benzyl salicylate was used in a competitive binding assay to the cytosolic oestrogen receptor (ER) of MCF7 cells; a competitive binding assay to human recombinant ERα and ERβ; a gene expression assay using the stably transfected ERE-CAT reporter gene in MCF7 cells; and a cell proliferation assay. Benzyl salicylate mimicked oestrogenic responses in all assays. In the competitive binding assays, 3H-oestradiol was partially displaced by benzyl salicylate (when used at 3×10^6 molar excess) from cytosolic ER of MCF7 cells and from human recombinant ERα and ERβ. In the gene expression assay, benzyl salicylate increased the expression of the oestrogen-responsive reporter gene (ERE-CAT) and the endogenous oestrogen-responsive pS2 gene when cells were exposed at concentrations of 0.05-0.5 mM. In the cell proliferation assay, benzyl salicylate increased proliferation of oestrogen-dependent cells over a seven day period; proliferation was inhibited by an anti-oestrogen drug (fulvestrant). However, it was reported that benzyl salicylate was less potent (requiring 1 mM versus 0.1 µM) and took 2.5-fold longer duration (35 days versus 14 days) to achieve a similar magnitude of proliferation as endogenous 17β-oestradiol.

Further conclusions on the endocrine disruption potential of benzyl salicylate cannot be made. This is an area of concern given the lack of data available for reproductive and developmental toxicity, and due to structural similarity of benzyl salicylate to monobenzyl phthalate (CAS No. 2528-16-7) (unscheduled) which is known to have anti-androgenic activity and the potential to impair fertility and cause teratogenic effects.

Observation in humans

Irritation

In several skin irritation studies in humans, benzyl salicylate at 15–100% was applied to the skin via an occluded patch for 4-48 h. One study reported irritation in 2/22 subjects exposed to benzyl salicylate at 30%.

Skin sensitisation

The International Fragrance Association (IFRA) reported a No Expected Sensitisation Induction Level (NESIL) of 17 700 µg/cm^2 based on a human maximisation test and therefore classified benzyl salicylate as a weak sensitiser.

Reports from the Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP), 1999 and the Scientific Committee on Consumer Safety (SCCS), 2011 lists benzyl salicylate as an allergen.

In human patch test studies, results for sensitisation were varied:

- In five maximisation tests using human volunteers (n = 22-25/study, males and females), benzyl salicylate was administered at 20-30% in petrolatum. Reactions were observed in two studies, affecting 2/25 and 1/25 subjects at 20%. No positive reactions were reported at 30%.
- In a study that was conducted to determine the optimal patch testing concentration of benzyl salicylate, humans (n = 212) were dermally exposed to benzyl salicylate at 5% in petrolatum. Positive reactions were reported in 12/212 subjects.
- In three human repeated insult patch tests (HRIPT) conducted on volunteers (n = 35, 52 or 101; males and females), benzyl salicylate was administered at 5-15% in various vehicles (diethyl phthalate:ethanol (3:1) or dimethyl phthalate or alcohol SD39) and observations were made up to 144 h after the final challenge exposure. Positive reactions were not observed in any study.
- In a human patch test (HPT), 30 volunteers were dermally exposed to 0.2 mL of benzyl salicylate via application to the skin of the upper outer arm for 4 h and observed for 72 h. No reactions were reported.

Public exposure

Benzyl salicylate has been identified to be used in cosmetic (perfumes and fragrances; personal care products; and as an ultraviolet radiation absorber) and domestic products (polishes and waxes; softeners; surface treatments; air care products; and washing and cleaning products) overseas at concentrations up to 7%. This use pattern is taken to be representative of its use in Australia.

Due to the use patterns of benzyl salicylate, direct dermal exposure is expected.

Pre-meeting public submissions

Three (3) public submissions were received. All three submissions opposed the scheduling proposal. The main points were:

- An Appendix B entry as has been previously considered for other flavour/fragrance ingredients used in cosmetic and household hygiene products with low acute toxicity and low public exposure.
- The EU only requires the inclusion of benzyl salicylate in the ingredients list if the concentration in the finished product is ≥0.001% in leave-on products, and ≥0.01% in rinse-off products.
- IFRA standards already exist for benzyl salicylate and therefore scheduling is not required. An Appendix B listing should be considered for benzyl salicylate. If scheduling is to proceed, any scheduling decisions should align with IFRA standards.

The public submissions will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee advised that a new Schedule 6 entry and Appendix E and F entries be created for benzyl salicylate:

Schedule 6 - New Entry

BENZYL SALICYLATE **except**:

a) in preparations intended for therapeutic use; or

b) in domestic preparations:

i) intended for skin contact containing 15 per cent or less of benzyl salicylate when included in the list of ingredients; or

ii) not intended for direct skin contact when included in the list of ingredients; or

c) in leave-on cosmetic and personal care preparations:

i) containing 0.001 per cent or less of benzyl salicylate; or

ii) when included in the list of ingredients; or

d) in rinse-off cosmetic and personal care preparations:

i) containing 0.01 per cent or less of benzyl salicylate; or

ii) when included in the list of ingredients.

Appendix E, Part 2 - New Entry

BENZYL SALICYLATE

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 - New Entry

BENZYL SALICYLATE

Warning statements: 28 [(Over) (Repeated) exposure may cause sensitisation].

Safety directions: 4 (Avoid contact with skin).

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

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

The reasons for the advice comprised the following:

- Benzyl salicylate is a fragrance excipient used in many medicinal, cosmetic and personal care products. It is included as an excipient in 331 products listed on the ARTG. It is used in cosmetics and domestic products.
- The EU Cosmetic Regulation states "This chemical may be used in cosmetics and personal care products, but the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products."

- The IFRA Standard restricts use to maximum of 12.8% depending on the product use (i.e. those with skin contact). Worldwide use is widespread in cosmetic and domestic products up to 7% concentrations.
- The risks at concentrations currently used appear low.
- The toxicity profile for benzyl salicylate shows evidence of skin sensitisation in animals and humans, it is reported to slightly irritate the skin in animals but human studies show inconsistent reports and it is reported as an eye irritant at 10% concentrations in mice. It is a known contact allergen in humans. The toxicity profile meets the SPF requirements of a Schedule 6 item.

Delegate's considerations

The delegate considered the following 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

Delegate's interim decision

The delegate has decided to defer the interim decision for benzyl salicylate to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new Schedule 6 entry with very low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to listed therapeutic products when applied topically.

2.7 Sodium α-olefin sulfonates

Referred scheduling proposal

The scheduling delegate is seeking advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on an application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a Schedule 6 entry for sodium α-olefin sulfonate and sodium alkyl sulfate.

Current scheduling status and relevant scheduling history

Sodium α-olefin sulfonate and sodium alkyl sulfate are not specifically scheduled and have not been previously considered for scheduling.

However, lauryl sulfate salts are similar surfactants listed in Schedule 6 and Appendix E, Part 2, as follows:

Schedule 6

LAURYL SULFATE SALTS (excluding their derivatives) **except**:

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

IF IN EYES WASH OUT IMMEDIATELY WITH WATER;

b) in leave-on preparations containing 1.5 per cent or less of lauryl sulfates;

c) in toothpaste and oral hygiene preparations containing 5 per cent or less of lauryl sulfates;

d) in other preparations for animal use containing 2 per cent or less of lauryl sulfates; or

e) in other preparations containing 30 per cent or less of lauryl sulfates and, if containing more than 5 per cent of lauryl sulfates, when labelled with warnings to the following effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

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

Appendix E

Lauryl sulfate salts	Warning statement
• leave-on or wash-off preparations above 5 per cent	E1 [If in eyes wash out immediately with water]
• other preparations above 5 per cent	E1 (as above) and S1 [If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.]

Scheduling application

This was a general application.

In July 2016, the NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) program, submitted a proposal to create new entries for sodium α-olefin sulfonate (sodium AOS) and sodium alkyl sulfate (sodium AS) in Schedule 6, paralleling that for lauryl sulfates, in order to restrict their use in cosmetic and domestic products. Exemption to scheduling might be applicable at low concentrations.

The applicant's reasons for the request are:

- Sodium α-olefin sulfonate and sodium alkyl sulfate have reported uses in a range of cosmetic and domestic products in Australia;
- Reported use of sodium α-olefin sulfonate and sodium alkyl sulfate in cosmetic and domestic products overseas, potentially available for use in Australia, at concentrations up to 16.5%;
- Sodium α-olefin sulfonate and sodium alkyl sulfate are potential moderate to strong skin irritants at 10% concentration;
- Sodium α-olefin sulfonate and sodium alkyl sulfate are severe eye irritants at concentrations ≥30%; and
- Sodium α-olefin sulfonate and sodium alkyl sulfate present similar issues as other surfactants already scheduled in the SUSMP, including sodium lauryl sulfate (SLS).
- There is potential for dermal and ocular exposure to occur at irritating concentrations based on its use pattern. This can be mitigated by labelling and concentration controls. Sodium α-olefin sulfonate and sodium alkyl sulfate are among a large number of surfactants used in Australia that are toxicologically similar to SLS, and these have been identified to be used in comparatively high concentrations.

Australian regulatory information

Sodium α-olefin sulfonate (as SODIUM C14-16 OLEFIN SULFONATE) is in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017 as an excipient only for use in topical medicines for dermal application.

Sodium C14-16 olefin sulfonate is in 3 registered products on the ARTG. It is allowed to be used as an excipient in biologicals, devices, export-only, listed medicines, OTC and prescription medicines; and as an active ingredient in biologicals and prescription medicines. Sodium α-olefin sulfonate is a declarable excipient (i.e. it is required to be declared on the label of a medicine) in accordance with Therapeutic Goods Order No. 69. When used in biologicals, sodium α-olefin sulfonate can be displayed as a starting material.

Sodium alkyl sulfate is not on the ARTG or on the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017.

International regulations

New Zealand

Sodium α-olefin sulfonate is included in one cosmetic product in NZ as an excipient.

Canada

Sodium α-olefin sulfonate (as sodium C14-16 olefin sulfonate) is listed as a surfactant - cleansing agent for topical use. Further, sodium α-olefin sulfonates (of chain lengths C12-14, C14-16, C14-18 and C16-18) are considered to be safe when used in rinse-off products and safe up to 2% in leave-on products. The concentration of the gamma sultone impurity of any formulation (leave-on or rinse-off) is limited to unsubstituted alkane sultones 10 ppm; chlorosultones 1 ppm; and unsaturated sultones 0.1 ppm. Sodium alkyl sulfate (as sodium C12-15 alkyl sulfate) is listed as a non-medical ingredient.

Substance summary

Table 2.7A: General information

Property	Sulfonic acids, C14-16-alkane hydroxyl and C14-16-alkene, sodium salts	Sulfuric acid, mono-C12-18-alkyl esters, sodium salts
CAS name	sodium C14-16-olefin sulfonate	sulfuric acid, mono-C12-18-alkyl (even numbered) esters, sodium salts
CAS number	68439-57-6	68955-19-1
IUPAC and/or common and/or other names	sodium α-olefin sulfonate; sodium AOS (INCI)	sodium alkyl sulfate; sodium AS (INCI)

The following information has been extracted from the NICNAS IMAP Human Health Tier II group assessment report for sodium α-olefin sulfonate and sodium alkyl sulfate (Attached A).[72]

[72] Publicly available on the NICNAS website: Human Health Tier II Assessment for selected anionic surfactants

Table 2.7B: Acute toxicity end-points for sodium α-olefin sulfonate and sodium alkyl sulfate

Toxicity	Species	Sodium α-olefin sulfonate and sodium alkyl sulfate	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat Mice	>2000 1400->2000	-
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	>2000	-
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rat	Low	-
Skin irritation	Rabbit	Moderate to severe skin irritants	Schedule 6
Eye irritation	Rabbit	Severe eye irritants	Schedule 6

Skin irritation

Sodium α-olefin sulfonate and sodium alkyl sulfate are considered skin irritants:

- In a skin irritation study conducted on six New Zealand White (NZW) rabbits, 0.5 mL of sodium AOS solution (38% active) was applied dermally to shaved, intact and abraded skin for 24 hours under occlusion. The treated site was not washed after the test substance was removed. Very slight irritation was observed on intact skin in 5/6 animals. One of the six animals had well-defined erythema, which had completely reversed by 72 hours after dosing. Five of the six animals showed well-defined erythema on the abraded skin at 24 hours after dosing. Very slight erythema in all animals and oedema in 2/6 animals were reported, which persisted after 72 hours post dosing on abraded skin (REACH).
- In another skin irritation study conducted in six NZW rabbits, 0.5 mL of sodium AOS solution (38% active) was applied dermally to shaved, intact and abraded skin for four hours under semi-occlusion. The applied site was washed to remove the test substance. All six animals showed moderate to severe reactions with eschar formation, one with cracking at the treatment site at 72 hours after dosing. The reactions were slightly worse in abraded skin than intact skin (REACH).
- In an irritation study conducted according to OECD Test Guideline (TG) 404, 0.5 g of sodium AS powder (88.7% purity) was applied dermally (semi-occlusive) to three New Zealand White rabbits for four hours. Erythema and moderate oedema were observed up to seven days after the patches were removed. All signs of irritation were completely resolved 14 days after dosing (REACH).
- Skin irritation (erythema and oedema) was also reported following a four-hour application of 5–25% sodium lauryl sulfate (SLS) solution on intact rabbit skin (NICNAS).

Eye irritation

Based on the data available, sodium α-olefin sulfonate and sodium alkyl sulfate are considered severe eye irritants:

- In an eye irritation study conducted according to OECD TG 405, 0.1 mL of sodium AOS (30% active) was applied to eyes of three NZW rabbits and observed for 21 days. Observed effects

included slight corneal redness, slight iritis and conjunctival effects (erythema, swelling and chemosis). Except for chemosis, all eye irritation effects persisted for up to 21 days (REACH).

- In another eye irritation study conducted in six NZW rabbits, 0.1 mL of sodium AOS (38% active) was applied to the eyes with or without washing. Observation times were 24, 48 and 72 hours after administration. Eye irritation effects, which persisted for up to 72 hours, were reported (REACH; HERA 2002).
- The eyes of three NZW rabbits were treated with concentrated (0.08 mL of 90% solution) sodium AOS. The test material was washed off and effects were observed at 24, 48 and 72 hours after application. Observed effects included clear to diffused beefy red erythema and severe swelling of the conjunctivae. Circumcorneal injection (enlargement of the ciliary and conjunctival blood vessels), corneal opacity and discharge (colourless, which changed to white viscous discharge) were also reported. The effects persisted for up to 21 days after dosing (REACH).
- Sodium AS administered at 6% resulted in eye irritation in rabbits, which was reversible within 72 hours of dosing (REACH).

The SLS chemical at 25% in an aqueous solution also caused eye irritation in rabbit eyes, which were not reversible within the 21-day observation period (NICNAS).

Observation in humans

Sodium α-olefin sulfonate and sodium alkyl sulfate are reported to have irritation potential in humans. Data on SLS are provided as read across since SLS has similar physicochemical properties and reactivity to sodium AOS and sodium AS.

- In a dermal irritation study, human cadaver skin was soaked in sodium olefin sulfonates (C10, 12, 14, 16 and 18) for one, three, six and 24 hour and was compared with skin soaked in distilled water for the same period. Maximum swelling was seen for the C12 and C14 olefin sulfonates (REACH).
- In a controlled human exposure, repeated application of 1% alkyl sulfates to the skin of human volunteers did not produce adverse reactions, while concentrations of 10% were regarded as moderate to strong irritants (HERA, 2002).
- Clinical studies in humans reported that SLS caused skin irritation following patch testing at a ≥2% concentration. The irritation increases with increasing concentration and length of contact with the skin (NICNAS).
- SLS has been reported to cause irritation in the respiratory tract and oral mucosa, especially in individuals predisposed to recurrent mouth ulcers (NICNAS).
- It has also been reported that SLS was the most common cause of eye irritation in commercial shampoos (NICNAS).

Sensitisation

Sodium α-olefin sulfonate and sodium alkyl sulfate are not expected to be skin sensitisers, based on the available information.

Repeat-dose toxicity

Based on the data available, sodium α-olefin sulfonate and sodium alkyl sulfate are not expected to cause serious damage to health from repeated oral and dermal exposure. No information was available for repeated dose toxicity by the inhalation route.

Genotoxicity

Based on the negative results observed in several *in vitro* and *in vivo* genotoxicity studies, sodium α-olefin sulfonate and sodium alkyl sulfate are not expected to be genotoxic.

Carcinogenicity

Based on available data, sodium α-olefin sulfonate and sodium alkyl sulfate are not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the limited available data, Sodium α-olefin sulfonate and sodium alkyl sulfate are not expected to have reproductive and developmental toxicity.

Public exposure

Sodium α-olefin sulfonate and sodium alkyl sulfate are reported to be used in cosmetic and domestic products in Australia.

Australian and overseas information suggests that sodium α-olefin sulfonate and sodium alkyl sulfate are generally used at concentrations up to 16% in cosmetics and at up to 16.5% for domestic purposes (i.e. hand dishwashing liquid) (HERA 2002).

Considering the critical health effects identified for sodium α-olefin sulfonate and sodium alkyl sulfate, the highest concern relates to skin and eye irritation. There is the potential for skin contact to occur when using domestic products such as laundry detergents or hand washing liquid. However, such products are intended to be rinsed off from the skin after use. There is also the potential for ocular exposure in a domestic setting.

Pre-meeting public submissions

Three (3) public submissions were received. All three submissions opposed the scheduling proposal. The main points were:

- A generic group entry of C12-C18 alkyl length surfactants cannot be supported due to differing characteristics of varying lengths of alkyl chains and would hinder attempts by industry to formulate less irritating surfactants.
- Due to surfactants being used for cleaning the body or domestic surfaces for decades, consumers are already knowledgeable in the appropriate use of surfactants and have a certain use pattern of these products due to this continued use over time.
- Scheduling of all surfactants individually is opposed by most submissions, due to this not aligning with international requirements. These substances are not restricted in cosmetics in the EU and the USA permits their use in rinse-off products at ≤2%.
- Scheduling will not generate a better risk management outcome.
- These surfactants do not require scheduling when used in cosmetic products.
- If scheduling is deemed appropriate, submissions suggested lauryl sulfates scheduling should act as a guide for concentration cut-offs and that a minimum of a 12 month lead-in time be implemented.

The public submissions will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee advised that based on the information contained in the application no scheduling entry could be developed for sodium α-olefin sulfonate and sodium alkyl sulfate at this time.

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

The reasons for the advice comprised the following:

- As surfactants, these substances are widely used domestically, including leave-on and wash-off products and cleaning products.
- There are major public health benefits for infection control within the domestic premises when alkyl sulphonate/sulphate surfactants are available without restriction. Despite their widespread use, there have been minimal adverse events associated with the use of these surfactant substances. However, the data may be inadequate to quantify the public health risks associated with this class of surfactants and that only one chain length tends to be hazardous.
- The chemicals captured by this proposal are very closely related to sodium lauryl sulphate, which has previously been scheduled.
- The toxicity profiles of these substances include potential eye damage at higher concentrations, possible cumulative dermal irritation in leave on applications, and eye irritancy at 30%. The short chain is more potent with strong irritation at lower concentrations compared with long chain. Skin irritation for leave-on products at is >2-5% with potency being chain-length dependent. SAS C16-18 appears to show only slight reactions at 31.5%, while C12 showed strong reactions at 25%, but slight at 5%.
- Also considered was the feasibility of industry to implement any scheduling decision without substituting to an unregulated or more toxic substance/s. There may be public health ramifications of substituted surfactants in relation to their purpose, such as cleaning.

Delegate's 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

Delegate's interim decision

The delegate's interim decision is that no scheduling entry be created for sodium α-olefin sulfonate and sodium alkyl sulfate.

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

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.

- As surfactants, these substances are widely used domestically, including leave-on and wash-off products and cleaning products.
- There are major public health benefits for infection control within the domestic premises when alkyl sulphonate/sulphate surfactants are available without restriction. Despite their widespread use, there have been minimal adverse events associated with the use of these surfactant substances. However the data may be inadequate to quantify the public health risks associated with this class of surfactants and that only one chain length tends to be hazardous.
- The chemicals captured by this proposal are very closely related to sodium lauryl sulphate, which has previously been scheduled.
- The toxicity profiles of these substances include potential eye damage at higher concentrations, possible cumulative dermal irritation in leave on applications, and eye irritancy at 30%. The short chain is more potent with strong irritation at lower concentrations compared with long chain. Skin irritation for leave-on products at is >2-5% with potency being chain-length dependent. SAS C16-18 appears to show only slight reactions at 31.5%, while C12 showed strong reactions at 25%, but slight at 5%.
- Also considered was the feasibility of industry to implement any scheduling decision without substituting to an unregulated or more toxic substance/s. There may be public health ramifications of substituted surfactants in relation to their purpose, such as cleaning.

2.8 Resorcinol

Referred scheduling proposal

The scheduling delegate is seeking advice from the Joint Advisory Committees on Chemicals and Medicines Scheduling (ACCS-ACMS) on an application submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under their IMAP program to create a new Schedule 6 entry for resorcinol (1,3-benzenediol) to reflect its use in cosmetic and domestic products.

Current scheduling status and relevant scheduling history

Resorcinol (1,3-benzenediol) is currently unscheduled.

In July 2016, NICNAS submitted a proposal to create a new entry for resorcinol in Schedule 6 for restriction in cosmetic and domestic products.

In January 2017, the delegate made a delegate-only final decision to enter resorcinol in Schedule 6 and Appendices E and F of the Poisons Standard as follows:

Schedule 6

RESORCINOL **except**:

a) in hair dye preparations containing 1.25 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

b) in hair lotions/shampoo products containing 0.5 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used on the eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

Appendix E – RESORCINOL

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).); E1 (if in eyes wash out immediately with water).

Appendix F – RESORCINOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The implementation date of this decision was 1 February 2017.

Following the release of the final decisions on 16 January 2017, feedback from industry indicated that resorcinol is used more broadly than initially considered. On 31 January 2017, the Schedule 6 entry for resorcinol was removed from the 1 February 2017 Poisons Standard to allow further review of its broader use pattern. This final decision was implemented as Amendment No. 1 of SUSMP 16. Resorcinol was subsequently referred to the March 2017 Joint ACCS-ACMS meeting.

An *isomer of resorcinol*, 1,2-benzenediol, is scheduled as follows:

Schedule 6

1,2-BENZENEDIOL.

Appendix E – 1,2-BENZENEDIOL (catechol)

Standard statements: A, E1, S1

Appendix F – 1,2-BENZENEDIOL (catechol)

Warning statements: 51, 59.

Safety directions: 1, 4, 8.

A homologue of resorcinol, 2-methylresorcinol, was considered by the ACCS in March 2016.

Effective 1 June 2017, 2-methylresorcinol will be listed in Schedule 6 as follows:

Schedule 6 - New Entry

2-METHYLRESORCINOL **except**:

a) in non-oxidative hair dye preparations containing 1.8 per cent or less of 2-methylresorcinol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING –This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 1.8 per cent or less of 2-methylresorcinol after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING –This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – new entry

2-METHYLRESORCINOL

Standard statements: A, E1

Appendix F, Part 3 – new entry

2-METHYLRESORCINOL

Safety direction: 1

Scheduling application

This was a delegate-initiated application. The applicant's proposed amendments to the SUSMP were as follows:

Schedule 6 – New Entry

1,3-BENZENEDIOL for cosmetic and domestic products.

Appendix E, Part 2

1,3-BENZENEDIOL

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3

1,3-BENZENEDIOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the proposal are:

- Resorcinol is used in permanent hair dye preparations in Australia (NICNAS, 2007) and in hair lotions and shampoos overseas (refer to Import, Manufacture and Use section of IMAP Tier II report);
- Resorcinol has moderate oral toxicity and has been shown to cause skin and eye irritation as well as skin sensitisation;
- Resorcinol has existing overseas restrictions in European Union (EU) for oxidative hair colouring products at a maximum concentration of 2.5 %, with labelling requirements at lower concentrations. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, resulting in a concentration of 1.25 % when applied to hair (SCCS, 2010). Use of the chemical is also restricted in hair lotions and shampoos with a maximum authorised concentration in the finished cosmetic product of 0.5 %;
- When resorcinol is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Australian regulatory information

Resorcinol is included in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017 for use as an excipient, with the following restrictions:

- Permitted for use only in combination with other permitted ingredients as a flavour.
- If used in a flavour the total flavour concentration in a medicine must be no more than 5%.

The ARTG[73] two registered OTC products and two listed export-only products containing resorcinol.

Resorcinol was reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007) and in overseas hair lotions and shampoos. Currently, there are no restrictions in Australia on using this chemical in hair dyes, hair lotions and shampoos. In the absence of any regulatory controls, the characterised critical health effects (skin and eye irritation, and skin sensitisation) have the potential to pose an unreasonable risk under the identified uses. The risk could be mitigated by implementing concentration limits and labelling requirements for use in hair dyes, hair lotions and shampoos.

International regulations

The EU has restricted the use of this chemical in oxidative hair colouring products at a maximum concentration of 2.5 %. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, which corresponds to a concentration of 1.25 % when applied to hair (SCCS, 2010). Restricted use in hair lotions and shampoos was also reported to be the maximum authorised concentration in the finished cosmetic product of 0.5 %.

Resorcinol is listed on the EU Cosmetic Directive 76/768/EEC Annex III Part 1: List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down below (Galleria Chemica): (a) Hair dye substance in oxidative hair dye products for general and professional use - after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.25 % (w/w); and (b) Hair lotions and shampoos - maximum authorised concentration in the finished cosmetic product of 0.5 % (w/w).

Resorcinol is also listed on the following:

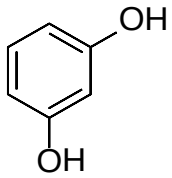
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- New Zealand Cosmetic Products Group Standard - Schedule 5 - Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist'); and
- Chile list of Cosmetic Ingredients with limited use or concentration.

Substance summary

Resorcinol is a colourless solid with a mild odour. Resorcinol has a number of chemical (dyes, resins, plasticisers, adhesives and polymers) and medical applications (antiseptic, disinfectant, antifungal).[74]

[73] Therapeutic Goods Administration Search results
[74] Dressler, H. (1994) 'm-Aminophenol', *Resorcinol: Its Uses and Derivatives*, Springer US, p 125-134.

Table 2.8A: General information

Property	Resorcinol
CAS number	108-46-3
Chemical structure	
IUPAC and/or common and/or other names	Resorcinol (INCI); 1,3-Benzenediol (CAS); 1,3-dihydroxybenzene; 3-hydroxyphenol
Molecular formula	$C_6H_6O_2$
Molecular weight	110.1 g/mol

The following toxicology information was extracted from the NICNAS IMAP Human Health Tier II assessment. Further information can also be found in the European Commission Scientific Committee on Consumer Safety (SCCS) report.

Table 2.8B: Acute toxicity end-points for resorcinol

Toxicity	Species	Resorcinol	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats (Sprague Dawley)	200-980 mg/kg bw/day.	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits	>2000 mg/kg bw/day.	N/A
Acute inhalational toxicity LC_{50} (mg/m³/4h)	Rats (Harlan Wistar)	>7800 mg/m 3/1–hour (equivalent to 7.8 mg/L or 1732 ppm); and >2800 mg/m 3/8–hours (equivalent to 2.8 mg/L or 622 ppm)	N/A
Skin irritation	Rabbit (albino)	Slight to severe skin irritant in diluted and semi-solid state, respectively (flaked and industrial grade).	Schedule 6
	Rabbit (New Zealand White)	Not irritating to skin (2.5 % solution in water; 98.8 % purity)	

Toxicity	Species	Resorcinol	SPF (2015) Classification
Eye irritation	Rabbit (albino)	Severe eye irritant (see below)	Schedule 6
Skin sensitisation (Guinea Pig Maximisation Test: GPMT)	Guinea pigs (Pirbright white)	Sensitiser (relative incidence of the positive reactions in animals was > 30 %) (99.9 % purity)	Schedule 6
Skin sensitisation (mouse local lymph node assay: LLNA)	Mice (CBA/Ca)	Moderate sensitiser with EC = 1.4 and 6.3% (unspecified purity)	Schedule 6

Acute toxicity

The acute toxicity end-points of resorcinol are summarised in the table above.

Skin irritation

Based on the weight of evidence, the chemical is considered to be slightly to severely irritating to skin when administered diluted in an aqueous solution or in semi-solid state (flaked or industrial grade):

- In a non-guideline (Federal Hazardous Substance Labelling Act (FHSLA)) skin irritation study, 0.5 g of the chemical (flaked grade) in saline was applied to the clipped belly skin (abraded and intact) of albino rabbits (six males) for 24 hours under occlusive patches. Observations were made at 24 and 72 hours post-treatment, and animals were kept under observation for a maximum of two weeks. Treatment-related effects were moderate irritation on intact skin and necrosis on abraded skin. Effects were more pronounced at 72 hours post-treatment. In the two week recovery period, necrotic areas were still encrusted or scarred. The primary dermal irritation index (PDII) was reported to be 4.4;
- In similar non-guideline (FHSLA) studies, a 24-hour occluded application of the chemical (flaked and industrial grade) at 0.5 g to the bellies of male albino rabbits produced moderate irritation on intact skin and necrosis on abraded sites. The chemical (industrial grade) was reported to cause slight to severe irritation of the intact areas, and from severe irritation to necrosis of the abraded areas, 24 hours after exposure. In the 2-week post-recovery period, necrotic areas were still encrusted or scarred. The primary dermal irritation index (PDII) for the chemical was reported to be 4.4 (flaked grade) and 5.4 (industrial grade); and
- In a study conducted according to the OECD Test Guideline 404 (acute dermal irritation/corrosion), 0.5 mL of the chemical (2.5 % aqueous solution) (98.8 % purity) was applied to the clipped back skin of New Zealand White rabbits (three males/group) for four hours under semi-occlusive patches. Observations were made at one, 24, 48 and 72 hours post-treatment. No adverse cutaneous reactions were reported at this low concentration.

Eye irritation

Data from one study using the chemical (flaked and industrial grade diluted in an aqueous solution and semi-solid state, respectively) indicated that the chemical should be considered a severe eye irritant:

- In a non-guideline (FHSLA) study, 0.1 g of the chemical (flaked and industrial grade) was instilled into the eyes of albino rabbits (6 males). Treatment-related effects upon administration included inflamed conjunctivae, opaque corneas and visible discomfort in animals. At 24 hours post-

exposure, observations included severe conjunctivitis, iritis, corneal opacity occluding most of the iris and corneal ulcerations. Irreversible effects on the eyes were reported and by day 14, all treated eyes had kerataconus (thinning of and irregularly shaped cornea) and pannus (abnormal layer of fibrovascular tissue or granulation tissue over the cornea) formation. Total mean eye irritation Draize scores were reported to be 105/110 at 24, 48 and 72 hours and the chemical was considered to be a severe eye irritant;

- The chemical was mildly irritating in six albino rats administered 0.1 g of the chemical (dry powder). Reported mean irritation scores were 56.3, 45.0 and 39.9 out of 110 over the observation period at 24, 48 and 72 hours, respectively. No further study details were available; and

- In a study conducted according to OECD TG 405 (acute eye irritation/corrosion), 0.1 mL of the chemical (2.5 % solution in water (98.8 % purity)) was instilled into the eyes (conjunctival sacs) of New Zealand White rabbits (three males) and left for 72 hours. Mean scores of zero were reported for chemosis, iris lesions and corneal opacity over 24, 48 and 72 hours. For redness of the conjunctivae, a mean score of 0.1 was reported.

Skin sensitisation

Based on the available animal and human data, the chemical is considered to be a moderate to strong contact skin sensitiser and is recommended for classification:

- In a GPMT conducted in accordance with OECD TG 406, Pirbright white guinea pigs (treatment group 10 animals, control group 5 animals and accompanying group 20 animals used for range finding) were administered 2 % (w/v) solution of the chemical (99.9 % purity as white flakes in sodium chloride) by intradermal injection followed by occlusive, epicutaneous application of 25 % the chemical. At the challenge exposure using 25 % of the chemical (occlusive epicutaneous application), very slight to distinct erythema was observed on the skin of 2-3 animals at 24 and 48 hours observation periods. At the second challenge and compared to the control group, very slight to distinct erythema was reported in 7/10 guinea pigs at 24 hours and on 5/10 guinea pigs at 48 hours and minor swelling was also observed in one animal at 24 hours after patch removal. The relative incidence of the positive reactions in animals was over the threshold value of 30 % and the chemical was considered to be a skin sensitiser;

- In a study conducted in accordance with OECD TG 429, positive skin sensitisation was reported in LLNA studies in two independent experiments. A positive control of a-hexylcinnamaldehyde (HCA), a moderate sensitiser, at the concentration of 25 % (v/v) in DMF was used. In the first experiment (range finding), female CBA/J mice (four animals/dose including negative and positive controls) were administered 25 µL of the chemical (in vehicle dimethylformamide at 2.5, 5, 10, 25 or 50 %) applied to the dorsal surface of each ear, once daily for three consecutive days. Stimulation indices (SI) of 3.83, 4.14, 3.97, 3.51 and 3.30 were reported, respectively. Positive lymphoproliferative responses (SI > 3) were reported at all concentrations, but no clear dose-response relationship was observed. In the second experiment, mice (four/dose) were administered daily applications of 0.1, 0.5, 1, 5 or 25 % chemical (w/v). Treatment resulted in stimulation indices of 1.58, 2.87, 1.97, 3.51 and 5.74, respectively. A dose-related increase in SI was seen and the threshold positive value of three was exceeded. The effective concentration at which a three-fold increase in SI was achieved (EC3) was reported to be 1.4 % and the chemical was considered to be a moderate skin sensitiser; and

- The chemical (purity unspecified) was not reported to be sensitising according to two non-guideline skin sensitisation (LLNA) studies in mice (concentrations of up to 2.5 % and 25 % w/v were tested, respectively). No further study details were available and the reliability of both studies was questioned due to outdated study methods (OECD, 2008). However, the chemical was reported to be a sensitiser in mice in a LLNA study (OECD TG 429). A group of CBA/Ca female mice (four/dose) were treated at daily concentrations of 0, 1, 5, 10, 25 and 50 % (w/v) of the chemical (purity unspecified) in acetone/olive oil (ratio of 4:1). SIs of 1.0, 0.7, 2.2, 5.2, 8.4 or 10.4 were measured respectively, and an EC value of 6.3 % was determined (REACH; OECD, 2008).

Repeat-dose toxicity

Based on the weight-of-evidence, the chemical is not considered to cause serious damage to health from repeated oral exposure.

No information was available for repeated dose toxicity by the dermal route.

There is insufficient evidence to evaluate repeated dose inhalation toxicity.

Genotoxicity

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

Carcinogenicity

Based on the available data, the chemical is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available data, the chemical is not considered to be a reproductive or developmental toxin.

Observation in humans

Human patch-testing using the chemical elicited allergic skin reactions in 0.7-0.8 % of 1694 dermatitis patients. In further case histories of 34 dermatitis patients, the chemical was reported to cause reactions after epicutaneous testing.

No dermatitis of the hands was reported for 42 workers from a tyre factory after an epicutaneous test with the chemical.

In human patch tests with the chemical (2 % in petrolatum), four out of 302 hairdressers suffering from contact dermatitis reported a positive reaction. No further details were available. In another case, one patient who developed contact dermatitis after application of paint to the skin was patch tested with the chemical (5 % in petrolatum) and showed a positive result after 48 hours. In a third case, three female patients suffering from acne and contact dermatitis gave a positive patch test for the chemical (2 % in petrolatum) after 48 and 72 hours.

Pre-meeting public submissions

Two (2) pre-meeting submissions were received. One had no objections to the proposed scheduling for resorcinol. The main points of the submission were:

- Resorcinol is permitted internationally in over the counter (OTC) and consumer products (such as hair dyes). The scheduling of resorcinol in Australia should reflect international regulations.
- Resorcinol is used in topical therapeutic goods, scheduling should not capture this use pattern.
- Scheduling of resorcinol should reflect recent decisions made on similar substances used in hair dyes, such as 2-methylresorcinol.
- An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified. There is no evidence to suggest immediate action is required for the risk management of this substance.

One submission requested a specific exemption for OTC products.

The public submissions will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee advised that a new Schedule 6 entry and Appendix E and F entries be created for resorcinol:

Schedule 6 - New Entry

RESORCINOL **except**:

a) in preparations for human therapeutic use; or

b) in oxidative hair dye preparations containing 1.25 per cent or less of resorcinol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

written in letters not less than 1.5 mm in height; or

c) in oxidative eyelash and eyebrow dye preparations containing 1.25 per cent or less of resorcinol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use; and

written in letters not less than 1.5 mm in height; or

d) in hair lotions/shampoo products containing 0.5 per cent or less of resorcinol when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 - New Entry

RESORCINOL

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.)

Appendix F, Part 3 - New Entry

RESORCINOL

Warning statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 [(Over) (Repeated) exposure may cause sensitisation], 79 (Will irritate eyes)

Safety directions: 1 (Avoid contact with eyes), 3 (Wear eye protections when mixing or using), 4 (Avoid contact with skin)

Index - New Entry

RESORCINOL
cross reference: 1,3-benzenediol

Schedule 6

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

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

The reasons for the advice comprised the following:

- Resorcinol is used as a reaction-modifying agent in hair dyes and dyes applied to eyebrows and eyelashes, as well as in hair lotions and shampoos. It is used in permanent oxidative hair dyes that are mixed prior to use. Use settings are both in-salon as well as packed and labelled products used by consumers. Resorcinol also has other domestic and industrial uses, such as use in adhesives and curing agents.
- The toxicity profile of resorcinol is primarily skin irritation, eye irritation, and moderate skin sensitisation. Resorcinol shows low oral and inhalation toxicity and it is not genotoxic or carcinogenic; there is no reproductive or developmental toxicity. The toxicological profile fits with the Schedule 6 criteria of the SPF.
- The proposed entry, including concentration cut-offs, allows consistency with international controls in the EU and ASEAN.

Delegate's considerations

The delegate considered the following 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

Delegate's interim decision

The delegate has decided to defer the interim decision for resorcinol to allow for further consideration of its use in therapeutic goods and the potential to elicit skin sensitisation reactions at very low concentrations. The advice of the scheduling committee was to create a new schedule 6 entry with low exemption cut-off concentrations for domestic or personal products that would result in skin contact during use due to potent skin sensitisation. Similar restrictions are likely to apply to therapeutic products when applied topically.

3. Advisory Committee on Chemicals Scheduling (ACCS #19)

Summary of delegate's interim decisions

Substance	Interim decision
Ethyl hexanediol	**Schedule 10 - Delete Entry** **Schedule 6 - New Entry** ETHYL HEXANEDIOL **except** in preparations containing 5 per cent or less of ethyl hexanediol. **Schedule 4 – Delete Entry** **Appendix E, Part 2 – New Entry** ETHYL HEXANEDIOL Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.) **Appendix F, Part 3 – New Entry** ETHYL HEXANEDIOL Warning Statements: 79 (will irritate eyes). Safety directions: 1 (avoid contact with eyes). *The proposed implementation date is **1 October 2017**.*
Climbazole	**Schedule 6 – Amend Entry** CLIMBAZOLE **except**: a) when included in Schedule 5; or b) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or c) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole. **Schedule 5 – Amend Entry** CLIMBAZOLE in preparations containing 40 per cent or less of climbazole **except:** a) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or b) in other preparations (that are not leave-on cosmetic

	preparations) containing 2 per cent or less of climbazole. *The proposed implementation date is **1 June 2018**.*
m-Aminophenol	**Schedule 6 - New Entry** *m*-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash preparations at a concentration of 1.2 per cent or less of *m*-aminophenol after mixing for use when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – New Entry** *m*-AMINOPHENOL Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water). **Appendix F, Part 3– New Entry** *m*-AMINOPHENOL Warning Statements: 28 ((over) (repeated) exposure may cause sensitisation). Safety directions: 4 (Avoid contact with skin), 8 (Avoid breathing dust (or) vapour (or) spray mist). *The proposed implementation date is **1 June 2018**.*
2-Chloro-6-(ethylamino)-4-nitrophenol	**Schedule 6 - New Entry** 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL **except:** a) in non-oxidative hair dye preparations containing 3 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and written in letters not less than 1.5 mm in height; or b) in oxidative hair dye preparations containing 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for

	use when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – New Entry** 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water). **Appendix F, Part 3 – New Entry** 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL Warning Statements: 28 ((over) (repeated) exposure may cause sensitisation). Safety directions: 4 (Avoid contact with skin). The proposed implementation date is **1 June 2018**.
2,4-Diamino-phenoxy-ethanol	**Schedule 6 - Amend Entry** 2,4-DIAMINOPHENOXYETHANOL **except** when used in hair dye and eyebrow/eyelash preparations at a concentration of 2 per cent or less of 2,4-diaminophenoxyethanol after mixing for use when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – Amend Entry** 2,4-DIAMINO-PHENOXYETHANOL Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

	Appendix F, Part 3 – Amend Entry 2,4-DIAMINO-PHENOXYETHANOL Warning statement: 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes). Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin). *The proposed implementation date is **1 June 2018**.*
Isoeugenol	**Schedule 6 – Amend Entry** ISOEUGENOL **except**: a) when included in Schedule 5; or b) in preparations not intended for skin contact containing 10 per cent or less of isoeugenol; or c) in preparations intended for skin contact containing 0.02 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 containing 10 per cent or less of isoeugenol. **Appendix E, Part 2 – New Entry** ISOEUGENOL 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, Part 3 – New Entry** ISOEUGENOL Warning statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes). Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin). *The proposed implementation date is **1 October 2018**.*
Aureobasidium pullulans (strains DSM 14940 and DSM 14941)	**Appendix B - New Entry** AUREOBASIDIUM PULLULANS (Strains DSM14940 and DSM14941). *The proposed implementation date is **1 October 2017**.*

3.1 Ethyl hexanediol

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to amend the scheduling of ethyl hexanediol by replacing the Schedule 10 entry with a Schedule 6 entry to allow for human use.

Current scheduling status and relevant scheduling history

Ethyl hexanediol is currently listed in Schedules 4 and 10 as follows:

Schedule 10

ETHYLHEXANEDIOL for human use.

Schedule 4

ETHYLHEXANEDIOL for animal use.

The structurally similar chemical 2-ethylhexanoic acid is in Schedule 6 and Appendices E and F as follows:

Schedule 6

2-ETHYLHEXANOIC ACID and its alkyl esters **except** in preparations containing 5 per cent or less calculated as 2-ethylhexanoic acid.

Appendix E, Part 2 – 2-ETHYLHEXANOIC ACID

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)].

Appendix F, Part 3 - 2-ETHYLHEXANOIC ACID

Warning statements: 53 (CAUTION – (Name of substance) should not be used by pregnant women).

Prior to 1991, ethyl hexanediol was listed in Appendix B of the then SUSDP. In November 1991, the Drugs and Poisons Scheduling Sub-Committee (DPSSC) considered a request from a member to remove ethyl hexanediol from Appendix B in view of reports linking the insect repellent to teratogenic effects. The committee advised deletion from Appendix B, while establishing whether the substance is used in Australia.

From February - May 1993, the DPSSC reviewed the toxicology of ethyl hexanediol following a US EPA cancellation of registrations prohibiting sale, distribution or use of existing stocks of ethyl hexanediol., At its November 1991 meeting, the DPSSC had requested that the Chemicals Safety Unit (CSU) establish whether ethyl hexanediol was used in Australia, and if so request relevant data from sponsors in order to establish a schedule. At that meeting, the DPSSC had advised that ethyl hexanediol be deleted from Appendix B. The committee considered and created a new Appendix C entry for ethyl hexanediol, following concerns about malformations evident in rat studies, which appeared to be dose-related.

In February 2000, the National Drugs and Poisons Schedule Committee (NDPSC) considered an exemption from Appendix C for cosmetic use. The committee did not support exemption of ethyl hexanediol from Appendix C because of unacceptable risk of teratogenicity associated with the use of the substance.

In October 2006, the NDPSC included ethyl hexanediol in Schedule 4 to harmonise with New Zealand. In February 2007 the NDPSC agreed that a Schedule 4 entry for ethyl hexanediol would conflict with the then existing Appendix C (now Schedule 10) entry. The committee agreed that the Schedule 4 entry was only intended to capture animal therapeutic use, and that it remained appropriate for

human therapeutic use to be captured by Appendix C. The February 2007 NDPSC Meeting confirmed that the Schedule 4 entry was intended to capture animal therapeutic use only.

The overlap between entries was considered by the NDPSC from June - October 2008. The NDPSC confirmed that the Appendix C entry for ethyl hexanediol captured all human use.

In February 2009, the NDPSC amended the Schedule 4 entry to reflect its use in animal treatment only with the addition 'for animal treatment'.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 10 - Delete Entry

~~ETHYLHEXANEDIOL for human use.~~

Schedule 6 - New Entry

ETHYL HEXANEDIOL.

Schedule 4 – Current Entry

ETHYL HEXANEDIOL for animal use.

Appendix E, Part 2 - ETHYL HEXANEDIOL

Standard statement: 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.)

The applicant's reasons for the request are:

- There are concerns about developmental toxicity for the current Schedule 10 entry for ethyl hexanediol (National Drugs and Poisons Scheduling Committee (NDPSC), 2012); however, publicly available data on reproductive toxicity indicated effects at high doses only and/or concurrent with maternal toxicity;
- The only critical health effect identified and classified was eye irritation;
- There are no international restrictions;
- International sources have determined that ethyl hexanediol is a safe cosmetic ingredient (Cosmetic Ingredient Review (CIR), 2011);
- Cosmetic and/or domestic use is considered to be limited; and
- Structurally similar chemicals, 2-ethylhexanoic acid (and its alkyl esters) and 2-ethylhexanol (and its derivatives), have similar uses but higher potency for critical health effects. 2-Ethylhexanoic acid is in Schedule 6 with a 5% exemption cut-off and 2-ethylhexanol is currently being considered by NICNAS as to whether Schedule 6 with appropriate low-level cut-offs are required.

Australian regulatory information

Ethyl hexanediol is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017, and a search of the Australian Register of Therapeutic Goods (ARTG) found it is neither an excipient nor active in any listed medicines.

Ethyl hexanediol is not in any currently registered products regulated by the APVMA.

International regulations

Ethyl hexanediol was listed as a hazardous substance by the EPA in New Zealand in December 2006 (HSNO Approval Code HSR003694).

Substance summary

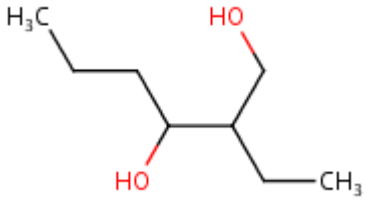


Figure 3.1: Chemical structure of ethyl hexanediol

Table 3.1A: Chemical information

Property	Ethyl hexanediol
CAS name	1,3-hexanediol, 2-ethyl-
CAS number	94-96-2
IUPAC and/or common and/or other names	Ethyl hexanediol (INCI); 1,3-hexanediol, 2-ethyl- (CAS); hexanediol; octylene glycol; ethohexadiol (AAN); 2-ethylhexane-1,3-diol (IUPAC)
Molecular formula	$C_8H_{18}O_2$
Molecular weight	146.3 g/mol

The following information was extracted from the NICNAS IMAP Human Health Tier II assessment report for ethyl hexanediol.[75]

Table 3.1B: Acute toxicity end-points for ethyl hexanediol

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats (strain not specified)	2710-9210	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits (strain not specified)	8960-18700	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rats (strain not specified)	>3800	Schedule 5

[75] Publicly available on the NICNAS website at: Human Health Tier II Assessment for 1,3-Hexanediol, 2-ethyl-

Toxicity	Species	Result	SPF (2015) Classification
Skin irritation	New Zealand White rabbits Guinea pigs (Strain not specified) Swiss mice	Mildly irritating (neat chemical)	Schedule 5
Eye irritation	New Zealand White rabbits	Irritating	Schedule 6
Skin sensitisation (Mangusson and Kigman maximisation test and Kodak footpad method)	Guinea pigs (strain not specified; Hartley)	No positive reactions	N/A

Acute toxicity

Based on the available oral, dermal and inhalation data, ethyl hexanediol has low acute toxicity.

Skin irritation

Ethyl hexanediol is reported to slightly irritate skin:

- In an acute dermal irritation/corrosion study conducted according to OECD TG 404 in New Zealand White rabbits (n = 3/sex), 0.5 mL of undiluted ethyl hexanediol was applied occlusively to clipped dorsal trunk skin for a duration of 4 h and animals were observed for 14 days. Five animals were reported to show slight local erythema (redness) and one showed well-defined local oedema (swelling). All the effects were fully reversed within 24-48 h. The study was concluded that ethyl hexanediol was slightly irritating to skin.
- In another study, 0.5 mL of undiluted ethyl hexanediol was applied occlusively to the shaved dorsal skin of guinea pigs (n = 5), nine times over 11 days. Slight erythema (in 2/5 animals) was observed after three applications and slight to moderate erythema (in 3/5 animals) was observed by the end of the study.
- In an acute toxicity study conducted on New Zealand White rabbits (n = 5/sex/group), undiluted ethyl hexanediol was applied once under occlusive patches to the clipped skin of the trunks for 24 h at a dose of 8, 11.3 or 16 mL/kg bw in males and 4, 8 or 16 mL/kg bw in females. The rabbits were observed for 14 days. There were signs of inflammation, redness and swelling at the dosing site. Redness and swelling reversed by day seven, but desquamation (skin peeling) was still evident at the end of the study.
- In a lifetime study in female Swiss mice (n = 50/dose), 0.2 mL of ethyl hexanediol at concentrations of 10, 50 or 100% in acetone was applied to shaved dorsal skin, twice weekly. Minimal local inflammatory changes including moderate dermatitis were observed.

Eye irritation

Based on the available data, ethyl hexanediol is considered to cause serious eye damage:

- In an ocular irritation study conducted in female rabbits (n = 3), 0.1 mL of undiluted ethyl hexanediol was applied into the conjunctival sac of the eyes. Clouding of the cornea, irritation of the iris and reddening and swelling of the conjunctiva were observed within one hour of administration. Effects on the cornea reversed within one week, effects on the conjunctivae reversed after 10 days, while the iris irritation remained after 21 days. Ethyl hexanediol was

reported to be moderately irritating, with a Draize score of 35/110. Similar effects were reported in another two studies. No further details are available.

- In an acute eye irritation study (similar to OECD TG 405) conducted in New Zealand White rabbits (n = 6/treatment), ethyl hexanediol was instilled into the conjunctival sac (0.1 mL) in one group and onto the cornea of the eye (0.01 or 0.005 mL) in two other groups. Animals were examined after 1 h, 24 h and 2, 3 and 7-14 days. The animals treated with 0.1 mL developed mild to severe conjunctivitis, mild to severe chemosis and mild to marked discharge. Moderate iris inflammation and moderate corneal injury were observed. Animals that were administered 0.01 or 0.005 mL had moderate to severe conjunctivitis at the 24 h observation. An overall irritation score of 80/110 was reported for the 1 h observation time point, with all effects being fully reversed within seven days.
- In another study conducted using New Zealand White rabbits (n = 6), 0.1 mL of neat ethyl hexanediol was instilled into the conjunctival sac of one eye; the eyes of three rabbits were washed immediately after chemical instillation, whilst the eyes of the other three rabbits remained unwashed. Both groups were observed immediately and after 1, 24, 48 and 72 h and 7 and 14 days after instillation. Fluorescein staining of the eyes was undertaken 24 h after dosing. Moderate to severe erythema and oedema of the conjunctivae and nictitating membranes (inner eyelids); slight erythema and oedema of the eyelids; slight corneal opacity; and discharge were observed in the unwashed eyes at 24 h. Irritation was less severe in the rinsed eyes, with slight to moderate erythema observed in the conjunctivae and nictitating membranes of the eyes at 1 h. Signs of irritation were reduced by seven days, and fully reversed by 14 days.

Sensitization

Based on the available data, ethyl hexanediol is not expected to be a skin sensitiser.

Repeat-dose toxicity

Based on available data ethyl hexanediol is not considered to cause serious health effects from repeated oral (NOAEL of 480 mg/kg bw/day was reported in rats) or dermal exposure (NOAEL of 1884 mg/kg bw/day was determined in rats). No data are available for inhalation repeat-dose toxicity.

Genotoxicity

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

Carcinogenicity

The limited available data do not indicate that ethyl hexanediol is a carcinogen.

Reproduction and developmental toxicity

Ethyl hexanediol shows specific developmental toxicity, but only at high doses.

- In a developmental toxicity study (similar to OECD TG 414) in pregnant SD rats (n = 8/dose), ethyl hexanediol (in corn oil) was administered by gavage at 500, 1000, 2000 or 4000 mg/kg bw/d on GD 6-15. The NOAEL for maternal and developmental toxicity was reported to be 1000 mg/kg bw/d. Mortalities were reported in the dams at 2000 mg/kg bw/d (1/8) and 4000 mg/kg bw/d (7/8). At doses ^{3}2000 mg/kg bw/d, signs of weakness, respiratory difficulty, dehydration, sialorrhoea (excess salivation), gait disturbances, nasal discharge, porphyrin tears, diarrhoea, decreased volume of faeces and unkempt coats were observed in the dams. Hypothermia, partially closed eyes and excessive tearing were observed in the high dose group only. Lesions at necropsy showed that ethyl hexanediol had the greatest effect in the stomach and duodenum; there was excess mucous in the caecum and atrophy of the thymus and adipose tissue. In foetuses from the 2000 mg/kg bw/d group, the incidences of malformations significantly increased (rudimentary or filamentous tails, malformation of rear limbs and joints, shortened trunk and umbilical hernia);

and there were also increases in the incidence of haematoma (nine foetuses out of four litters). Two foetuses from different litters exposed to ethyl hexanediol at 1000 mg/kg bw/d and one in the 500 mg/kg bw/d group had rudimentary tails.

- In a developmental toxicity study (similar to OECD TG 414) in pregnant SD rats (n = 25 mated females/dose), ethyl hexanediol was dermally applied (occlusively) at 0, 1, 2 or 4 mL/kg bw/day (equivalent to 0, 935, 1870 and 3740 mg/kg bw/d) for 6 h per day on gestation days (GD) 6–15. Animals were euthanised on GD 21. The NOAEL for maternal reproductive toxicity was reported to be >3768 mg/kg bw/d based on no reported variations in the number of pregnancies, foetal body weights or reproductive factors. At the highest dose, terminal maternal body weights were decreased, and absolute liver weights were significantly increased. Mild skin irritation with exfoliation and crusting were observed in a few females at the mid and high doses. The NOAEL for developmental toxicity was reported to be 942 mg/kg bw/d based on a statistically significant but non-dose-dependent increase in the incidences of skeletal malformation (related to reduced ossification) in the foetuses from the mid and high dose groups, and visceral malformation (e.g. unilateral hydroureter) in the foetuses from the high dose groups. It was concluded that ethyl hexanediol is a weak developmental toxicant (CIR, 1994; Ballantyne, 2005; REACH). In two developmental toxicity studies (similar to OECD TG 414) in pregnant SD rats (n=8 - 25/dose), ethyl hexanediol was administered by gavage at 500, 1000, 2000 or 4000 mg/kg bw/day or occlusively 6 h/day at 0, 1, 2 or 4 mL/kg bw/day (equivalent to 0, 935, 1870 and 3740 mg/kg bw/day), on gestation days 6-15.

Observation in humans

Irritation

Slight irritation was observed in humans:

- Mild skin irritation was seen in humans administered ethyl hexanediol under semi-occlusive and occlusive conditions for 24 h, repeated 15 times over 21 consecutive days;
- Barely perceivable erythema was observed in 1/106 human subjects under occlusive and semi-occlusive conditions when exposed to ethyl hexanediol at 5%;
- Barely perceivable erythema in 2/30 under semi-occlusive and 4/30 under occlusive conditions were observed immediately and 24 h after application of ethyl hexanediol at 100%. One subject had definite erythema after 72 h.

Skin sensitisation

Ethyl hexanediol was reported to be a weak skin sensitiser following a human repeated insult patch test. Undiluted ethyl hexanediol was applied occlusively for 24 h, three times per week for three weeks. They were challenged with ethyl hexanediol two weeks later, on an untreated area of skin for 24 h and observed after 24-48 h. There were two incidences of definite erythema 48 h after the challenge patch was removed. Further testing, showed that one of these subjects had a definite sensitisation response.

Public exposure

Ethyl hexanediol is reported to be used in cosmetic and/or domestic products overseas. Cosmetic use is reported to be limited overseas and domestic use is prohibited in Australia (currently listed in Schedule 10 of the SUSMP). The cosmetic use overseas is assumed to be representative of its potential use in Australia. Existing controls are such that ethyl hexanediol cannot be used in such products in Australia.

Pre-meeting public submissions

Two (2) public submissions were received. Both submissions supported the scheduling proposal. The main points of the submissions were:

- Ethyl hexanediol does not require scheduling control when in human use preparations as the only health concern is eye irritancy (developmental toxicity has been shown to no longer be an issue).
- Scheduling of ethyl hexanediol should align with EU regulations for use in cosmetics.
- There should be low concentration cut-offs for cosmetic and domestic use preparations. If an exemption for cosmetic use at 5% is made, then household products not intended for contact with skin should be exempted at a higher cut-off concentration. This is due to the risk of accidental eye contact being less in domestic products than cosmetics.

The public submissions will be made available on the TGA website.

Summary of ACCS advice to the delegate

The committee recommends that the current Schedule 10 and 4 entries for ethyl hexanediol be deleted and that a new Schedule 6 entry be created as follows:

Schedule 10 - Delete Entry

~~ETHYLHEXANEDIOL for human use.~~

Schedule 6 - New Entry

ETHYL HEXANEDIOL **except** in preparations containing 5 per cent or less of ethyl hexanediol.

Schedule 4 – Delete Entry

~~ETHYL HEXANEDIOL for animal use~~.

The committee recommended Appendix E/F entries be created as follows:

Appendix E, Part 2 – New Entry

ETHYL HEXANEDIOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.)

Appendix F, Part 3 – New Entry

ETHYL HEXANEDIOL

Warning Statements: 79 (will irritate eyes).
Safety directions: 1 (avoid contact with eyes).

The committee also advised an implementation date of **1 October 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 (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice comprised the following:

- The substance is used as an ingredient in cosmetic and domestic products internationally, and down-scheduling will allow for this use in Australia.
- It is likely to be in imported products or used in Australia for such purposes if re-scheduled.
- Ethyl hexanediol causes serious eye damage and poses a risk to public health if certain controls are not in place.

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)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is that the current Schedule 10 and 4 entries for ethyl hexanediol be deleted and that a new Schedule 6 entry be created. The proposed Schedule entry is as follows:

Schedule 10 - Delete Entry

Schedule 6 - New Entry

ETHYL HEXANEDIOL **except** in preparations containing 5 per cent or less of ethyl hexanediol.

Schedule 4 – Delete Entry

Appendix E, Part 2 – New Entry

ETHYL HEXANEDIOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.)

Appendix F, Part 3 – New Entry

ETHYL HEXANEDIOL

Warning Statements: 79 (will irritate eyes).
Safety directions: 1 (avoid contact with eyes).

The proposed implementation date is **1 October 2017**, as this is the earliest possible implementation date.

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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- The substance is used as an ingredient in cosmetic and domestic products internationally, and down-scheduling will allow for this use in Australia.
- It is likely to be in imported products or used in Australia for such purposes if re-scheduled
- Ethyl hexanediol causes serious eye damage and poses a risk to public health if certain controls are not in place.

3.2 Climbazole

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to amend the current entries for climbazole in Schedules 5 and 6, to restrict its use in cosmetic products except at concentrations below 0.5% in leave-on hair and face cosmetics, and up to 2% for rinse-off hair cosmetics.

Current scheduling status

Climbazole is in Schedule 5 and Schedule 6 of the Poisons Standard as follows:

Schedule 6

CLIMBAZOLE **except**:

a) when included in Schedule 5; or

b) in preparations containing 2 per cent or less of climbazole.

Schedule 5

CLIMBAZOLE in preparations containing 40 per cent or less of climbazole **except** in preparations containing 2 per cent or less of climbazole.

Climbazole is also listed in Appendix E as follows:

Appendix E, Part 2

CLIMBAZOLE

Standard statement: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).].

Scheduling history

Climbazole was first considered for scheduling by the Poisons Schedule Committee (PSC) in November 1980. Although the original application specified use as a household and industrial fungicide, at that time the committee decided that the absence of chronic toxicological data warranted restrictions for human use, and that Schedule 4 was appropriate.

In November 1985 the Poisons Schedule Committee (PSC) considered rescheduling climbazole from Schedule 4 to Schedule 5 (for human use), to permit its use in an antidandruff shampoo. However, the committee did not accept this rescheduling application given the lack of chronic toxicological data.

In November 1986 the Drugs and Poisons Scheduling Committee (DPSC) considered an amended application to the one received in November 1985 to reschedule climbazole from Schedule 4 to Schedule 5 (for human use) in order to permit its use in an antidandruff shampoo. In its deliberations,

the committee noted that climbazole would be incorporated into the proposed Australian Cosmetic Standard at 0.5% or less. The committee agreed to delete the Schedule 4 entry for climbazole and create: a new Schedule 5 entry for preparations containing 40% or less except in preparations containing 2% or less (as in the current Schedule 5 entry); and a new Schedule 6 entry with an exemption for preparations containing 2% or less of climbazole (as in the current Schedule 6 entry).

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – Amend Entry

CLIMBAZOLE **except**:

a) when included in Schedule 5; or

b) in leave-on hair and face cosmetic preparations containing 0.5 per cent or less of climbazole; ~~or in preparations containing 2 per cent or less of climbazole.~~

c) in rinse-off hair and face cosmetic preparations containing 2 per cent or less of climbazole.

Schedule 5 – Amend Entry

CLIMBAZOLE in preparations containing 40 per cent or less of climbazole **except** ~~in preparations containing 2 per cent or less of climbazole.~~:

a) in leave-on hair and face cosmetic preparations containing 0.5 per cent or less of climbazole; or

b) in rinse-off hair and face cosmetic preparations containing 2 per cent or less of climbazole.

The applicant's reasons for the request are:

- Climbazole is readily bioavailable following oral exposure and has moderate acute oral toxicity;
- Climbazole is not an eye irritant at 0.5% and not a skin irritant at 2%;
- Climbazole has been selected as a candidate for the European Union (EU) Community Action Rolling Plan (CoRAP) initiative for further evaluation of reproductive and developmental toxicity;
- Climbazole is reported to be used in cosmetic products overseas (as a preservative or antimicrobial agent); in the absence of Australian specific data, this is assumed to be representative of its use in Australia; and
- According to the SCCP Opinion (2009), climbazole is 'regulated in the Cosmetics Directive as a preservative in Annex [V], with a maximum authorized concentration of 0.5%' and 'is used as an anti-dandruff active agent in hair cosmetic preparations up to a maximum concentration of 2.0% in rinse-off products or up to a maximum concentration of 0.5% in leave-on products. In addition, it is used in leave-on face creams up to a maximum concentration of 0.5%'.

Australian regulatory information

Climbazole is permitted to be used as both an excipient and active ingredient in biological and prescription medicines; however a search of the Australian Register of Therapeutic Goods (ARTG) found it is not currently used in any listed products.

Climbazole is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017.

The use of climbazole was approved by the Medicines Evaluation Committee (MEC) in 2004 for dermal use only. Climbazole can be used in hair care products at concentration of up to 0.5% for leave-on products and up to 2% for rinse-off products.

International regulations

Climbazole is listed on the EU Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products. The maximum concentration allowed is 0.5% in ready for use preparations.

The SCCS has concluded (SCCS 2013) that climbazole 'may be used as a preservative (or non-preservative) ingredient up to a maximum concentration of 0.5% in leave-on hair and face cosmetics. Its non-preservative use in rinse-off hair cosmetics up to a maximum concentration of 2% was also considered to be safe. Its use in leave-on products other than those mentioned above was, however, not considered safe'. Furthermore, 'the non-preservative use of Climbazole either in foot care cosmetics alone at a concentration of up to 0.5% or in combination with either shampoo (at a maximum concentration of 2%) or face cream (at a maximum concentration of up to 0.5%) or with hair lotion (at a maximum concentration of up to 0.5%), does not pose a risk to the health of the consumer. In the case, however, that 3 products, although each safe when used separately, are combined, the combinations of either shampoo, hair lotion and a foot care product or face cream, hair lotion and a foot care product (all containing Climbazole at the maximum requested concentration) cannot be considered safe for the consumer'.

Substance summary

Climbazole is an imidazole topical antifungal agent commonly used in the treatment of human fungal skin infections such as dandruff, eczema and Seborrheic dermatitis.[76,77]

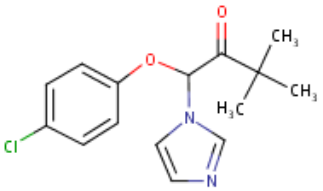


Figure 3.2: Chemical structure of Climbazole

[76] Pérez-Rivera, Alex A., et al. "Evaluation of the genotoxicity of the imidazole antifungal climbazole: comparison to published results for other azole compounds." *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* 672.1 (2009): 27-39.

[77] Youn H, Kim S, Ahn K, et al. Efficacy and Safety of Cream Containing Climbazole/Piroctone Olamine for Facial Seborrheic Dermatitis: A Single-Center, Open-Label Split-Face Clinical Study. *Annals Of Dermatology* [serial online]. December 2016;28(6):733-739

Table 3.2A: Chemical information for climbazole

Property	Climbazole
CAS name	2-butanone, 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethyl-
CAS number	38083-17-9
IUPAC and/or common and/or other names	climbazole (INCI and AAN); Crinipan AD; Baypival; (RS)-1-(4-Chlorophenoxy)-1-imidazol-1-yl-3,3-dimethylbutan-2-one (IUPAC); 1-[(4-chlorophenoxy)(tert-butylcarbonyl)methyl; 1-(4-chlorophenoxy)-1-(1H-imidazolyl)-3,3-dimethyl-2-butanone
Molecular formula	$C_{15}H_{17}ClN_2O_2$
Molecular weight	292.76 g/mol

The following data was extracted from the NICNAS IMAP Human Health Tier II report for climbazole.[78]

Table 3.2B: Acute toxicity end-points for climbazole

Toxicity	Species	Climbazole	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Mouse (male CF1/W68)	664	Schedule 6
	Rat (Wistar)	400	
	Rabbit (female Chinchilla)	250	
	Dog (Beagle)	250–500	
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>5000	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	N/A
Skin irritation	Rabbit	Slightly irritating at 0.5% concentration	Limited data
	Guinea pig	Irritating at 10% concentration	

[78] This report is publicly available on the NICNAS website at Human Health Tier II Assessment for 2-Butanone, 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethyl-

Toxicity	Species	Climbazole	SPF (2015) Classification
	Human volunteers	Not a skin irritant at 2% concentration	
Eye irritation	Rabbit	Not irritating at 0.5% concentration	Limited data
	Chicken Enucleated Eye Test	Negative results up to 2% concentration	
	Hen's Egg Test-Chorioallantoic Membrane (HET-CAM) assay	Negative results for the neat chemical	
Skin sensitisation	Mouse (LLNA) Guinea pig (GPMT) Guinea pig (Buehler)	Not sensitising	N/A

Acute toxicity

Based on the available data, climbazole has moderate acute oral toxicity and low acute dermal toxicity. No data is available for acute inhalation toxicity.

Skin irritation

No skin irritation data are available using neat climbazole however, climbazole at 0.5% concentration was slightly irritating to the skin of New Zealand White rabbits, and an irritant in female Bor:DHPW guinea pigs at 10% concentration. In patch tests, climbazole was not a skin irritant at 2% concentration in human volunteers (SCCP 2009).

Eye irritation

No *in vivo* eye irritation studies are available using neat climbazole, however climbazole was not irritating to rabbit eyes at 0.5% concentration. A Chicken Enucleated Eye Test (screening assay) gave negative results for climbazole up to 2% concentration. A Hen's Egg Test-Chorioallantoic Membrane (HET-CAM) assay showed negative results for neat climbazole; however, this assay detects only strong eye irritants (SCCP 2009).

Climbazole is not expected to be an eye irritant in humans at 2% concentration (SCCP 2009).

Skin sensitisation

Based on the results of a local lymph node assay (LLNA) in CBA/J mice (OECD TG 429), climbazole up to 20% concentration does not have potential to induce skin sensitisation (SCCP 2009).

Climbazole gave negative results for skin sensitisation in two non-guideline studies (Magnusson Kligman Guinea Pig Maximisation test and Buehler test) in female guinea pigs (Bor:DHPW and Hartley). [However, it should be noted that the SCCP report stated that these studies were either not valid or impossible to assess.]

Repeat-dose toxicity

Based on the available data in rats and dogs, climbazole is not considered to cause severe effects following repeated oral or inhalation exposure. However, repeated dose oral toxicity studies in rats showed increased liver enzyme activity from doses at or above 15 mg/kg bw/day. No data are available on repeated dose dermal toxicity.

The SCCP report stated that the available studies were conducted between 1975 and 1983, before GLP-regulations were in place. The descriptions were brief and the raw data incomplete. For ethical reasons and after a thorough re-examination of the available information, the SCCP proposed to accept the use of a cautious NOEL-value of 5 mg/kg bw/day, deduced from the 90 day oral study with the rat. This No observed effect level (NOEL) was used in the margin of safety (MoS) calculations for the specific use scenarios of climbazole.

The SCCP report calculated the MoS to be 701 for a 60 kg person using an anti-dandruff shampoo containing 2% climbazole, using an *in vitro* dermal penetration rate of 0.297 μg/cm^2 (0.15%) through human skin. This indicates that climbazole at 2% is safe for use in anti-dandruff shampoo (rinse-off products). The MoS for a 60 kg person using hair lotions, face cream and leave-on body lotion (all containing 0.5% climbazole) were calculated to be 189, 425 and 13, respectively, using *in vitro* dermal penetration rates of 1.10 μg/cm^2 (2.23%) or 1.25 μg/cm^2 (3.46%) through pig skin. Considering these MoS values, using a leave-on body lotion containing 0.5% climbazole for whole body (area of 18,000 cm^2) was not considered safe as the MoS was calculated to be <100. The SCCP concluded that, 'To generate an acceptable MoS (≥ 100), the treated surface area for leave-on products containing 0.5% Climbazole should not exceed 2400 cm^2.'

Genotoxicity

Based on the results from the available *in vitro* and *in vivo* genotoxicity studies, climbazole is not considered to be genotoxic. Some *in vitro* genotoxicity tests indicated positive results, but all *in vivo* tests were negative.

Reproduction and developmental toxicity

Based on the available data, climbazole is not considered to cause specific reproductive or developmental toxicity, as effects were only observed secondary to maternal toxicity. However, climbazole is a candidate for the EU CoRAP initiative for further evaluation of reproductive and developmental toxicity.

Public exposure

Climbazole is reported to be used in cosmetic products overseas as a preservative or antimicrobial agent. In the absence of Australian specific data, this is assumed to be representative of its use in Australia.

Pre-meeting public submissions

Two (2) public submissions were received. Both submissions did not support the proposal. The submissions noted that there should be alignment with EU regulations for use in cosmetics but special consideration should then be made for domestic preparations. Currently EU regulations permits up to 0.5% in cosmetics; however there is ongoing assessment by the SCCS in Europe and therefore the rescheduling should be deferred until a decision is made by the SCCS in Europe. A delayed Poisons Standard entry of 12 months to allow implementation was requested.

The public submissions will be made available on the TGA website.

Summary of ACCS advice to the delegate

The committee recommends that the current Schedule 6 and 5 entries for climbazole be amended as follows:

Schedule 6 – Amend Entry

CLIMBAZOLE **except**:

a) when included in Schedule 5; or

b) ~~in preparations containing 2 per cent or less of climbazole~~ in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or

c) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.

Schedule 5 – Amend Entry

CLIMBAZOLE in preparations containing 40 per cent or less of climbazole **except** ~~in preparations containing 2 per cent or less of climbazole.~~:

a) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or

b) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.

The committee also recommended an implementation date of **1 June 2018** to allow adequate time for industry to make the necessary labelling changes.

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

The reasons for the advice comprised the following:

- Climbazole is an effective fungicidal preservative.
- Moderate acute oral and low acute dermal toxicity, but high dermal absorption.
- There is a risk of toxicity if climbazole is used at concentrations up to the maximum unscheduled cut-off and/or simultaneous use of multiple preparations for different purposes; especially if preparations are intended to be left on the skin/hair. However this risk can be mitigated by the reduced exposure dermally for exempted products.

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)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to amend the current Schedule 6 and 5 entries for climbazole. The proposed Schedule entry is as follows:

Schedule 6 – Amend Entry

CLIMBAZOLE **except**:

a) when included in Schedule 5; or

b) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or

c) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.

Schedule 5 – Amend Entry

CLIMBAZOLE in preparations containing 40 per cent or less of climbazole **except:**

a) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or

b) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.

The proposed implementation date is **1 June 2018**.

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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Climbazole is an effective fungicidal preservative.
- Moderate acute oral and low acute dermal toxicity, but high dermal absorption.
- There is a risk of toxicity if climbazole is used at concentrations up to the maximum unscheduled cut-off and/or simultaneous use of multiple preparations for different purposes; especially if preparations are intended to be left on the skin/hair. However this risk can be mitigated by the reduced exposure dermally for exempted products.
- A long implementation date is proposed in order to allow adequate time for industry to make the necessary labelling changes.

3.3 *m*-Aminophenol

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for *m*-aminophenol with an appropriate exemption cut-off for hair dye use.

Current scheduling status and relevant scheduling history

m-Aminophenol is not currently scheduled.

In August 2016, NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) Scheme submitted a proposal to create a new entry for *m*-aminophenol in Schedule 6 for restriction in cosmetic and domestic products. Prior to this date, *m*-aminophenol was unscheduled and had not previously been considered for scheduling.

In January 2017, the delegate made a delegate-only final decision to enter *m*-aminophenol in Schedule 6 and Appendices E and F of the Poisons Standard as follows:

Schedule 6

m-AMINOPHENOL **except** when in hair dye preparations containing 1.2 per cent or less of *m*-aminophenol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – *m*-AMINOPHENOL

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, Part 3 – *m*-AMINOPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The implementation date of this decision was 1 February 2017.

Following the release of the final decision on 16 January 2017, feedback from industry indicated that the wording of the Schedule 6 entry may require further amendment.

On 31 January 2017, the Schedule 6 entry for *m*-aminophenol was removed by amendment from the 1 February 2017 Poisons Standard. This final decision was implemented as Amendment No. 1 of SUSMP 16. *m*-Aminophenol was subsequently referred to the March 2017 ACCS meeting to enable a consultation process on the proposed scheduling.

An isomer of *m*-aminophenol, *p*-aminophenol is in Schedule 6 and Appendices E and F of the Poisons Standard as follows:

Schedule 6

p-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1 per cent or less of *p*-aminophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – *p*-AMINOPHENOL

Standard statements: A, S1.

Appendix F, Part 3 – *p*-AMINOPHENOL

Warning Statement: 28.

Homologues of *m*-aminophenol, 4-amino-*m*-cresol and 4-amino-2-hydroxytoluene, are listed with reference to use in hair dyes with 1.5 per cent or less cut-offs in the SUSMP as follows:

Current schedule of related substance 4-amino-m-cresol

Schedule 6

4-AMINO-*m*-CRESOL in hair dyes and eyebrow/eyelash colouring preparations **except**:

a) in hair dye preparations containing 1.5 per cent or less of 4-amino-m-cresol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5mm in height; or

b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 4-amino-*m*-cresol after mixing for use when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height.

Appendix E, Part 2 – 4-AMINO-*m*-CRESOL

Standard statements: A, E1.

Appendix F, Part 3 – 4-AMINO-*m*-CRESOL

Warning statement: 28.

Current schedule of related substance 4-amino-2-hydroxytoluene

Schedule 6

4-AMINO-2-HYDROXYTOLUENE in hair dyes and eyebrow/eyelash colouring products **except**:

a) in hair dye preparations containing 1.5 per cent or less of 4-amino-2-hydroxytoluene after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5mm in height; or

b) in eyelash and eyebrow tinting products containing 1.5 per cent or less of 4-amino-2-hydroxytoluene after mixing for use when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height.

Appendix E, Part 2 – 4-AMINO-2-HYDROXYTOLUENE

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, Part 3 – 4-AMINO-2-HYDROXYTOLUENE

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

Index

4-AMINO-2-HYDROXYTOLUENE

Schedule 6
Appendix E, Part 2
Appendix F, Part 3

5-AMINO-*o*-CRESOL
cross reference: 4-AMINO-2-HYDROXYTOLUENE

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

m-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 1.2 per cent or less after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

m-AMINOPHENOL

Standard statements: E1 – If in eyes wash out immediately with water.

Appendix F, Part 3 – New Entry

m-AMINOPHENOL

Warning statement: Repeated exposure may cause sensitisation (28)

The applicant's reasons for the request are:

- Currently, there are no restrictions on introducing or using *m*-aminophenol in Australia. In the absence of any regulatory controls, the characterised critical health effects (particularly skin sensitisation) have the potential to pose an unreasonable risk if *m*-aminophenol is used in cosmetic products without an appropriate concentration cut-off (exemption) for hair dye use. Whilst domestic use of m-aminophenol will result in lower levels of exposure, there is sufficient uncertainty regarding the safety of such products to warrant some restriction;
- *m*-Aminophenol was reported to be used in permanent hair dye preparations in Australia, and overseas hair products and other personal care products;
- *m*-Aminophenol is a contact allergen in humans;
- *m*-Aminophenol is a strong skin sensitiser in animals, based on a local lymph node assay (LLNA)-derived EC3 (estimated concentration to produce a three-fold increase in lymphocyte proliferation) value of 0.24-3.2%;
- The existing overseas restrictions (Association of Southeast Asian Nations (ASEAN), New Zealand, European Union (EU)) on the use of m-aminophenol in cosmetic products, where the use of m-aminophenol in hair dyes is restricted to a maximum concentration of 1.2% applied to hair after mixing under oxidative conditions (a 1:1 mixture of 2.4% 3-aminophenol with hydrogen peroxide); and
- When *m*-aminophenol is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Australian regulatory information

m-Aminophenol is listed on the Australian Inventory of Chemical Substances (AICS).[79] Currently there are no restrictions on the use of *m*-aminophenol in cosmetics or domestic products in Australia. *m*-Aminophenol is not listed in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017 and a search of the Australian Register of Therapeutic Goods (ARTG) found it is not an ingredient in any listed products.

International regulations

Use of *m*-aminophenol in cosmetics in the EU is subject to the restrictions described in EU Cosmetics Regulation 344/2013 (as an amendment to the listing under Annex III of Regulation 1223/2009). The use of *m*-aminophenol in hair dyes is restricted to a maximum concentration of 1.2% applied to hair after mixing under oxidative conditions (1:1 ratio with hydrogen peroxide). If *m*-aminophenol is present at lower concentrations, sensitisation labelling is required.

Use of *m*-aminophenol in cosmetics and domestic products is also restricted in several other countries as follows:

- ASEAN Cosmetic Directive Annex III Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions; and
- New Zealand Cosmetic Products Group Standard—Schedule 5, Table 1: Components cosmetic products must not contain except subject to restrictions and conditions.

Under the above regulations, the use of *m*-aminophenol in hair dyes is restricted to a maximum concentration of 1.2% applied to hair after mixing under oxidative conditions.

[79] Phenol, 3-amino-

Substance summary

m-Aminophenol is used in hair colourants and is an important starting material for dyes, including a variety of latent dyes used in imaging technology, optical bleaches and fluorescent agents, drugs, agricultural chemicals and high performance polymers.[80]

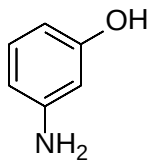


Figure 3.3: Chemical structure of *m*-aminophenol.

Table 3.3A: Chemical information

Property	*m*-aminophenol
CAS names	Phenol, 3-amino
CAS numbers	591-27-5
IUPAC and/or common and/or other names	3-hydroxyaniline *m*-aminophenol (INCI)
Molecular formula	C_6H_7NO
Molecular weight	109.13 g/mol

The following toxicology information was extracted from the NICNAS IMAP Human Health Tier II assessment report for 3-aminophenol.[81] Further information can also be found in the SCCP report for *m*-aminophenol.[82]

Table 3.3B: Acute toxicity end-points for *m*-aminophenol

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bodyweight (bw))	Rat	812-1000	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	1162	Schedule 6

[80] Dressler, H. (1994) 'm-Aminophenol', *Resorcinol: Its Uses and Derivatives*, Springer US, p 125-134.
[81] Publicly available on the NICNAS website at: Human Health Tier II Assessment for Phenol,3-amino-
[82] Publicly available at Opinion on M-aminophenol (pdf,222kb)

Skin irritation	Rabbit	No irritation (2% *m*-aminophenol in a suspension of 0.5% methylcellulose in purified water)	N/A
Eye irritation	Rabbit	Mild irritation (2% *m*-aminophenol in a suspension of 0.5% methylcellulose in purified water)	N/A
Skin sensitisation	Mouse (LLNA)	Moderate to strong skin sensitiser (EC3 0.24-3.2%)	Schedule 6
	Guinea pig (GPMT)	Sensitiser. Positive reactions in 100% of animals tested at 5%, following 1% intradermal induction and 10% topical induction.	

Acute toxicity

m-Aminophenol has moderate acute oral and inhalation toxicity, warranting hazard classification. No data were available for acute dermal toxicity.

Irritation

The available data from animal and human studies indicate that *m*-aminophenol is not irritating to the skin or eyes.

Sensitisation

Based on the available animal and human data, *m*-aminophenol is considered to be a moderate to strong skin sensitiser and is recommended for classification.

- In an *in vivo* mouse LLNA conducted in accordance with OECD Test Guideline (TG) 429, 28 female CBA/J mice (four animals/group) were administered m-aminophenol at concentrations of 0, 1, 2.5, 5, 10 or 25% (w/v) in dimethylformamide. Stimulation indices (SI) of 0, 7.6, 12.6, 10.4, 7.2 and 6.0 were reported, respectively. In a second experiment, concentrations of 0, 0.05, 0.1, 0.5, 1.0 and 2.5% of m-aminophenol in the same vehicle were administered to the animals. SIs of 1.0, 1.4, 5.9, 9.0 and 11.0 were reported, respectively. The calculated EC3 value (0.24%) indicated strong sensitisation potential for m-aminophenol.
- In another mouse LLNA study, CBA/Ca mice were administered m-aminophenol at concentrations of 0, 2.5, 5 or 10% (w/v) in acetone/olive oil (ratio of 4:1). SIs of 0, 2.8, 3.5 and 5.7 were reported, respectively. The EC3 value was reported to be 3.2%.
- In a non-guideline GPMT, guinea pigs were administered *m*-aminophenol at a concentration of 1.0% (v/v) in acetone/olive oil (ratio of 4:1) by intradermal injection, followed by topical induction with a 10% solution of *m*-aminophenol one week later. After two weeks, a topical challenge dose of 5% resulted in positive reactions observed in all animals tested.

Repeat-dose toxicity

Based on the available information, *m*-aminophenol is not considered to cause serious damage to health through repeated oral exposure at low doses. Systemic toxicity has not been demonstrated via the dermal route. No information was available for repeated dose toxicity by inhalation.

Genotoxicity

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

Carcinogenicity

Based on the available data and the lack of genotoxicity, *m*-aminophenol is not expected to be carcinogenic.

Reproduction and developmental toxicity

Based on the available information, *m*-aminophenol is not expected to be a reproductive or developmental toxin.

Observation in humans

Sensitisation

Sensitisation in humans exposed to *m*-aminophenol has been observed both in repeat insult patch tests and during diagnostic patch testing.

In two semi-occlusive repeat insult patch tests, 0.1 mL doses of *m*-aminophenol (3% solution in Schultz vehicle II or similar) were applied to the backs of 98 and 99 test subjects over a six week period. There were 10 consecutive induction patch applications at 48-72 hours, followed by one day of no application. Challenge patch applications on previously unexposed skin on backs of humans were conducted 48 hours following the rest period. In both studies, irritant effects (erythema) were observed in several subjects during the induction phase. In the first study (98 subjects), no reactions to the challenge patches were observed. In the second study (99 subjects), two subjects showed reactions following application of the challenge patches, as well as following application of additional rechallenge patches on different parts of the body.

In an Australian case study, 164 hairdressers and hairdressing apprentices who presented with allergic contact dermatitis at a dermatology clinic were patch-tested against 36 chemicals used in hair salons. Four subjects, previously exposed to *m*-aminophenol in the workplace, had positive reactions when patch tested with *m*-aminophenol.

Pre-meeting public submissions

One (1) pre-meeting public submission was received with no objections to the proposed scheduling for *m*-aminophenol. The main points of the submission were:

- The scheduling of m-Aminophenol should align with regulations in other international jurisdictions, such as the EU.
- *m*-Aminophenol is used in approximately 85-95% of hair dye products in Australia.

An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

The public submissions will be made available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that a new Schedule 6 entry for *m*-aminophenol be created as follows:

Schedule 6 - New Entry

m-AMINOPHENOL except when used in hair dye and eyebrow/eyelash preparations at a concentration of 1.2 per cent or less of *m*-aminophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

The committee recommends Appendix E/F entries be created as follows:

Appendix E, Part 2 – New Entry

m-AMINOPHENOL

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

m-AMINOPHENOL

Warning Statements: 28 ((over) (repeated) exposure may cause sensitisation).

Safety directions: 4 (Avoid contact with skin), 8 (Avoid breathing dust (or) vapour (or) spray mist).

The committee also recommended an implementation date of **1 June 2018** to allow for the necessary labelling changes to be implemented by industry.

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 and extent of use; and (c) the toxicity of a substance.

The reasons for the advice comprised the following:

- *m*-Aminophenol is a strong to moderate skin sensitiser.
- The primary consumer use of m-aminophenol is in hair dye and eyelash dye products, and therefore dermal contact is unavoidable. However, risk can be managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of m-aminophenol are consistent with the factors for Schedule 6.

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)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for *m*-aminophenol. The proposed Schedule entry is as follows:

Schedule 6 - New Entry

m-AMINOPHENOL **except** when used in hair dye and eyebrow/eyelash preparations at a concentration of 1.2 per cent or less of *m*-aminophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

m-AMINOPHENOL

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

m-AMINOPHENOL

Warning Statements: 28 ((over) (repeated) exposure may cause sensitisation).

Safety directions: 4 (Avoid contact with skin), 8 (Avoid breathing dust (or) vapour (or) spray mist).

The proposed implementation date is **1 June 2018**.

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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- *m*-Aminophenol is a strong to moderate skin sensitiser.
- The primary consumer use of m-aminophenol is in hair dye and eyelash dye products, and therefore dermal contact is unavoidable. However, risk can be managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of m-aminophenol are consistent with the factors for Schedule 6.
- A long implementation date is proposed in order to allow for the necessary labelling changes to be implemented by industry.

3.4 2-Chloro-6-(ethylamino)-4-nitrophenol

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for 2-chloro-6-(ethylamino)-4-nitrophenol to restrict its use in hair dyes and to determine an appropriate exemption concentration cut-off.

Current scheduling status and relevant scheduling history

2-Chloro-6-(ethylamino)-4-nitrophenol is not currently scheduled.

On 16 January 2017, the delegate made a delegate-only final decision to enter 2-chloro-6-(ethylamino)-4-nitrophenol in Schedule 6 and Appendices E and F of the Poisons Standard as follows:

Schedule 6

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL except when in hair dye preparations containing 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

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, Part 3 – 2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The implementation date of this decision was 1 February 2017.

Following the release of the final decision on 16 January 2017, industry feedback indicated that the wording of the Schedule 6 entry may require further amendment. On 31 January 2017, the Schedule 6 entry for 2-chloro-6-(ethylamino)-4-nitrophenol was removed (by amendment) from the 1 February 2017 Poisons Standard. This final decision was implemented as Amendment No. 1 of SUSMP 16. 2-Chloro-6-(ethylamino)-4-nitrophenol was subsequently referred to the March 2017 ACCS meeting to enable a consultation process on the proposed scheduling.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 3 per cent for ready-for-use preparations and 1.5 % after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Standard statements: E1 – If in eyes wash out immediately with water.

Appendix F – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Warning statement: Repeated exposure may cause sensitisation (28)

The applicant's reasons for the request are:

- Reported use of 2-chloro-6-(ethylamino)-4-nitrophenol as an ingredient in both permanent and semi-permanent hair dyes in Australia;
- 2-Chloro-6-(ethylamino)-4-nitrophenol is a skin sensitiser;
- 2-Chloro-6-(ethylamino)-4-nitrophenol is acutely toxic following oral exposure;
- Overseas restrictions for use of 2-chloro-6-(ethylamino)-4-nitrophenol in hair dyes; and
- When 2-chloro-6-(ethylamino)-4-nitrophenol is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Australian regulatory information

2-Chloro-6-(ethylamino)-4-nitrophenol is present on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

2-Chloro-6-(ethylamino)-4-nitrophenol is not listed on the Therapeutic Goods (Permissible Ingredients, 26BB) Determination No. 1 of 2017 and a search of the Australian Register of Therapeutic Goods (ARTG) found it not listed in any products.

International regulations

Use of 2-chloro-6-(ethylamino)-4-nitrophenol in cosmetics in the European Union (EU) is subject to the restrictions described in EU Cosmetics Regulation 344/2013 (as an amendment to the listing under Annex III of Regulation 1223/2009). 2-Chloro-6-(ethylamino)-4-nitrophenol may be used at maximum concentrations of 3.0% in ready-for-use preparations of oxidising (permanent) and non-oxidising (semi-permanent) colouring agents for hair dyeing. Additionally, after mixing under oxidative conditions (i.e. with hydrogen peroxide) the maximum concentration applied to hair must not exceed 1.5% for both permanent and semi-permanent application types. The Cosmetics Regulation also mandates label warning statements relating to the sensitisation potential of 2-chloro-6-(ethylamino)-4-nitrophenol.

Use of 2-chloro-6-(ethylamino)-4-nitrophenol in hair dyes is also restricted in several other countries as according to inclusion in the following listings:

- the Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1, with the same use restrictions as described above for the EU; and

- the New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to restrictions and conditions laid down. While a maximum concentration (of 3.0%) only appears to apply to ready for use preparations of non-oxidising (semi-permanent) colouring agents for hair dyeing, the maximum concentration applied to hair must not exceed 1.5% for both permanent and semi-permanent application types.

Substance summary

2-Chloro-6-(ethylamino)-4-nitrophenol has reported cosmetic use as an ingredient in both permanent and semi-permanent hair dyes in Australia and internationally.

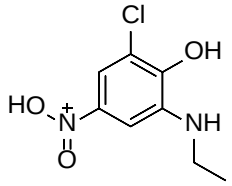


Figure 3.4: Chemical structure of 2-Chloro-6-(ethylamino)-4-nitrophenol

Table 3.4A: Chemical information

Property	2-chloro-6-(ethylamino)-4-nitrophenol
CAS names	Phenol, 2-chloro-6-(ethylamino)-4-nitro-
CAS numbers	131657-78-8
IUPAC and/or common and/or other names	2-Chloro-6-(ethylamino)-4-nitrophenol (INCI and IUPAC)
Molecular formula	$C_8H_9ClN_2O_3$
Molecular weight	216.62 g/mol

The following toxicology information was extracted from the NICNAS IMAP Human Health Tier II assessment report for 2-chloro-6-(ethylamino)-4-nitro-phenol.[83]

Table 3.4B: Acute toxicity end-points for 2-chloro-6-(ethylamino)-4-nitrophenol

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1728	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	Schedule 5
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	-	No data	N/A
Skin irritation	Rabbit	Not irritating to the skin	N/A

[83] Publicly available on the NICNAS website at: Human Health Tier II Assessment for Phenol,2-chloro-6-(ethylamino)-4-nitro.

Eye irritation	Rabbit	Insufficient data	N/A
Skin sensitisation (Local lymph node assay, LLNA)	Mouse	Skin sensitiser	Schedule 6

Acute toxicity

2-Chloro-6-(ethylamino)-4-nitrophenol has moderate acute oral toxicity, but low acute dermal toxicity based on results from animal tests. Additionally, 2-chloro-6-(ethylamino)-4-nitrophenol is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS. The available data support this classification.

Irritation

The available data from animal studies indicate that 2-chloro-6-(ethylamino)-4-nitrophenol is not irritating to the skin, but is a potential eye irritant. However, insufficient details on the eye irritation study are available, which do not allow for hazard classification.

Sensitisation

2-Chloro-6-(ethylamino)-4-nitrophenol is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in the HSIS. The positive results, reported in a local lymph node assay (LLNA), support this classification.

In an LLNA conducted according to OECD TG 429, the skin sensitising potential of 2-chloro-6-(ethylamino)-4-nitrophenol was tested in mice (5 animals/dose group) at concentrations ranging from 0.5–10% using a DMSO vehicle, and at 0.5-2.5% using an acetone/water/olive oil vehicle (mix ratio of 2:2:1). The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) value of 2.79% was determined based on the concentrations used with the DMSO vehicle; a stimulation index greater than three was not observed at the lower concentrations used with the acetone/water/olive oil vehicle (up to 2.5%).

Repeat-dose toxicity

Based on the available information, 2-chloro-6-(ethylamino)-4-nitrophenol is not considered to cause serious damage to health through repeated oral exposure.

Mutagenicity/Genotoxicity

Based on the weight of evidence from the available, well-conducted, *in vitro* and *in vivo* genotoxicity studies, 2-chloro-6-(ethylamino)-4-nitrophenol is not considered to be genotoxic.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of 2-chloro-6-(ethylamino)-4-nitrophenol. Based on the available genotoxicity data and mechanistic information, 2-chloro-6-(ethylamino)-4-nitrophenol is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available information, 2-chloro-6-(ethylamino)-4-nitrophenol is not expected to be a developmental toxin. No reliable data examining the effect of 2-chloro-6-(ethylamino)-4-nitrophenol on fertility are available.

Observation in humans

No information was available.

Public exposure

Considering that 2-chloro-6-(ethylamino)-4-nitrophenol is reported to be used in hair dye products in Australia, the main route of public exposure is expected to be dermal.

Pre-meeting public submissions

One (1) pre-meeting public submission was received with no objections to the proposed scheduling for 2-chloro-6-(ethylamino)-4-nitrophenol. The main points of the submission were:

- Scheduling of 2-chloro-6-(ethylamino)-4-nitrophenol should align with regulations in other international jurisdictions, such as the EU.
- 2-chloro-6-(ethylamino)-4-nitrophenol substance is used in the approximately 24% of hair dye products in Australia.
- An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified. There is no evidence to suggest immediate action is required for the risk management of this substance.

The public submission is available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that a new Schedule 6 entry for 2-chloro-6-(ethylamino)-4-nitrophenol be created as follows:

Schedule 6 - New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL **except:**

a) in non-oxidative hair dye preparations containing 3 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

written in letters not less than 1.5 mm in height.

The committee recommends Appendix E/F entries be created as follows:

Appendix E, Part 2 – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Warning Statements: 28 ((over) (repeated) exposure may cause sensitisation).

Safety directions: 4 (Avoid contact with skin).

The committee also recommended an implementation date of **1 June 2018** to allow for the necessary labelling changes to be implemented by industry.

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 and extent of use; and (c) the toxicity of a substance.

The reasons for the advice comprised the following:

- 2-Chloro-6-(ethylamino)-4-nitrophenol is a strong to moderate skin sensitiser.
- Primary consumer use of 2-chloro-6-(ethylamino)-4-nitrophenol is in hair dye and eyelash dye products, and therefore dermal contact is unavoidable. However risk can be managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of 2-chloro-6-(ethylamino)-4-nitrophenol are consistent with the factors for Schedule 6.

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)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create new Schedule 6 and Appendix E/F entries for 2-chloro-6-(ethylamino)-4-nitrophenol. The proposed Schedule entry is as follows:

Schedule 6 - New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL **except:**

a) in non-oxidative hair dye preparations containing 3 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 1.5 per cent or less of 2-chloro-6-(ethylamino)-4-nitrophenol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

2-CHLORO-6-(ETHYLAMINO)-4-NITROPHENOL

Warning Statements: 28 ((over) (repeated) exposure may cause sensitisation).

Safety directions: 4 (Avoid contact with skin).

The proposed implementation date is **1 June 2018**. This implementation date is proposed in order to allow for the necessary labelling changes to be implemented by industry.

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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- 2-Chloro-6-(ethylamino)-4-nitrophenol is a strong to moderate skin sensitiser.
- Primary consumer use of 2-chloro-6-(ethylamino)-4-nitrophenol is in hair dye and eyelash dye products, and therefore dermal contact is unavoidable. However risk can be managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of 2-chloro-6-(ethylamino)-4-nitrophenol are consistent with the factors for Schedule 6.

3.5 2,4-Diaminophenoxyethanol

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a Schedule 6 entry for 2,4-diaminophenoxyethanol with appropriate concentration cut-off for use in hair dyes.

Current scheduling status

2,4-Diaminophenoxyethanol is currently in Schedule 6 and Appendices E and F of the Poisons Standard as follows:

Schedule 6

2,4-DIAMINO-PHENOXYETHANOL in hair dye preparations **except** in preparations containing 4 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following:

KEEP OUT OF REACH OF CHILDREN

WARNING – this product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dying eyelashes and eyebrow; to do so may be injurious to the eye.

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – 2,4-DIAMINO-PHENOXYETHANOL

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, Part 3 – 2,4-DIAMINO-PHENOXYETHANOL

Warning statement: 21 (WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye).

Scheduling history

In March 2014, the Advisory Committee on Chemicals Scheduling (ACCS) included 2,4-diaminophenoxyethanol in Schedule 6 and Appendices E and F of the Poisons Standard. Although the applicant's scheduling proposal specifically referenced the sulfate salt, it was noted at the meeting that the hydrochloride salt (2,4-diaminophenoxyethanol dihydrochloride) was used in the toxicity assessment and that the sulfate salt and free alcohol will likely have comparable physical/chemical and toxicological properties. The implementation date was 1 October 2014.

In August 2016, NICNAS, under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) Scheme submitted a proposal to create a new Schedule 6 entry [*Secretariat note: an entry already exists*] for 2,4-diaminophenoxyethanol except when used in hair dye and eyebrow/eyelash colouring products at a concentration of 2 per cent or less after mixing for use when the immediate container and primary pack are labelled appropriately.

On 16 January 2017, the delegate made a delegate-only final decision to amend the Schedule 6 entry for 2,4-diaminophenoxyethanol as follows:

Schedule 6

2,4-DIAMINOPHENOXYETHANOL (including its salts) **except**:

a) in non-oxidative hair dye preparations containing 4 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 2 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

written in letters not less than 1.5 mm in height.

The delegate also amended the Appendix F, Part 3 warning statement from 21[84] to 28.[85]

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6

ETHANOL, 2-(2,4-DIAMINOPHENOXY)-, DIHYDROCHLORIDE **except** when used in hair dye and eyebrow/eyelash colouring products at a concentration of 2 per cent or less of Ethanol, 2-(2,4-diaminophenoxy)-, dihydrochloride after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

Appendix E, Part 2

ETHANOL, 2-(2,4-DIAMINOPHENOXY)-, DIHYDROCHLORIDE

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, Part 3

ETHANOL, 2-(2,4-DIAMINOPHENOXY)-, DIHYDROCHLORIDE

Warning statement: Repeated exposure may cause sensitisation (28)

[84] (WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye).
[85] ((Over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- 2,4-Diaminophenoxy)ethanol dihydrochloride has overseas restrictions, where the maximum concentration allowed in hair and eyelash products must not exceed 2.0% (as hydrochloride) and for professional use only;
- 2,4-Diaminophenoxyethanol dihydrochloride has reported cosmetic use in permanent hair dye preparations in Australia;
- 2,4-diaminophenoxyethanol dihydrochloride has moderate oral acute toxicity, is an eye irritant and a moderate skin sensitiser;
- The risk could be controlled by including warning statements on the label of hair dye formulations containing 2,4-diaminophenoxyethanol dihydrochloride at any concentration; and
- When 2,4-diaminophenoxyethanol dihydrochloride is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Australian regulatory information

2,4-Diaminophenoxyethanol dihydrochloride is listed on the Australian Inventory of Chemical Substances (AICS) and is reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007).

2,4-Diaminophenoxyethanol dihydrochloride is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017.

A search of the Australian Register of Therapeutic Goods (ARTG) found 2,4-diaminophenoxyethanol dihydrochloride not in any listed products.

International regulations

The Association of South East Asian Nations (ASEAN), Canada, New Zealand and the European Union (EU) have restricted the use of 2,4-diaminophenoxyethanol in cosmetics. Following a safety evaluation, the Scientific Committee on Consumer Products (SCCP) concluded that the use of 2,4-diaminophenoxyethanol 'as an oxidative hair dye at a maximum concentration of 2.0% in the finished cosmetic product (after mixing with hydrogen peroxide) does not pose a risk to the health of the consumer, apart from its sensitising potential' (SCCP 2006).

2,4-Diaminophenoxyethanol is listed on the following:

- The ASEAN Cosmetic Directive Annex III—Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down: 'After mixing under oxidative conditions the maximum concentration applied to hair must not exceed 2.0% (as hydrochloride)';
- The EU Regulation (EC) No 1197/2013 of the European Parliament and of the Council of 1 July 2014 on cosmetic products Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: 'After mixing under oxidative conditions the maximum concentration applied to hair or eyelashes must not exceed 2.0% (as hydrochloride) and for professional use only'. The Cosmetic Regulation also mandates label warning statements relating to the sensitisation potential of 2,4-diaminophenoxyethanol;
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: 'In combination with hydrogen peroxide the maximum use concentration upon application is 2.0% as hydrochloride'; and

- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist').

Substance summary

2,4-Diaminophenoxyethanol is a light grey to light pink (dihydrochloride) or white powder (sulfate) used primarily in hair dye formulations.

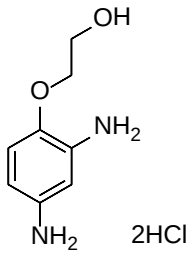


Figure 3.5: Chemical structure of 2,4-Diaminophenoxyethanol

Table 3.5A: Chemical information

Property	2,4-diaminophenoxyethanol dihydrochloride
CAS names	ethanol, 2-(2,4-diaminophenoxy)-, dihydrochloride
CAS numbers	66422-95-5
IUPAC and/or common and/or other names	2,4-diaminophenoxyethanol HCL (INCI); 2-(2,4-diaminophenoxy)ethanol dihydrochloride (IUPAC).
Molecular formula	$C_8H_{14}Cl_2N_2O_2$
Molecular weight	241.1 g/mol

The following information was extracted from the NICNAS IMAP Human Health Tier II group assessment report for Ethanol, 2-(2,4-diaminophenoxy)-, dihydrochloride.[86]

Table 3.5B: Acute toxicity end-points for 2-(2,4-diaminophenoxy)ethanol dihydrochloride

Toxicity	Species	Result	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat Mouse	1000 1160	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A

[86] Publicly available at Human Health Tier II Assessment for Ethanol, 2-(2,4-diaminophenoxy)-, dihydrochloride.

Skin irritation	Rabbit	Non-irritant	N/A
Eye irritation	Rabbit	Irritant	Schedule 5/6
Skin sensitisation (local lymph node assay, LLNA)	Guinea pig Mouse	Moderate sensitiser	Schedule 6

Acute toxicity

2,4-Diaminophenoxyethanol is considered to have moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD_{50}) was approximately 1000 mg/kg bw in Sprague Dawley (SD) rats and 1160 mg/kg bw in Swiss albino mice. No data were available for acute dermal and inhalation toxicity.

Skin irritation

Based on the limited available data, 2,4-diaminophenoxyethanol is not considered to be a skin irritant.

Eye irritation

Based on the available data, 2,4-diaminophenoxyethanol is considered to be an eye irritant:

- In an eye irritation study conducted according to OECD TG 405 with three female New Zealand White rabbits, the undiluted 2,4-diaminophenoxyethanol dihydrochloride was instilled into the conjunctival sac of the left eye of each animal. The eyes were not rinsed following instillation of 2,4-diaminophenoxyethanol. Moderate to marked chemosis, slight to moderate conjunctival redness, slight to moderate corneal opacification and slight iridial lesions were observed in the animals. These effects were not fully reversed at the end of the study (day 15). It was concluded that the undiluted chemical was irritating to rabbit eyes.
- In two other eye irritation studies carried out in three female New Zealand White rabbits and three albino Bouscat rabbits, a 4% solution of 2,4-diaminophenoxyethanol did not produce any irritation.

Sensitisation

Based on the available data, 2,4-diaminophenoxyethanol is considered to be a moderate skin sensitiser:

- One LLNA was conducted according to OECD TG 429 in female CBA/J mice (n=4/group). 2,4-Diaminophenoxyethanol at 0.5, 1.0, 2.5, 5.0 or 10% dilutions produced a stimulation index (SI) of 0.92, 1.56, 1.17, 4.21 and 7.42, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 3.2%, indicating a moderate sensitising potential.
- In a Buehler test (OECD TG 406) conducted using ten Dunkin Hartley guinea pigs per sex, no sensitisation reaction was observed with topical induction and challenge applications of the undiluted chemical after 48 hours.

Repeat-dose toxicity

Based on the available data, 2,4-diaminophenoxyethanol dihydrochloride is not expected to cause serious damage to health from repeated oral exposure. No information was available for repeated dose toxicity by dermal and inhalation routes.

Genotoxicity

Based on the negative results observed in several *in vitro* and *in vivo* genotoxicity studies, 2,4-diaminophenoxyethanol are not expected to be genotoxic.

Carcinogenicity

Based on the available data, 2,4-diaminophenoxyethanol is not considered to be carcinogenic.

Reproduction and developmental toxicity

Based on the available data, 2,4-diaminophenoxyethanol is not expected to have reproductive and developmental toxicity.

Pre-meeting submissions

One (1) pre-meeting public submission was received with no objections to the proposed scheduling for 2,4-diaminophenoxyethanol. The main points of the submission were:

- Scheduling of 2,4-diaminophenoxy-ethanol should align with regulations in other international jurisdictions, such as the EU.
- 2,4-Diaminophenoxy-ethanol is used in approximately 70-95% of hair dye products in Australia.
- An adequate transition period of at least 12 months in requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified. There is no evidence to suggest immediate action is required for the risk management of this substance.

The public submission is available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that the Schedule 6 and Appendix E/F entries for 2,4-diaminophenoxyethanol be amended as follows:

Schedule 6 - Amend Entry

2,4-DIAMINOPHENOXYETHANOL ~~in hair dye preparations **except** in preparations containing 4~~ **except** when used in hair dye and eyebrow/eyelash preparations at a concentration of 2 per cent or less of 2,4-diaminophenoxyethanol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – Amend Entry

2,4-DIAMINO-PHENOXYETHANOL

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.),~~ E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – Amend Entry

2,4-DIAMINO-PHENOXYETHANOL

Warning statement: ~~21 (WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye),~~ 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

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

The committee also advised an implementation date of **1 June 2018** to allow industry to make the necessary changes to labelling.

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 and extent of use; and (c) the toxicity of a substance.

The reasons for the advice comprised the following:

- 2,4-Diaminophenoxyethanol is a strong to moderate skin sensitiser.
- Primary consumer use of 2,4-diaminophenoxyethanol is in hair dye and eyelash dye products. Although dermal contact of 2,4-diaminophenoxyethanol is unavoidable when used in hair dye preparations, risk can be appropriately managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of 2,4-diaminophenoxyethanol is consistent with the factors for Schedule 6.
- 2,4-Diaminophenoxyethanol is an irreversible eye irritant at high concentrations.

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)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 6 and Appendix E/F entries for 2,4-diaminophenoxyethanol. The proposed Schedule entry is as follows:

Schedule 6 - Amend Entry

2,4-DIAMINOPHENOXYETHANOL **except** when used in hair dye and eyebrow/eyelash preparations at a concentration of 2 per cent or less of 2,4-diaminophenoxyethanol after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – Amend Entry

2,4-DIAMINO-PHENOXYETHANOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – Amend Entry

2,4-DIAMINO-PHENOXYETHANOL

Warning statement: 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

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

The proposed implementation date is **1 June 2018**.

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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- 2,4-Diaminophenoxyethanol is a strong to moderate skin sensitiser.
- Primary consumer use of 2,4-diaminophenoxyethanol is in hair dye and eyelash dye products. Although dermal contact of 2,4-diaminophenoxyethanol is unavoidable when used in hair dye preparations, risk can be appropriately managed by limiting concentration and applying warning statements.
- The acute oral toxicity and skin sensitisation of 2,4-diaminophenoxyethanol is consistent with the factors for Schedule 6.
- 2,4-Diaminophenoxyethanol is an irreversible eye irritant at high concentrations.
- A long implementation date is proposed in order to allow industry to make the necessary changes to labelling.

3.6 Isoeugenol

Referred scheduling proposal

An application was initiated by the chemicals scheduling delegate to amend the Schedule 5 and Schedule 6 entries for isoeugenol to specify concentration cut-offs in products both intended and not intended for skin contact.

Current scheduling status

Isoeugenol is currently in Schedules 5 and 6 of the Poisons Standard (February 2017) as follows:

Schedule 6

ISOEUGENOL **except**:

a) when included in Schedule 5; or

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

Schedule 5

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

On 1 June 2017 (decision from the July 2016 ACCS meeting), the Schedule 5 and 6 entries for isoeugenol were to be amended in the Poisons Standard; however, this decision has been deferred to accommodate this recent proposal to amend the scheduling entry.

July 2016 ACCS scheduling decision:

Schedule 6

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

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.

Scheduling history

Isoeugenol was first considered for scheduling in November 1996 by the NDPSC and at that time, the acute toxicity profile of isoeugenol warranted inclusion in Schedules 5 and 6 because of skin and eye irritancy, skin sensitisation potential and the oral LD_{50}.

Isoeugenol was considered for scheduling again in July 2016 at the Advisory Committee on Chemicals Scheduling (ACCS). The committee advised that the Schedule 5 and Schedule 6 cut-off should be amended from 10% to 0.5% in preparations intended for contact with the skin due to the use pattern and skin sensitisation potential of isoeugenol. The implementation date for this decision was to be 1 June 2017.

After publication of the July 2016 ACCS final decision industry indicated that, while the exemption cut-off of 0.5% of isoeugenol in products intended for skin contact was appropriate, there should be a separate concentration cut-off for products not intended for skin contact (and that 10% was appropriate).

Scheduling application

The delegate-initiated scheduling proposal is to amend the Schedule 5 and Schedule 6 entries for isoeugenol to specify concentration cut-offs in products both intended and not intended for skin contact. Consideration has been given to the current Schedule 5 and Schedule 6 entries with a specified 10 per cent cut-off, and the previous application to amend the Schedule 5 and Schedule 6 entries for isoeugenol, with a specified 1 per cent cut-off.

The proposed changes to the Poisons Standard are:

Schedule 6 – Amend Entry

ISOEUGENOL **except**:

a) when included in Schedule 5; or

b) in preparations not intended for skin contact containing 10/1 per cent or less of isoeugenol; or

c) in preparations intended for skin contact 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**:

a) in preparations not intended for skin contact containing 10/1 per cent or less of isoeugenol; or

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

Australian regulatory information

Isoeugenol is listed on the Australian Inventory of Chemical Substances (AICS) (NICNAS, 2007). No specific Australian industrial use, import, or manufacturing information has been identified.

Isoeugenol is available for use as an Active Ingredient in: Biologicals, Prescription Medicines and is available for use as an Excipient Ingredient in: Biologicals, Devices, Listed Medicines, Prescription Medicines. Isoeugenol is permitted for use in a medicine as a flavour, at no more than 5 per cent, or a fragrance at no more 1 per cent.

Isoeugenol is not listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017.

Isoeugenol is included in 171 listed products on the ARTG. The types of product vary, ranging from sunscreens and skin lotions, complementary medicines and dietary supplements, cough preparations, epilepsy drugs, anti-fungal ointments and hospital-grade disinfectants.

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%; and
- 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.
- 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%.

Substance summary

Isoeugenol is one of several structurally similar phenylpropenoid compounds produced by plants. It has been extracted from calamus, savoury, basil, ylang-ylang, clove, tuberose, jonquil, nutmeg, tobacco, sandalwood, dill seed, mace, gardenia, petunia, and other flowers. Isoeugenol can also be produced by isomerization of eugenol, which occurs naturally in clove, pimento, bay leaf, and cinnamon.

As a fragrance with a spicy, carnation-like odour, isoeugenol is incorporated into numerous household and personal hygiene products, including perfumes, cream lotions, soaps, and detergents. As a flavouring agent, isoeugenol is added to non-alcoholic drinks, baked foods, and chewing gums.[87]

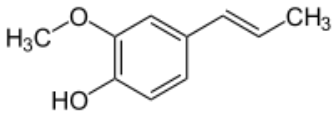


Figure 3.6: Chemical structure of Isoeugenol

Table 3.6A: Chemical information

Property	Isoeugenol
CAS name	phenol, 2-methoxy-4-(1-propenyl)
CAS number	97-54-1
Alternative names	2-methoxy-4-(prop-1-en-1-yl)phenol; phenol, 2-methoxy-4-(1-propenyl)
Molecular formula	$C_{10}H_{12}O_2$
Molecular weight	164.2 g/mol

The following has been extracted from the NICNAS IMAP Human Health Tier II assessment report for phenol, 2-methoxy-4-(1-propenyl)-.[88]

Table 3.6B: Acute toxicity endpoints for isoeugenol

Toxicity	Species	Result	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

[87] *Natl Toxicol Program Tech Rep Ser*. 2010 Sep;(551):1-178
[88] Publicly available on the NICNAS website: Human Health Tier II Assessment for Phenol, 2-methoxy-4-(1-propenyl)-

Acute toxicity

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.

Irritation

The potential for isoeugenol to irritate the skin has been assessed in a number of animal studies. In a non-guideline study, undiluted isoeugenol was applied to the dorsal skin of albino Angora rabbits and guinea pigs under occlusion for 24 hours. Patches were removed and a second application was made 30 minutes later. Macro and microscopic examination of excised skin revealed evidence of severe irritation.

Sensitisation

Isoeugenol is considered to be a skin sensitiser based on human data, positive results seen in guinea pig maximisation tests (GPMT) and LLNAs.

The estimated concentration to produce a three-fold increase in lymphocyte proliferation (EC3) was determined from over 40 separate LLNA tests conducted using isoeugenol. The weighted mean EC3 value of 2% was reported from the combined data. Lower EC3 values have been reported elsewhere in the literature, including as low as 0.54%.

In a GPMT with isoeugenol, animals were intra-dermally induced at 0.15% followed by topical induction at 25%. A challenge phase was conducted seven days later with topical application of a 5% solution. Responses were seen in 100% of animals.

Similar effects were observed when isoeugenol was tested in Freund's complete adjuvant tests. In one test, guinea pigs (10/group) were intra-dermally induced at 1, 3 or 10% followed by a challenge using a topical application of isoeugenol at the same respective concentrations. Responses were seen in 5/10, 9/10 and 10/10 animals in the 1, 3 and 10% induction and challenge groups, respectively. In another FCA test, eight guinea pigs were intra-dermally induced at 5%, followed by a challenge by topical application at the same concentration. Responses were seen in all eight animals.

HRIPTs have also indicated that isoeugenol is a skin sensitiser in humans.

Repeat-dose toxicity

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

Genotoxicity

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, isoeugenol is not considered to be genotoxic. Some in vitro genotoxicity tests indicated weakly positive results, but all *in vivo* tests were negative.

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).

Reproduction and developmental toxicity

Isoeugenol does not show specific reproductive or developmental toxicity. The reproductive and developmental effects seen in studies were secondary to maternal toxicity.

Public exposure

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

Pre-meeting public submissions

One (1) pre-meeting public submission was received with no objections to the proposed scheduling for isoeugenol. The main points of the submission were:

- Scheduling of isoeugenol should align with regulations in other international jurisdictions, such as the EU, as well as IFRA standards.
- Isoeugenol scheduling has been ambiguous and it is appreciated by industry that the wording of the Schedule 5 entry is being revisited.
- An adequate transition period of at least 12 months is requested to allow for any labelling changes and/or reformulation that may be required where no immediate risk has been identified. There is no evidence to suggest immediate action is required for the risk management of this substance.

The public submission is available on the TGA website.

Summary of ACCS advice to the delegate

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

Schedule 6 – Amend Entry

ISOEUGENOL **except**:

a) when included in Schedule 5; or

b) in preparations not intended for skin contact containing 10 per cent or less of isoeugenol; or

c) in preparations intended for skin contact containing 0.02 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 containing 10 per cent or less of isoeugenol.

Appendix E, Part 2 – New Entry

ISOEUGENOL

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, Part 3 – New Entry

ISOEUGENOL

Warning statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

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

The committee also advised an implementation date of **1 October 2017** to allow industry to make the necessary changes to product labelling.

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

The reasons for the advice comprised the following:

- Isoeugenol has moderate acute toxicity consistent with Schedule 6 criteria. Isoeugenol is a skin and eye irritant at 1% and a strong sensitiser at low concentrations (EC3 0.54%). There is evidence of carcinogenicity in male mice and possible carcinogen in female mice and male rats.
- Isoeugenol is used widely internationally in a large range of products including foods, therapeutic, household and cosmetic products.
- Risk can be mitigated with appropriate warning and first aid statements.

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)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to amend Schedule 6 and Schedule 5 for isoeugenol and to create new entries for isoeugenol in Appendix E/F. The proposed Schedule entry is as follows:

Schedule 6 – Amend Entry

ISOEUGENOL **except**:

a) when included in Schedule 5; or

b) in preparations not intended for skin contact containing 10 per cent or less of isoeugenol; or

c) in preparations intended for skin contact containing 0.02 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 containing 10 per cent or less of isoeugenol.

Appendix E, Part 2 – New Entry

ISOEUGENOL

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, Part 3 – New Entry

ISOEUGENOL

Warning statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

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

The proposed implementation date is **1 October 2018**.

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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Isoeugenol has moderate acute toxicity consistent with Schedule 6 criteria. Isoeugenol is a skin and eye irritant at 1% and a strong sensitiser at low concentrations (EC3 0.54%). There is evidence of carcinogenicity in male mice and possible carcinogen in female mice and male rats.
- Isoeugenol is used widely internationally in a large range of products including foods, therapeutic, household and cosmetic products.
- Risk can be mitigated with appropriate warning and first aid statements.
- The long implementation date is proposed in order to allow industry to make the necessary changes to product labelling.

3.7 *Aureobasidium pullulans* (strains DSM 14940 and DSM 14941)

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to create a Schedule 5 entry for *Aureobasidium pullulans (A. pullulans)* (strains DSM 14940 and DSM 14941) with no exemption cut-offs.

Current scheduling status and relevant scheduling history

A. pullulans is not currently scheduled and has not been previously considered for scheduling; therefore a scheduling history is not available.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 5 – New Entry

AUREOBASIDIUM PULLULANS.

The applicant's reasons for the request are:

- *A. pullulans* is a saprophytic fungus (feeding on dead and decaying organic matter) ubiquitous in the environment, readily isolated from soil, decaying vegetation, wood, air, shower curtains and other damp surfaces. Background levels of the organism on apple leaves for example are approximately 104 to 105 Colony Forming Units (CFU – i.e. viable organisms) per gram dry weight.
- The proposed fungicide consists solely of the freeze dried fermentation liquid containing the cultured strains of *A. pullulans* (DSM 14940 & 14941) and food grade constituents that act as drying and granulating aids.
- The fungicide is intended for use as a fungicide for the prevention of Botrytis cinerea infection of grapes through spray application, at a maximum rate of 1 kg/ha. XXX fungicide contains 5 x 109 CFU/g of *A. pullulans* mixed strains DSM14940 and DSM14941. The fungicide will be applied to vineyards as a foliar spray after dilution of the product (wettable granule) in water by vineyard workers. The fungicide is not proposed for home garden use or for use in urban environments.
- In support of the application the applicant has submitted acute toxicity studies on a European Registered product, XXXX, which contains the same two strains at approximately 2.5 x 109 CFU per strain making up 44%, with the balance of that product consisting of food grade non-active constituents.
- XXXX protect has low acute oral & dermal toxicity in rats (LD_{50} > 2000 mg/kg bw and > 6 x 109 CFU/kg, respectively) producing no deaths or signs of toxicity or infectivity at the limit doses. A 10% suspension of XXXXX in water had an LC_{50} of > 5170 mg/m^3 with no deaths and no clinical signs of toxicity or infectivity, however the actual concentration of the product in the air was only 497 mg/m^3 (1.5 x 109 CFU /m^3). The product was not a skin or eye irritant in rabbits but was a moderate skin sensitiser in Guinea pigs by the Buehler method. XXXXX was not genotoxic in the mouse in vivo micronucleus assay. When XXXXX was administered subcutaneously to rats at 2000 mg/kg bw (3 x 109 CFU/kg bw) 1/5 males had to be euthanised at day 5 due to massive inflammation at the injection site, but all other animals survived to scheduled sacrifice. In all animals, the spleen was visibly enlarged, and mature puss filled abscesses were present at the injection sites. These observations reflect both route of administration and the large quantity of foreign biological materials injected rather than infection or pathogenesis per se.
- *A. pullulans* strain DSM 14941 was not infectious, toxic or pathogenic when administered to rats by the oral (4 x 108 CFU), subcutaneous (107 CFU), or intratracheal routes (0.8 x 108 CFU) and viable

organisms did not persist at the site of administration or migrate to other tissues. Following intratracheal administration, viable spores were isolatable from the lungs only at 3 hours after administration but were not present at or after 3 days. Acute pulmonary inflammation was observed at 3 hrs and 3 days after application, progressing towards resolution by day 21.

- As *A. pullulans* is an ubiquitous non-pathogenic/infectious fungi that does not produce toxins or antimicrobials, studies of carcinogenicity, reproductive, developmental and neuro-toxicity are not required and have not been provided.
- When isolated from human clinical specimens *A. pullulans* is generally considered to be a laboratory contaminant, but under specific circumstances where the patient is debilitated or immune-suppressed some strains of this organism have infrequently been identified as pathogens. Pathogenic strains, where investigated, are able to grow at, or close to, body temperatures whereas strains isolated from the environment are generally unable to grow or survive at temperatures above 30 - 35°C or so, as has been shown to be the case for the two strains in the fungicide. No skin or pulmonary sensitisation or allergenic response of, or clinical findings in, any of the production or agricultural workers handling the fungus or XXXXX have been observed.
- XXXXX is registered in Europe and both the fungicide and XXXXX have been registered in the USA. Neither jurisdiction has considered the establishment of an ADI or ARfD to be required for Aureobasidium pullulans DSM 14940 & 14941.

Australian regulatory information

There is one product (registered medicine) on the Australian Register of Therapeutic Goods (ARTG) that contains *A. pullulans.* The indicated use of the product is for the diagnosis and treatment (hypo-sensitization therapy) of patients who experience allergic symptoms.

According to the TGA Ingredient database, *A. pullulans* is available for use as an Active Ingredient in Export Only, List Medicines, Over the Counter and Prescription Medicines. It is also available for use as a homeopathic ingredient in Listed Medicines and as an Excipient and Equivalent Ingredient in Prescription Medicines.[89]

A. pullulans is listed on the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017, permitted for use as an Active and Homeopathic preparation Ingredient. There are no specific requirements specified in the determination.

International regulations

A. pullulans is registered for use as a fungicide in the USA (January 2012) and Canada (December 2012) for the control of botrytis in grapes. It is also registered in New Zealand (June 2015) for control of fire blight in pip fruit and control of Psa in kiwifruit.

A. pullulans has been registered by the European Food Safety Authority (EFSA) for control of fire blight in pome fruit with appropriate personal protective equipment (PPE) requirements.

A. pullulans is unclassified in New Zealand.

Substance summary

The genus *Aureobasidium* includes between 14 and 26 named species depending on the consulted registry. Among these, *A. pullulans* is the only well-known species, of which two well documented varieties are associated with indoor environment and health problems: *A. pullulans var. pullulans* and

[89] Note: Only the name and definition of a substance have been reviewed to allow it to be included in the ingredient repository. The approval for use of the ingredient in therapeutic goods is a decision made by the relevant TGA regulatory area. This approval process may require submission of further information, for example safety data for the ingredient or for the finished goods, to meet legislative and regulatory requirements.

A. pullulans var. melanogenum. On the other hand, the fungal database of the International Mycological Association lists 6 varieties of *A. pullulans*.

Aureobasidium pullulans is an ubiquitous saprophyte mould, which is generally considered as an environmental contaminant. It is most common in temperate zones with numerous recordings from the British Isles and the USA, but also found in Canada, Alaska, Antarctica, Europe and Russia. It is found in forest soil, freshwater, aerial portions and on leaf surfaces of plants as well as on seeds (wheat), cereals (barley, oats) and some nuts such as pecans. It is also found as spoilage agent on fruits (pears, grapes and tomatoes) or in fruit drinks. It has been associated with the deterioration of pears and oranges in storage or in transit.

A. pullulans is commercially used for the production of pullulan, a linear homopolysaccharide of glucose (α-(1→6) maltotriose). Together with its derivatives, *Aureobasidium pullulans* has a range of uses in foods, pharmaceuticals, manufacturing, and electronics, such as un-derivatised films which readily dissolve in water and which can be used as edible food coatings.

Table 3.7A: General information

Property	***A. pullulans***
CAS names	N/A
CAS numbers	N/A
IUPAC and/or common and/or other names	*Aureobasidium pullulans* DSM 14940, CF10; *Aureobasidium pullulans* DSM 14941, CF40; Pullularia pullulans Fungus; *A. pullulans*
Approved Herbal Name (AHN)	*Aureobasidium pullulans*
Taxonomy	Kingdom: Fungi Phylum: Ascomycota Class: Dothideomycetes Order: Dothideales Family: Dothioraceae Genus: Aureobasidium Species: Pullulans

XXXXX consists solely of the freeze dried fermentation liquid containing the cultured strains of *A. pullulans* (DSM 14940 & 14941) and food grade constituents that act as drying and granulating aids.

The strains were isolated at the University of Konstanz in 1989 from apple leaves of an untreated apple plantation (*Malus sylvestris var. domestica* cv. "Golden Delicious") and were designated CF10 and CF40. The manufacturing code has designated CF10 as *Aureobasidium pullulans* DSM 14940, and CF40 as *Aureobasidium pullulans* DSM 14941.

Table 3.7B: Acute toxicity end-points for *A. pullulans* strains DSM14940 and DSM14941

Toxicity	Species	Result [90]	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000 mg/kg bw	Schedule 5 / Appendix B
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000 mg/kg bw	Schedule 5 / Appendix B
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	>5170 mg/m^3 for a 10% suspension in water	Schedule 5 / Appendix B
Skin irritation	Rabbit	Not irritant	Nil
Eye irritation	Rabbit	Not irritant	Nil
Skin sensitisation (Buehler)	Guinea Pigs	Moderate sensitiser	Schedule 5 or Schedule 6

A technical report for the toxicology of *A. pullulans* strains DSM14940 and DSM1494 was provided to the committee and the delegate.

Mutagenicity

Not mutagenic *in vivo* (mouse micronucleus test).

Public exposure

Specific toxicity, pathogenicity and infectiveness studies were not provided.

Pre-meeting public submissions

One (1) public submission was received, which supported the proposal due to purported low toxicological profile and that it is not an infective agent.

The public submission is available on the TGA website.

Summary of ACCS advice to the delegate

The committee advised that a new Appendix B entry be created.

Appendix B - New Entry

AUREOBASIDIUM PULLULANS (Strains DSM14940 and DSM14941).

The committee also advised an implementation date of **1 October 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; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

[90] Based on the product, XXXX, containing 2 x 10^9 CFU/g of each of DSM14940 and 14941.

The reasons for the advice comprised the following:

- There are no known cases of skin sensitisation or pulmonary hypersensitivity to the two strains of *A. pullulans* being considered.
- There is a wide range of benefits from the use of pullulans manufactured using *A. pullulans*. Pullulans is used in a wide range of products including in food, cosmetics, pharmaceuticals, electronics and biomedical applications.
- The toxicity of *A. pullulans* is very low to nil with no evidence of skin or eye irritancy. *A. pullulans* is not mutagenic, pathogenic or infective and does not product toxins or active metabolites. *A. pullulans* is a moderate skin sensitiser (Buehler method); however there are no known reports of occupational sensitisation despite industrial and farm use.
- Risk of sensitisation to *A. pullulans* can be mitigated through personal protective equipment controlled through APVMA labelling regulations.

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)
- Other relevant information

Delegate's interim decision

The delegate's interim decision is to create a new Appendix B for Aureobasidium pullulans. The proposed Schedule entry is as follows:

Appendix B - New Entry

AUREOBASIDIUM PULLULANS (Strains DSM14940 and DSM14941).

The proposed implementation date is **1 October 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; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- There are no known cases of skin sensitisation or pulmonary hypersensitivity to the two strains of *A. pullulans* being considered.
- There is a wide range of benefits from the use of pullulans manufactured using *A. pullulans*. Pullulans is used in a wide range of products including in food, cosmetics, pharmaceuticals, electronics and biomedical applications.
- The toxicity of *A. pullulans* is very low to nil with no evidence of skin or eye irritancy. *A. pullulans* is not mutagenic, pathogenic or infective and does not product toxins or active metabolites. *A.*

pullulans is a moderate skin sensitiser (Buehler method); however there are no known reports of occupational sensitisation despite industrial and farm use.

- Risk of sensitisation to *A. pullulans* can be mitigated through personal protective equipment controlled through APVMA labelling regulations.