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

April 2014

Notice under subsections 42ZXZS and 42ZCZX of the Therapeutic Goods Regulations 1990 (the Regulations)

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

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the November 2013 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#9);
- scheduling proposals initially referred to the November 2013 meeting of the Advisory Committee on Medicines Scheduling (ACMS#10);
- scheduling proposals initially referred to the November 2013 joint meeting of the ACCS and the ACMS (joint ACCS-ACMS#7);
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to the expert advisory committees

Pre-meeting public notice

- The first 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 29 August 2013 at <http://www.tga.gov.au/newsroom/consult-scheduling-acms-1311.htm>and the second public notice was published on 17 October 2013 at <http://www.tga.gov.au/newsroom/consult-scheduling-accs-1311.htm>.
- Redacted versions of the public submissions received in response to this invitation were published on 3 March 2014 at <http://www.tga.gov.au/industry/scheduling-submissions-1311.htm#.Uzt1MW-i1cY>.

Interim decisions

- The delegates' interim decisions on recommendations by the ACCS#9, ACMS#10 and joint ACCS-ACMS#7 were published on 27 February 2014 at <http://www.tga.gov.au/industry/scheduling-decisions-1402-interim.htm#.Uzt1pm-i1cY>. This public notice also invited further comment from the applicant and from those parties who made a valid submission in response to the original invitation for submissions.

- 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, may not be considered by the delegate.
- Redacted versions of public submissions received in response to the interim decisions will be published in April 2014at <http://www.tga.gov.au/industry/scheduling-submissions.htm.

Final decisions

- In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, the delegate may make a final decision either confirming varying or setting aside the interim decision, but only after considering any valid submissions received in response to the interim decisions.

Matters not referred to an advisory committee

A delegate may decide not to refer a scheduling application to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer an application to an expert advisory committee for advice, the delegate considers the scheduling guidelines as set out in the Scheduling Policy Framework (SPF) accessible at <http://www.tga.gov.au/industry/scheduling-spf.htm>.

Implementation

The SUSMP and its amendments are available electronically at the ComLaw website, a link to which can be found at <http://www.tga.gov.au/industry/scheduling-poisons-standard.htm>.

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
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods

Abbreviation	Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
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 for 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
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
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])

Abbreviation	Name
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])
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
STANZHA	States and Territories and New Zealand Health Authorities

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

Part A - Final decisions on matters referred to an expert advisory committee

1. Scheduling proposals referred to the November 2013 meeting of the Advisory Committee on Chemicals Scheduling (ACCS) – ACCS # 9

1.1 AMINOPYRALID

Scheduling proposal

On 23 August 2013, Office of Chemical Safety (OCS) requested that the delegate consider a proposal to amend the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) to include aminopyralid, present as the triisopropanolamine (TIPA) salt in Schedule 5. The testing provided by the applicant was not conducted by using 100 per cent aminopyralid TIPA and therefore, the OCS considers there is insufficient information to support a recommendation for a Schedule 5 entry for aminopyralid TIPA as a separate active constituent from aminopyralid to the scheduling delegate.

The applicant also proposed an alternative, which is to include the product in Schedule 5. Since scheduling is compound specific rather than product specific, it is not possible to include the applied product in Schedule 5 directly.

The product contains aminopyralid and is therefore currently classified as a Schedule 6 poison. Based on the acute toxicology profile of the product as demonstrated by the acute toxicity testing supplied by the applicant and given that there is a low hazard from repeated use, this classification is not considered appropriate.

The OCS recommends a new Schedule 5 entry for aminopyralid. This amended entry would result in a Schedule 5 classification for the product.

The delegate considered the proposal for referring this scheduling proposal to the Advisory Committee on Chemicals Scheduling (ACCS) was that, in accordance with section 4.2 of the Scheduling Policy Framework[1] (SPF, 2010), advice is required to be obtained from an expert advisory committee for all rescheduling proposals.

The delegate sought for the following specific advice from the ACCS:

- Does the ACCS support the scheduling proposal to amend the current Schedule 6 entry for aminopyralid to provide a cut-off to Schedule 5 at 0.5 per cent for the product under consideration in the OCS report?

- Noting that the Schedule 6 entry for aminopyralid appears to be primarily driven by its severe eye irritancy, rather than other aspects of its toxicity profile (which appear to be consistent with Appendix B), does the ACCS consider that a further review of aminopyralid scheduling is warranted?

Noting that the toxicity profile of picloram, the other active component of the product, is possibly more consistent with SPF factors for Schedule 5 than Appendix B, and that the Appendix B status for picloram was conferred in 1987, is there any basis for review of the schedule entry for picloram? There are 89 products containing picloram on PUBCRIS[2], although many of them may not be impacted by a scheduling change because of multiple active ingredients.

Substance details

The product contains the active constituents, aminopyralid and picloram which are structurally related to compounds such as triclopyr, fluroxypyr and 2,4-D. Aminopyralid causes epinasty (curled leaves) followed by necrosis.

The product is intended for use by direct application to control woody weeds, wild tobacco trees, rhizomatous plants, wandering jew and herbaceous weeds.

Aminopyralid is a synthetic auxin and picloram is an auxin mimic.

Acute toxicity

The summary of acute toxicity studies is shown in the table below.

End-point of acute toxicity	Aminopyralid	Picloram	Product	SPF*
Acute oral toxicity LD_{50} (mg/kg bw)	>5000	3536 (Female)	>5000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	>5000	>2000	>5000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/kg bw/4h)	>5500	>1630	>5080	Low toxicity/moderate to high toxicity
Skin irritation	Non-irritant	Slight irritant	Non-irritant	
Eye irritation	Severe irritant	Slight - moderate irritant	Slight irritant	
Respiratory irritation	No data	No data	No data	
Skin sensitisation	Non-sensitiser	Sensitiser	Non-sensitiser	

**Scheduling Policy Framework for Medicines and Chemicals (2010)*

Repeat-dose toxicity

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

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

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

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

Neurotoxicity

A chronic neurotoxicity study found occurrences of sinusoidal dilatation within the pars distalis of the pituitary gland in male and female rats at dose levels of 1000 mg/kg bw/d.

Genotoxicity

A range of genotoxicity studies were performed with aminopyralid and aminopyralid TIPA. The only effect was a weak clastogenic response in rat lymphocyte cultures treated continuously with aminopyralid for 24 hours without activation by S9.

Reproduction and developmental toxicity

A reproductive study in rats found no effects of aminopyralid in terms of reproductive or neonatal toxicity at 1000 mg/kg bw/d, the highest dose level tested. A variety of developmental studies using aminopyralid or aminopyralid TIPA found no effects on foetal development, with the possible exception that certain skeletal variations were more common in foetuses from rats treated with aminopyralid TIPA, although there were no dose-response effects.

A neurotoxic effect, viz. incoordinated gait, was first observed in developmental studies on aminopyralid involving rabbits. A study using aminopyralid TIPA found three cases of transient incoordination, associated with repetitive chewing behaviour in two of the three cases, among 26 rabbits at a dose level of 150 mg/kg bw/d. A no observed effect level (NOEL) for maternal effects was established at 50 mg/kg bw/d of aminopyralid TIPA (equivalent to 26 mg/kg bw/d of aminopyralid).

Scheduling status

Aminopyralid is currently listed in Schedule 6.

Scheduling history

Aminopyralid was first considered by the NDPSC at their June 2005 meeting as a new active constituent.

The committee considered an application for the registration of a herbicide product, an emulsion, oil in water, formulation containing 10 g/L of the new active ingredient aminopyralid, present as the triisopropanolamine (TIPA) salt. As part of this application for the registration of the herbicide product, approval was also sought for the new active constituent aminopyralid.

The committee noted the following points raised by the OCS evaluation report for consideration.

- Aminopyralid has low oral toxicity in rats with an LD_{50} > 5000 mg/kg (relative to body mass) in males and females. It has a low dermal toxicity (LD_{50} > 5000 mg/kg) in male and female rats and low inhalation toxicity (LC_{50} > 5500 mg/m^3) in male and female rats. It is non-irritating to

rabbit skin and non-sensitising to guinea pig skin. Aminopyralid is, however, a severe eye irritant in rabbits.

- Oral repeat dose studies produced a range of effects, but common effects at lower doses were increased caecum size and weight, increased urine volume, decreased urine specific gravity, decreased urine pH.
- No carcinogenic effects were observed.
- No reproductive, neonatal, foetotoxic or teratogenic effects were observed.
- The only genotoxic effect was a weak clastogenic response in rat lymphocyte cultures treated with aminopyralid for 24 h without activation by S9. A range of other studies were negative: Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay; Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay; mouse bone marrow micronucleus test; (with product containing 41.3 per cent aminopyralid TIPA in aqueous solution) Salmonella-Escherichia *coli*/mammalian-microsome reverse mutation assay; *in vitro* chromosomal aberration assay utilising rat lymphocytes; Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward mutation assay; mouse bone marrow micronucleus test.
- Transient incoordination was seen in pregnant rabbits at single doses of aminopyralid TIPA of 150 mg/kg.
- Overall, the noteworthy toxicological effects of aminopyralid were severe eye irritancy and transient incoordination in pregnant rabbits shortly after dosing with 150 mg/kg (equivalent to 78 mg/kg aminopyralid). Given the potential for eye irritation, NDPSC in 2005 considered that aminopyralid be placed in Schedule 6.
- An aqueous gel formulation containing 0.5% aminopyralid has a low oral LD_{50} of 5000 mg/kg in female rats, a low dermal toxicity with an LD_{50} > 5000 mg/kg in male and female rats, and low inhalation toxicity with an LC_{50} > 5260 mg/m^3 in male and female rats. It is a moderate skin irritant in rabbits but not a skin sensitiser in guinea pigs. It is a severe eye irritant in rabbits.

The committee considered that the severe eye irritancy of an aqueous gel formulation may be related to the presence of aminopyralid, despite its relatively low concentration in this product. The other active ingredient in the formulation was only a slight eye irritant. However other excipients undoubtedly contributed to the severe eye irritancy of the formulation. The eye irritancy of aminopyralid was the principal toxicological finding for placing to it in Schedule 6. The company had not provided any data to support a cut-off to a lower schedule.

The NDPSC agreed that based on the assessment of toxicity and having regard to severe eye irritancy, aminopyralid be included in Schedule 6 of the SUSDP.

Public pre-meeting submissions

No public submissions were received for aminopyralid.

ACCS advice to the delegate

The committee recommends that the current Schedule 6 entry for aminopyralid be amended to provide a cut-off to Schedule 5 at 0.5 per cent with an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- Significantly reduced eye irritation.
- Some scheduling control retained as the product is in the domestic market.
- Water soluble gel formulation.

Delegate's interim decision

The delegate agrees with the advice of the ACCS that the current Schedule 6 entry be amended to allow an aqueous gel formulation containing 0.5% aminopyralid to be down-scheduled to Schedule 5. While the toxicity profile of the pure chemical is consistent with the SPF factors for listing in Schedule 6, the reduction in eye irritancy associated with the diluted preparation is consistent with SPF factors for Schedule 5. The new Schedule 5 entry is specific for preparations containing 0.5% or less of aminopyralid in an aqueous gel formulation.

The delegate agrees to an implementation date of 1 June 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: c) the toxicity of the substance and d) the dosage, formulation, labelling, packaging and presentation of a substance.

Submissions on interim decision

One public submission was received. The submission indicated that as the delegate's interim decision on aminopyralid had no impact on therapeutic goods, it had no further comments in relation to the delegate's interim decision on the substance.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision. The delegate has proposed an early implementation date of 1 June 2014 to facilitate marketing of the product when registered by the APVMA.

Scheduling entry

SCHEDULE 6 – RESCHEDULE

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

SCHEDULE 5 – NEW ENTRY

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

1.2 PHOSPHONIUM, TRIBUTYLOCTYL-, CHLORIDE (1:1)

On 29 August 2013, the delegate received an application proposing the inclusion of phosphonium, tributyloctyl-, chloride (1:1) in Schedule 7. The Schedule 7 proposal was based on data which suggested that the substance has moderate to high acute oral toxicity and is corrosive having the potential to cause severe eye damage. In addition, the substance was classified as being toxic in contact with skin.

The delegate referred the scheduling proposal to the ACCS as phosphonium, tributyloctyl-, chloride (1:1) as data provided regarding the substances toxicological profile warrants scheduling.

While the toxicological profile appears to be consistent with the Scheduling Policy Framework[1] (SPF, 2010) factors for listing in Schedule 7 (based on corrosivity and other acute toxicity), there is little (if any) potential for the general public to be exposed to the chemical or products containing it.

The delegate questioned the need for this chemical to be listed in any schedule of the SUSMP given the limitation of its use to industrial settings.

The delegate sought ACCS advice to confirm this opinion and asked that the committee considers the following:

- Does the ACCS support the delegate's proposal that listing this chemical in any of the schedules of the SUSMP is unnecessary, given its presumed exclusive use in an industrial or manufacturing setting? In an industrial setting, it is presumed the Global Harmonized System or the National Occupational Health and Safety Commission labelling provisions would apply.
- If not, does the ACCS support listing in Schedule 7? There appears to be some precedent for listing highly toxic industrial chemicals in S7 (e.g. vinyl chloride).
- Is there a need to develop Appendix E, F and J statements?

Substance details

Phosphonium, tributyloctyl-, chloride (1:1) is an extractant for the removal of impurities during metal refining at ≤73 per cent concentration in aqueous solution.

End-point of acute toxicity	Phosphonium, tributyloctyl-, chloride (1:1)	SPF*
Acute oral toxicity LD_{50} (mg/kg bw)	50-300	Moderate to highly toxic
Skin irritation	Corrosive	[redacted]

**Scheduling Policy Framework for Medicines and Chemicals (2010)*

Due to the corrosive nature of the chemical, acute dermal, acute inhalation, and eye irritancy studies have not been conducted. However, for corrosive substances, the risk of severe damage to the eyes is considered implicit. In addition, the notifier has classified the chemical (at ≤ 73 per cent concentration in aqueous solution) as being toxic in contact with skin.

Repeat-dose toxicity

A repeat dose oral toxicity study (chemical at ≤73 per cent concentration in aqueous solution) established a NOEL of 5 mg/kg bw/day. Toxicological significant effects that were recorded at mid- and/or high dose (30 and 75 mg/kg bw/day) levels included increased salivation and noisy respiration. Reduced kidney, liver and thymus weights were also noted in males treated with 75 mg/kg bw/day. However, these results were not considered by the study authors to be of clinical significance as they were within historical ranges.

Statistically significant increases in haematocrit and haemoglobin were observed in all female treatment groups and there was a statistically significant increase in platelet levels in females treated with 75 mg/kg bw/day. The study authors noted that these results were within historical ranges and

[1] [1] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

therefore considered them to be toxicologically insignificant. There were no noted effects for blood chemistry parameters.

Genotoxicity/Mutagenicity

Bacterial reverse mutation and in vivo micronucleus studies on the notified chemical were negative.

Observations in humans

Not reported.

Occupational Health and Safety

The primary risks associated with worker exposure will be due to the corrosive and sensitising nature of the chemical (and the toxicity of the chemical via the dermal route). However, dermal and ocular exposure is expected to be minimised by the wearing of PPE. While the chemical is considered to be toxic via the oral route, ingestion is unlikely under the proposed use scenario. Exposure to the chemical via inhalation is not expected under the proposed use scenario.

Provided that control measures are in place to minimise worker exposure, the risk to the health of workers from use of the chemical is not considered to be unreasonable.

Public health

The chemical is intended for use in industrial settings by trained workers. When used in the proposed manner, the risk to public health from the chemical is not considered to be unreasonable.

Scheduling status

Phosphonium, tributyloctyl-, chloride (1:1) has not been specifically scheduled.

Scheduling history

Not applicable.

Public pre-meeting submissions

One public submission was received.

The submitter did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that phosphonium, tributyloctyl-, chloride (1:1) does not require a schedule listing.

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

- Industrial chemicals are managed under occupational, packaging and transport legislation.
- Solely industrial only. No domestic use flagged. No likelihood of public access.

Delegate's interim decision

The delegate accepts the advice of the ACCS that, given the proposed use patterns for phosphonium, tributyloctyl-, chloride (1:1) are mostly industrial with little potential for public

exposures, listing in the Schedules of the SUSMP is not needed to protect public health. Industrial uses are adequately regulated under other legislation.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[2];
- Other relevant information.

Submissions on interim decision

One public submission was received. The submission indicated that as the delegate's interim decision on the substance had no impact on therapeutic goods, it had no further comments on the delegate's interim decision.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.3 PYRIDINE, 2-CHLORO-6- (TRICHLOROMETHYL)

Scheduling proposal

On 16 September 2013, the delegate received an application proposing the inclusion of pyridine, 2-chloro-6-(trichloromethyl)- in Schedule 6 based on the following reasons as outlined in the Scheduling Policy Framework for Medicines and Chemicals (SPF, 2010):

- Acute oral and dermal toxicity data indicate the chemical has moderate to high toxicity which may cause death or severe injury if taken internally or in contact with skin or eyes; this profile is consistent with Schedule 6 factors.
- Skin irritation data indicate the chemical in either encapsulated or non-encapsulated form is a slight irritant which meets the factors for listing in Schedule 5.
- Eye irritation data indicate the chemical in either encapsulated or non-encapsulated form is a slight to moderate irritant which meets the factors for listing in Schedule 5.

[2] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

- Skin sensitisation data indicate the chemical is a moderate skin sensitiser which meets the factors for listing in Schedule 6.
- Carcinogenicity data indicate the chemical exhibits a moderate risk of producing irreversible toxicity which meets the factors for listing in Schedule 6.

Based on the data provided for the substance, the application also recommends including pyridine, 2-chloro-6-(trichloromethyl)- in Appendix F as the applicant believes that strong warnings and the use of distinctive packaging should apply to the substance.

The delegate sought the following specific advice from the ACCS:

- Given the proposed use pattern for this chemical, as a nitrogen stabiliser component of fertilizers, with limited direct public exposure potential, is listing in the SUSMP appropriate?
- If so, is the preferred chemical name for listing 2-chloro-6-(trichloromethyl)-pyridine or the marketing name nitrapyrin?
- Is Schedule 6 the most appropriate listing, or does the ACCS consider that the potential for carcinogenicity warrants inclusion in Schedule 7?
- Does the apparently lower acute toxicity profile of a micro-encapsulated (20 per cent) formulation warrant a scheduling exemption at this level?
- Noting that the application suggests hazard labelling for potential sensitisation and carcinogenicity for mixtures >1 per cent, is any scheduling cut-off appropriate? [The application notes that ≥1per cent Conc. <10 per cent: H317, H351. Skin sensitisation (Category 1): H317 – May cause an allergic skin reaction and Carcinogenicity (Category 2): H351 – Suspected of causing cancer].
- To what extent is there likely to be conflict between any labelling controls applied through scheduling and hazard labelling imposed under workplace labelling controls (GHS)?
- Given that the agricultural application pattern is comparable to that for pesticides, but the chemical is apparently not eligible for registration by the APVMA, will mixer-loaders, appliers and bystanders be adequately informed of the potential risks by Appendix E & F statements? If so, what Appendix E & F statements does the ACCS recommend?

Substance details

The chemical (at ≤22 per cent concentration) is intended to be used as a nitrogen stabiliser for use on crops and pastures. The chemical acts by delaying nitrification of ammonia and urea nitrogen fertilisers through the inhibition of soil bacteria. The chemical will be introduced (and used) in a microencapsulated form (suspension capsules), which is designed to decrease the loss of the notified chemical through volatilisation during use. The capsules are within the respirable range (<10 μm).

Pyridine, 2-chloro-6-(trichloromethyl)- acts by delaying nitrification of ammonia and urea nitrogen fertiliser through the inhibition of soil bacteria. It will be mixed with other products (e.g. fertiliser or pesticides) and then applied to crops or pastures, most likely via low boom spray.

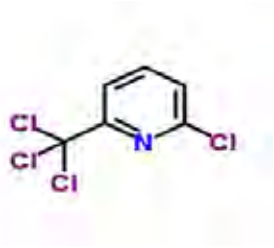

Figure 1. Structure of 2-chloro-6-(trichloromethyl)-pyridine

End-point of acute toxicity	Pyridine, 2-chloro-6-(trichloromethyl)-	SPF*
Acute Oral Toxicity LD_{50} (mg/kg bw)	< 252 in guinea pigs, 1072 in rats	Moderate to high toxicity
Acute Dermal Toxicity LD_{50} (mg/kg bw)	848	Moderate to high toxicity
Acute Inhalation Toxicity LD_{50} (mg/m^3)	Inconclusive	Inconclusive
Skin irritation	Slight irritant	[redacted]
Eye irritation	Moderate irritant	
Respiratory irritation	Inconclusive	
Skin sensitisation	Sensitiser	

**Scheduling Policy Framework for Medicines and Chemicals (2010)*

Repeated dose toxicity

Oral

In a subchronic oral study, rats (10/sex/dose) were administered dietary doses of the notified chemical at 0, 10, 40 or 120 mg/kg bw/day. The no observed adverse effect level (NOAEL) was established as 10 mg/kg bw/day in this study, based on increased liver weights, nephrosis and tubule degeneration/regeneration in males treated at 40 mg/kg bw/day and above, and brown pigment in the convoluted tubule in females treated at 40 mg/kg bw/day and above.

In a subchronic oral study, mice were administered dietary doses of the notified chemical up to 800 mg/kg bw/day. Mortalities were observed in all 600 mg/kg bw/day (10 males and 10 females) and 800 mg/kg bw/day (10 females) groups. The females treated at 800 mg/kg bw/day died mostly within the first week of treatment. The males and females treated at 600 mg/kg bw/day died between one to two months of treatment. Male groups that completed 3 months treatment were administered 0, 200, 300 or 400 mg/kg bw/day (10/dose), and females were administered 0, 200 or 400 mg/kg bw/day (10/dose). There were numerous treatment related haematology changes in males and females treated at 400 mg/kg bw/day. Additionally there were increases in aspartate aminotransferase in males treated at 400 mg/kg bw/day, and increases in alanine aminotransferase in males and females treated at 400 mg/kg bw/day and in males treated at 300 mg/kg bw/day. There were dose related increases in liver weights in all treatment groups, accompanied by dose related hypertrophy. Other histopathological findings were in the liver and were observed at 300 mg/kg

bw/day and above. Liver toxicity was evident from this study and a lowest observed effect level (LOAEL) was established as 200 mg/kg bw/day based on effects observed at the lowest dose.

Dermal

In a 21-day dermal study, rabbits (5/sex/dose) were administered the notified chemical at 0, 100, 500 or 1 000 mg/kg bw/day. The NOAEL for systemic toxicity was 500 mg/kg bw/day based on increased liver weights at 1000 mg/kg bw/day. Slight to well defined erythema and oedema were observed in all treated groups, indicating dermal irritation.

Inhalation

The acute inhalation study tested a vapour concentration of ~0.03 mg/L. Based on the low concentration of the notified chemical tested in this study, a conclusion on the potential for acute inhalation toxicity (and relevant hazard classification) could not be drawn. However, it is noted that the notified chemical has an airborne exposure standard: TWA = 10 mg/m3, STEL = 20 mg/m3.

Mutagenicity/Genotoxicity

Pyridine, 2-chloro-6-(trichloromethyl)-l is not considered to be mutagenic in vivo based on negative results in two separate bacterial reverse mutation tests, in an in vitro mammalian cell gene mutation test, in an in vivo unscheduled DNA synthesis study and in an in vivo micronucleus study in mice.

Carcinogenicity

Carcinogenic effects (in the liver, stomach, epididymis and Harderian gland) were noted in mice treated with pyridine, 2-chloro-6-(trichloromethyl)- at 125 and 250 mg/kg bw/day. In 2005, the notified chemical was classified by the US EPA as 'Likely to be carcinogenic to humans', The epididymal sarcomas that were observed in mice administered the notified chemical at 125 (2/50) and 250 mg/kg bw/day (4/50), but not in the concurrent control group, were originally considered to be treatment related by the US EPA and formed part of the basis for carcinogenicity classification. Epididymal tumours were also observed in another 2-year carcinogenicity study in mice treated with the notified chemical at 25-75 mg/kg bw/day (at 75 mg/kg bw/day; 1/50 Leydig cell tumour) and in control animals (2/50 Leydig cell tumour and 1/50 histiocytic sarcoma).

Samples from these studies were recently re-evaluated by a pathology working group by immunohistochemical staining. The tumours that were originally classified as Leydig cell tumours by the original study pathologists, were subsequently classified by the pathology working group as histiocytic sarcomas (i.e., 3/50 in controls and 1/50 in the 75 mg/kg bw/day group). Similarly, the working group confirmed that the epididymal sarcomas that were observed in the mice treated at 125 and 250 mg/kg bw/day were histiocytic sarcomas. The US EPA agreed with the findings of the working group, and considered that when the data from the two studies are combined, the occurrence of the epididymal histiocytic sarcomas was not related to the notified chemical (US EPA, 2012a).

Regarding the treatment-related increased incidences of liver tumours in mice administered the notified chemical at 125 and 250 mg/kg bw/day, mechanistic data (as discussed above) were submitted to the US EPA to support the proposed mode of action of tumour formation [i.e., induction through activation of the constitutive androstane nuclear receptor (CAR)]. The US EPA considered that cell proliferation and PROD induction data did not support the proposed mode of action for the induction of liver tumours and that the tumours cannot be excluded from being relevant for human cancer hazard assessment. However, it was considered that evidence for the reversibility of the key events had been provided, indicating that a threshold exists for the induction of the liver tumours (US EPA, 2012a).

Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, as a Category 2 carcinogen.

Developmental toxicity

Studies concluded that pyridine, 2-chloro-6-(trichloromethyl)- was not teratogenic under the conditions of the study, as foetal toxicity was only observed at maternally toxic doses.

Reproductive Toxicity

Studies concluded that pyridine, 2-chloro-6-(trichloromethyl)- was not a reproductive toxicant.

Scheduling status

Pyridine, 2-chloro-6-(trichloromethyl)- is not specifically scheduled.

Scheduling history

Not applicable

Public pre-meeting submissions

Two public submissions were received.

One submission noted that although the delegate's proposal did not appear to have any impact on therapeutic goods, the submission requested that the drafting of any scheduling amendment should be in such a way to avoid any unintended impact on therapeutic goods.

The other submitter did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that 2-chloro-6-(trichloromethyl)-pyridine be included in Schedule 6.

The ACCS recommended an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- The risk is the potential toxicity to end users. The benefit is enhancing the efficacy of agricultural fertilizers.
- Concern of the potential leakage of the commercial products getting to the domestic market.
- Toxicity profile is consistent with S6 factors in SPF.
- Microcapsule presentation reduces human exposure.

Delegate's interim decision

The delegate accepts the advice of the ACCS that a new listing in Schedule 6 be created for 2-chloro-6-(trichloromethyl)-pyridine, with no exemption cut-off. The toxicity profile of the chemical is consistent with SPF factors for listing in Schedule 6, with acute toxicity, skin/eye irritancy and sensitisation potential and some evidence of carcinogenic potential driving this classification. The

delegate also notes ACCS advice that the microencapsulated formulation may ameliorate skin-eye irritancy potential to some extent, but this formulation approach does not warrant a lower schedule. The delegate also notes that the ACCS did not propose allocating First Aid, Warning Statements or Safety Directions via listing in Appendices E & F. The ACCS advice was that such label warnings would be addressed under GHS labelling code provisions.

The delegate agrees with the implementation date being 1 June 2014.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[3];
- Other relevant information.

Submissions on interim decision

One public submission was received. The submission indicated that as the delegate's interim decision would not have impact on therapeutic goods, it had no further comments on the delegate's interim decision.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

SCHEDULE 6 – New entry

2-CHLORO-6-(TRICHLOROMETHYL)-PYRIDINE.

1.4 SULFITES

Scheduling proposal

On 17 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) Tier II human health assessment process, recommended that the delegate consider a proposal to include sulfites (salts of sulfurous and disulfurous acids) in Schedule 5 with potential lower concentration cut-off level.

[3] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

The NICNAS IMAP report includes the following chemicals:

- Sulfurous acid, monosodium salt
- Disulfurous acid, disodium salt (1:2)
- Disulfurous acid, disodium salt
- Sulfurous acid, disodium salt
- Sulfurous acid, dipotassium salt
- Sulfurous acid, monoammonium salt
- Sulfurous acid, diammonium salt
- Disulfurous acid, dipotassium salt.

The NICNAS proposal for these substances is based on the following considerations:

- The general public may be exposed to the chemical through oral, dermal and inhalation routes when using cosmetic/domestic products containing these chemicals.
- New Zealand and the European Union (EU) have restricted the use of these chemicals in cosmetics. The EU also has restrictions on using sodium bisulfite (CAS no: 7631-90-5) in plastics with food contact use.
- The characterised critical health effects (such as severe eye irritation and liberating toxic gas when in contact with acid) have the potential to pose an unreasonable risk under the uses identified. The risks could be mitigated by implementing concentration limits for certain uses to reduce exposure.
- Sensitivity to sulfites is more likely to be related to exposure via food and beverages than to circumstances related to industrial use

The IMAP report stated that the EU Scientific Committee on Cosmetic products and Non Food Products (SCCNFP) concluded that sulfites (as free SO2) do not pose any unacceptable risk to human health when used in cosmetic formulations at the intended use concentrations (up to 0.67 per cent in oxidative hair dye products, up to 6.7 per cent in hair waving/straightening products, up to 0.45 per cent in self-tanning products for the face and up to 0.40 per cent in self-tanning products for the body).

The delegate considered the proposal for creating a new Schedule 5 for sulphites, i.e. salts of sulfurous and disulfurous acids, with appropriate amendments to the current Schedule 5 entry for sodium metabisulfite, to align with EU restrictions on the use of sulfites in cosmetics and to consider appropriate cut-offs to exemption from the proposed Schedule 5 entry.

Sodium metabisulfite is the only sulfite (salt of sulfurous or disulfurous acid) currently listed (Schedule 5) in the SUSMP with a cut-off to exempt at 10 per cent. The NICNAS IMAP report addresses the need to create a new Schedule 5 entry covering all the sulfites evaluated under the IMAP program, primarily to address the potential for inhalational irritancy associated with their use as preservatives in a variety of consumer products. The intent is to align Australian scheduling restrictions with those in EU Health and Consumers Cosmetic regulations (Annex III/99 and VI/9). Because of the potential impact on Australian industry associated with this scheduling proposal, the advice of the ACCS is required.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support the need for new scheduling restrictions on consumer products containing sulfites as a preservative? Note that because of the general Appendix A exemption for food additives in food, this should not impact on those uses.
- Can the ACCS propose a suitable cut-off to exempt from such an entry in Schedule 5 (noting that the current sodium metabisulfite entry has a 10 per cent cut-off)?
- Is implementation of the NICNAS-proposed restrictions on use of sulfites in cosmetics best achieved through drafting a new specific entry in Appendix C, or should the proposed Schedule 5 entry provide a sufficient level of control? Does the ACCS support listing in Schedule 5 under the generic name sulfites, rather than the full list of names included in the NICNAS IMAP report?

Is there a need for Appendix E and F statements for sulfites when included in Schedule 5? For sodium and potassium metabisulfite these statements are inconsistent in the current SUSMP. Appendix E First Aid statements for the potassium salt are A (only), while the sodium salt requires A and G3; the Appendix E warning statements for both the potassium and sodium salts are 5, 26, with safety directions 1,4, but for the sodium salt, they are only applicable to preparations containing 50 per cent or more. Use of SD 4 (avoid contact with skin) seems inappropriate if applicable to cosmetic products.

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=187.

Scheduling status

The above sulfites are not currently scheduled.

Sodium metabisulphite and potassium metabisulphite (both of which belongs to the group of sulfites) are scheduled as follows:

SCHEDULE 5

SODIUM METABISULPHITE when packed for domestic use **except** in preparations containing 10 per cent or less of sodium metabisulphite.

POTASSIUM METABISULPHITE when packed for domestic use except in preparations containing 10 per cent or less of potassium metabisulphite.

Scheduling history

A scheduling history for the sulfites is not available.

Public pre-meeting submissions

Three submissions were received.

One submission indicated that sulfites are naturally occurring in food and are also commonly added to food as preservatives. Sulphites are also used in medicines. The submission noted that sulphites in cosmetics can be considered in isolation without considering the prevalent nature of sulphites in foods, beverages and medicines. There are a significant number of individuals with sulfite allergies, serious reactions to sulfites are rare and ingredient labelling disclosure (required by the Australian

Competition and Consumer Commission) should inform those individuals suffering from sulfite allergies. This submission did not support scheduling of sulfites.

Another indicated that some of the agenda items include broad substance such as 'sulfites' which a search of the TGA e-BS site shows are present in many different salts and derivatives and are also included in therapeutic goods.

The submission expressed concern that some therapeutic goods regulated by the TGA may inadvertently be affected by the proposed amendments and urges the ACCS to consider that:

- Amendments to schedules for any of the chemicals should be carefully drafted and worded in such a way that therapeutic goods are excluded.
- Care should be taken so that entries are as specific as possible so as not to affect all salts and derivatives (unless clearly intended), as some salts and derivatives of substances may be present in therapeutic goods.

The last submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that sulfites do not require a schedule listing and that the current scheduling of sodium metabisulphite remains appropriate.

Delegate's interim decision

The Delegate accepts the advice of the ACCS that there is no need to amend the current schedule 5 entries for sodium and potassium metabisulfites, with their current exemption levels at 10%, nor to create additional schedule entries for the other listed salts of sulfurous and disulfurous acids (or a more generic entry covering all salts of these acids). The delegate notes the intent of the NICNAS recommendation to limit the use of these SO2-generating preservatives in cosmetics and other consumer products, but it also notes the potential for a more generic schedule entry to inadvertently capture therapeutic goods that use sulphur dioxide (SO_2) as a preservative. The delegate notes ACCS advice that there is insufficient evidence of public health concerns associated with long and widespread use of SO2-generating preservatives in cosmetics and other consumer products and that the use of the Schedules to regulate uses beyond existing controls over sodium and potassium metabisulfites is not warranted.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;

- Scheduling factors[4];
- Other relevant information.

Submissions on interim decision

Two public submissions were received. Both submissions support the delegate's decision of not to amend the current Schedule 5 sodium and potassium metabisulfites entries.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.5 BENZIDINE-BASED AZO DYES

Scheduling proposal

On 29 August 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, requested that the delegate consider a proposal to include a group of 11 benzidine-based dyes in Appendix C. The basis for this recommendation is that benzidine-based dyes have the characteristic diazotized benzidine structure but differ with respect to the chemical groups attached at the diazo linkages. All the chemicals are expected to be metabolised *in vivo* to benzidine (CAS No. 92-87-5), a known human carcinogen. Critical health effects of these chemicals are carcinogenicity, developmental and reproductive toxicity. These chemicals have similar uses.

The delegate's reason for referring this scheduling proposal to the ACCS was that this (referral from the NICNAS IMAP program relates to a group of diazotized benzidine derivatives) chemical is likely to be a component of dyes and stains. NICNAS suggests that the toxicological profile of the chemical warrants scheduling. While the toxicological profile appears to be consistent with the Scheduling Policy Framework factors for listing in Schedule 7 (based on their mutagenicity and carcinogenicity profile and ability to be metabolised to benzidine, a known human carcinogen), listing in Appendix C is another option. The advice of the ACCS was requested to confirm this scheduling proposal.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support listing of benzidine-based dyes in Schedule 7, or is a listing in Appendix C more appropriate? The implied objective of the NICNAS IMAP report is to effectively 'ban' the use of these benzidine-based dyes in Australia.
- Since the NICNAS IMAP report lists eleven separate dyes in this grouping, is it necessary to list each chemical separately, or will a generic entry 'benzidine-based dyes' suffice?
- There is no current listing of the known human carcinogen benzidine in any schedule (possibly because there are no commercial products containing this chemical. Is a listing for benzidine also warranted in Schedule 7 or Appendix C?
- What is the potential regulatory impact of scheduling in the way proposed? Are there likely to be any products in retail or domestic use that could be affected?

[4] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

- Is there a need to develop specific Appendix E & F statements (and Appendix J if listed in S7)? If so, what does the ACCS suggest?

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=513>.

Scheduling status

Benzidine-based substances are not specifically scheduled.

Scheduling history

Not applicable.

Public pre-meeting submissions

Two submissions were received.

The first submission did not support the proposal to include benzidine and its salts in Schedule 7. The submitter noted that benzidine and its salts are regulated in jurisdictions that have adopted the Model Work Health and Safety legislation, since it is a prohibited carcinogen. They also noted that it did not believe that benzidine or its salts are being used in any formulated chemical products in Australia. On this basis, and based on the hazard posed by the substance, it supports including benzidine and its salts (excluding derivatives) in Appendix C with a scheduling cut-off of 0.1 per cent to align with the Model Work Health and Safety Regulations. In addition, it did not support including all benzidine derived dyes in Appendix C. The submission raised concern that generic Appendix C Scheduling entry for all benzidine based dyes would have unintended consequences of banning currently useful substances, without properly considering the risks and benefits of each dye.

The second submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that benzidine-based dyes for domestic used be included in Schedule 7.

The committee also recommended an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- These are useful chemicals but, because they are metabolised to a known human carcinogen (benzidine), access for domestic use needs to be restricted.
- Concerns about carcinogenicity.

Delegate's interim decision

The delegate accepts ACCS advice that inclusion of benzidine-based dyes in Appendix C is not the most appropriate way of regulating the use of these substances. It is also noted that some of the dyes may have use in laboratory and analytical reagents, but that their carcinogenic potential, via

conversion to benzidine (a known human carcinogen), indicates they should not be used in products available in the domestic market. While there are stringent existing controls under Model Work Health and Safety legislation, and industry advises that they have been largely phased out of many uses, the delegate accepts ACCS advice that the specific dyes assessed in the NICNAS IMAP report should be listed in Schedule 7, based on their carcinogenic potential.

A nomenclature issue is raised by this scheduling proposal. It is not feasible to list the chemicals assessed as a group in the NICNAS without further specification of their individual names. Accordingly, the delegate proposes to create a generic entry for BENZIDINE-BASED DYES in Schedule 7, with additional sub-listing of the chemical names, dyestuff common names and descriptors, and possibly CAS numbers. The nomenclature issues should be further addressed during the consultation phase of this interim decision.

The delegate agrees to the implementation date of 1 June 2014.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[5];
- Other relevant information.

Submissions on interim decision

Two submissions were received.

One submission supported the delegate's interim decision. The submission indicated that the EU Cosmetics Regulation refer this substance as benzidine-based azo dyes and requested that an alignment of terminology with the EU may be helpful for industry.

The other submission indicated that as the delegate's interim decision on benzidine-based dyes had no impact on therapeutic goods, it had no further comments regarding the delegate's interim decision on this substance.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision, with a slightly modified listing nomenclature, as no evidence has been received to alter the substance of the interim decision. However, noting a comment about the utility of aligning the nomenclature used in schedule listing with EU Regulations, the delegate has decided to modify the name used in the Schedule 7 listing by adding the word 'AZO'. The delegate

[5] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

The name used in the primary schedule listing has been slightly modified to reflect that these are benzidine-based **azo** dyes.

Scheduling entry

SCHEDULE 7 – NEW ENTRY

BENZIDINE-BASED AZO DYES being:

2,2'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[N-(4-chlorophenyl)-3-oxobutanamide]
CAS No. 94249-03-3

Acid Red 85 (Acid Fast Red A)
1,3-Naphthalenedisulfonic acid, 7-hydroxy-8-[[4'-[[4-[[(4-methylphenyl)sulfonyl]oxy]phenyl]azo][1,1'-biphenyl]-4-yl]azo]-, disodium salt
CAS No. 3567-65-5

Direct Black 38
2,7-Naphthalenedisulfonic acid, 4-amino-3-[[4'-[(2,4-diaminophenyl)azo][1,1'-biphenyl]-4-yl]azo]-5-hydroxy-6-(phenylazo)-, disodium salt
CAS No. 1937-37-7

Direct Blue 2
2,7-Naphthalenedisulfonic acid, 5-amino-3-[[4'-[(7-amino-1-hydroxy-3-sulfo-2-naphthalenyl)azo][1,1'-biphenyl]-4-yl]azo]-4-hydroxy-, trisodium salt
CAS No. 2429-73-4

Direct Blue 6
2,7-Naphthalenedisulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[5-amino-4-hydroxy-, tetrasodium salt
CAS No. 2602-46-2

Direct Brown 2
5-[[4'-[(7-amino-1-hydroxy-3-sulfo-2-naphthalenyl)azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxy-benzoic acid disodium salt
CAS No. 2429-82-5

Direct Brown 95
Cuprate(2-), [5-[[4'-[[2,6-dihydroxy-3-[(2-hydroxy-5-sulfophenyl)azo]phenyl]azo][1,1'-biphenyl]-4-yl]azo]-2-hydroxybenzoato(4-)]-, disodium salt
CAS No. 16071-86-6

Direct Green 1
2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-3-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-6-(phenylazo)-, disodium salt
CAS No. 3626-28-6

Direct Green 6
2,7-Naphthalenedisulfonic acid, 4-amino-5-hydroxy-6-[[4'-[(4-hydroxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-3-[(4-nitrophenyl)azo]-, disodium salt
CAS No. 4335-09-5

Direct Red 28 (Congo Red)
1-Naphthalenesulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis[4-amino-, disodium salt

CAS No. 573-58-0

Direct Red 37
1,3-Naphthalenedisulfonic acid, 8-[[4'-[(4-ethoxyphenyl)azo][1,1'-biphenyl]-4-yl]azo]-7-hydroxy-, disodium salt
CAS No. 3530-19-6

1.6 2-AMINO-5-ETHYLPHENOL

Scheduling proposal

On 16 September 2013, the delegate received an application proposing inclusion of preparations containing more than 1 per cent of 2-amino-5-ethylphenol in Schedule 6.

The delegate's reason for referring this scheduling proposal to the ACCS was that this substance is likely to be an oxidative colorant component of hair dyes (at concentrations up to 1 per cent). The toxicological profile of the chemical warrants scheduling (based mainly on limited acute toxicity data, including irritancy and sensitisation potential) and that the toxicological profile appears to be consistent with the Scheduling Policy Framework factors for listing in Schedule 6. The advice of the ACCS was requested to confirm this scheduling proposal.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support listing of 2-amino-5-ethylphenol in Schedule 6?
- Is 2-amino-5-ethylphenol the most appropriate name for any listing (no need to specify the HCl salt?), or is another name appropriate (e.g. phenol, 2-amino-5-ethyl, hydrochloride)?
- Is there a need to schedule the chemical at all, given that public exposure is only likely to occur with products in which this chemical is as a component of hair dyes used professionally in salons?
- In the absence of any chronic toxicity studies, is the equivocal evidence of potential genotoxicity (micronucleus induction in vitro, but not in vivo) suggestive of a cautionary approach to scheduling this chemical?
- While data suggests that there are unlikely to be health risks associated with hair dye preparations containing up to 1 per cent of 2-amino-5-ethylphenol HCl, is a cut-off from Schedule 6 at 1 per cent warranted?
- Is there a need to develop specific Appendix E & F statements? If so, what does the ACCS suggest?
- If exempted from scheduling at 1per cent, salon operators would not see any Schedule 6 labelling requirements, including signal heading and Appendix E & F statements. Does this argue against a cut-off to be applied to the Schedule 6 listing?

Substance details

Phenol, 2-amino-5-ethyl-, hydrochloride is an oxidative colouring agent for hair dye formulations at concentrations of up to 1 per cent.

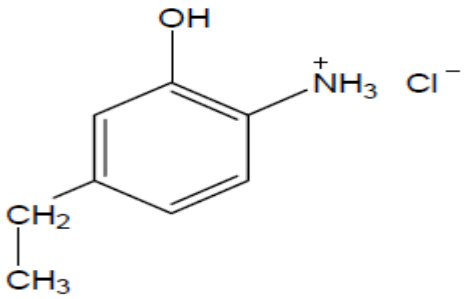

Figure 2. Structure of 2-amino-5-ethylphenol

Acute toxicity

No acute toxicity studies were performed with the hydrochloride salt. The chemical showed low toxicity in the acute oral toxicity test with phosphate salt with LD_{50} > 2000 mg/kg bw. Taking into account the differences in molecular weight of the hydrochloride and phosphate salts and differences in pKa (Hydrochloride salt = 5.17; Phosphate salt = 5.28), it is calculated that the hydrochloride salt will contain 148 per cent more of the free base (assumed to be the main cause of toxicity) than the phosphate salt. This implies that a dose of 2000 mg/kg for the phosphate salt is equivalent to a dosing of 1350 mg/kg of the chloride salt (the notified chemical). Given a dose of 2000 mg/kg bw of the phosphate salt resulted in the death of 1 animal and other clinical signs of toxicity, it is expected that the LD_{50} of the hydrochloride salt will be less than 2000 mg/kg bw.

The neat chemical is considered likely to produce skin corrosion or irritation in in vitro tests. Further, the neat chemical is a severe eye irritant in an isolated chicken eye test with moderate swelling, severe corneal opacity and severe fluorescein retention by damaged epithelial cells.

An analogue of the chemical exhibits potential for skin sensitisation in a mouse local lymph node assay with an EC3 of 8.9 per cent.

Repeat toxicity

In a repeat-dose toxicity studies, the no observed adverse effect level (NOAEL) of the chemical was 16 mg/kg bw/day in an oral 13-week study in rats with organ changes consistent with haemolytic anaemia.

Carcinogenicity

There is no data provided on carcinogenicity of the chemical.

Genotoxicity

An analogue of the notified chemical is genotoxic *in vitro* in a human peripheral blood lymphocyte micronucleus test.

Developmental toxicity

Looking at developmental toxicity, the chemical induced a range of foetal effects at doses causing maternal toxicity. The NOAEL was 74 mg/kg bw/day.

Public exposure

It is expected that exposure to the general public and during transport, formulation and storage would be low.

Scheduling status

Phenol, 2-amino-5-ethyl-, hydrochloride is not currently scheduled.

Scheduling history

No scheduling history is available for phenol, 2-amino-5-ethyl-, hydrochloride.

Substances have previously been included in Schedules 5 and 6 in relation to their use in hair dye preparations. There are also exemptions relating to this use.

Public pre-meeting submissions

Two public submissions were received.

One submission indicated in principle it did not support the delegate's proposal. The submission requested that any consideration on scheduling of 2-amino-5-ethylphenol should ensure that the limitation applies to the diluted hair dye for in-use preparation i.e. diluted for use, rather than in the purchased concentrated products use rather than to the product packaged for sale.

The other submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that 2-amino-5-ethylphenol HCL in hair dye preparations be included in Schedule 6 with an exception cut-off for hair dye preparations containing 1 per cent or less 2-amino-5-ethylphenol HCL when the immediate container and primary pack are labelled with the appropriate warning statements located in the SUSMP.

The ACCS also recommended that 2-amino-5-ethylphenol HCL be listed in Appendix E and Appendix F.

The committee also recommended an implementation date of 1 February 2015.

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

The reasons for the recommendation comprised the following:

- Risk associated with use outside of professional salon requires mandated labelling.
- Potential skin sensitisation, corrosion of the skin and severe eye irritation in its concentrated form.

Delegate's interim decision

The delegate agrees with the advice of the ACCS that new entries be created in Schedule 6 and Appendices E & F, to regulate the use of 2-amino-5-ethylphenol HCl in hair dyes. The main source of exposure is expected to be associated with this use and the schedule wording is specific for this use, to reduce the likelihood of inadvertent capture of other types of products. Furthermore, consistent with Schedule 6 entries for some other hair dye ingredients with a similar toxicological profile, an exemption from Schedule 6 has been provided for products that meet specific labelling requirements.

The delegate agrees with the implementation date being 1 February 2015.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: (c) the toxicity of a substance and (d) the dosage, formulation, labelling, packaging and presentation of the substance.

The reasons for the recommendation comprised the following:

- The toxicity profile is consistent with SPF Schedule 6 factors, including severe skin and eye irritancy potential for preparations containing high concentrations.
- There is a need for warning statements on product labels to facilitate safe use; for products used either inside or outside professional hair salons.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[6];
- Other relevant information.

Submissions on interim decision

Two submissions were received. One noted that as the delegate's interim decision had no impact on therapeutic goods, it had no further comments on delegate's interim decision on this item.

The other indicated that the proposed 1% exemption cut-off would not allow for higher strength preparations currently available overseas to be exempted from schedule 6, even if labelled with the required warning statements. Such higher-strength preparations are intended to be mixed with other solutions to achieve an 'on-head' final concentration of no more than 1% 2-amino-5-ethylphenol. The submission proposed changes to the wording of the Schedule 6 entry to allow for this, by modifying the words to: ' ….except in preparations giving rise to 1 per cent or less on-head concentration of 2-amino-5-ethylphenol when the immediate container and primary pack are labelled with the following statements.."

Delegate's final decision

The delegate has considered the submission received following publication of the interim decision to list 2-amino-5-ethylphenol in Schedule 6. The submission calls for clarification of the schedule entry to allow higher strength preparations to meet the 1% exemption cut-off, provided they are labelled with appropriate warning statements and directions to be diluted to no more than 1% in the final 'on-head' preparation.

However, this advice is in conflict with advice considered by the ACCS, that the concentration in hair dye products are likely to be 1% or less, and further diluted to an 'on-head' concentration of 0.5% or less. Given the need to provide appropriate warnings to professional users in-salon and to non-professional users in a domestic setting, the delegate has determined that the interim scheduling

[6] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

decision should stand. This means that preparations containing more than 1% 2-amino-5-ethylphenol would have the full labelling required by Schedule 6 listing, while products containing 1% or less would have only the required warning statements.

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

SCHEDULE 6 – New entry

2 AMINO 5 ETHYLPHENOL in hair dye preparations **except** in preparations containing 1 per cent or less of 2-amino-5-ethylphenol 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 irritation 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 and 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

Poison	Standard Statements
2-amino-5-ethylphenol	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 washout immediately with water.

APPENDIX F, PART 3

Poison	Warning Statements	Safety Direction
2-amino-5-ethylphenol	21. 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 dyeing eyelashes and eyebrows; to do so may be injurious to the eye.	-

1.7 2-BUTANONE, OXIME (ALSO KNOWN AS METHYL ETHYL KETONE OXIME)

Scheduling proposal

On 29 August 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, requested that the delegate consider a proposal to include the substance in Schedule 6, due to concerns regarding critical effects to human health namely, severe eye irritation, skin sensitisation and harmful effects through contact with skin during short-term or acute exposure. Long-term exposure may cause carcinogenicity.

The delegate's reason for referring this scheduling proposal to the ACCS was that this referral from the NICNAS IMAP program relates to a chemical likely to be a component of alkyd paints, lacquers, varnishes and adhesives (at concentrations up to 1 per cent in finished products) that might be used in a domestic setting. NICNAS suggests that the toxicological profile of the chemical warrants scheduling (based mainly on limited acute toxicity data, including severe eye irritancy and sensitisation potential) and that the toxicological profile appears to be consistent with the Scheduling Policy Framework factors for listing in Schedule 6. The advice of the ACCS was requested to confirm this scheduling proposal.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support listing of 2-butanone, oxime in Schedule 6?
- Is 2-butanone, oxime the most appropriate name for any listing, or is another name appropriate (e.g. Methyl ethyl ketoxime, MEKO, Butanone, Ethyl methyl ketoxime Methyl ethyl ketone oxime)?
- There are existing Schedule 5 entries for methyl ethyl ketone and methyl ethyl ketone peroxide. To what extent would these entries cover MEKO or inform its scheduling? Is the 25 per cent concentration exemption to unscheduled for MEK an appropriate cut-off for MEKO, or is 5 per cent a more appropriate cut-off, based on the presumed threshold for sensitisation effects?
- Is there a need to schedule the chemical at all, given that public exposure is only likely to occur where it is a component of alkyd paints, lacquers, varnishes and adhesives, at such low concentrations that are unlikely to represent a health hazard?
- Is there a need to develop specific Appendix E & F statements? If so, what does the ACCS suggest?

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website:

<http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=103>.

Scheduling status

2-Butanone, oxime is not specifically scheduled.

Methyl ethyl ketone and methyl ethyl ketone peroxide are included in Schedule 5 and Appendices E and F.

Schedule 5

METHYL ETHYL KETONE except in preparations containing 25 per cent or less of designated solvents.

Schedule 5

METHYL ETHYL KETONE PEROXIDE.

Scheduling history

In May 1978, the Poisons Scheduling (Standing) Committee decided to amend the Schedule 5 ketones entry (including methyl ethyl ketone) to exclude from scheduling for preparations containing 25 per cent or less of designated solvents.

Public pre-meeting submissions

Two submissions were received.

One submission indicated that the proposed amendment is not limited to cosmetic products and noted that the TGA ARTG contains an ingredient entry for methyl ethyl ketone. Given that the schedule entry applicable to salts and derivatives, the submission was concerned about the possibility that there may be some impact on therapeutic goods.

The other submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that methyl ethyl ketone oxime be included in Schedule 6 except in preparations containing 1 per cent or less of methyl ethyl ketone oxime.

The ACCS also recommended that Appendix E and F statements were required.

The ACCS recommended an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- Potential use in the wide range of products available for domestic use and the risk of sensitisation and severe eye irritation.
- Cut-off level is based on skin sensitisation to exempt based on default limit supply by GHS and Hazard Substances Information System (HSIS.)

Delegate's interim decision

The delegate accepts the advice of the ACCS to include methyl ethyl ketone oxime in Schedule 6. The critical toxicological endpoints driving this categorisation (severe eye irritancy and sensitisation potential) are consistent with SPF factors for listing in Schedule 6, with the public health risk sufficiently ameliorated for products containing less than 1% to be exempted from scheduling. The delegate noted ACCS advice that intermittent use of products containing this chemical would be unlikely to pose a significant carcinogenic risk, despite the '*Limited evidence of carcinogenic effect*' noted in the NICNAS report. The delegate supports a separate listing for methyl ethyl ketone oxime in Schedule 6, noting that the current Schedule 5 entries for apparently related chemicals (methyl ethyl ketone and methyl ethyl ketone peroxide) would not generically cover methyl ethyl ketone oxime.

The delegate agrees with the implementation date being 1 June 2014.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;

- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[7];
- Other relevant information.

Submissions on interim decision

One public submission was received. The submission indicated that as the delegate's interim decision on the substance had no impact on therapeutic goods, it had no further comments in relation to the delegate's interim decision.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

SCHEDULE 6 – NEW ENTRY

METHYL ETHYL KETONE OXIME **except** in preparations containing 1 per cent or less of methyl ethyl ketone oxime.

APPENDIX E, PART 2

Poison	Standard Statements
Methyl ethyl ketone oxime	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 washout 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

Poison	Warning Statements	Safety Direction
Methyl ethyl ketone oxime	5. Irritant. 28. (Over) (Repeated) exposure may cause sensitisation	1. Avoid contact with eyes. 4. Avoid contact with skin

1.8 DIETHYLENE GLYCOL MONOBUTYL ETHER

Scheduling proposal

On 13 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, recommended that the delegate consider amending the current Schedule 5

[7] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

diethylene glycol monobutyl ether (DEGBE) entry, and amending the SUSMP to include requirements for first aid instructions, warning statements and safety directions for DEGBE.

NICNAS proposed that these include safety directions such as avoid skin and eye contact, avoid breathing aerosols and use of products in well-ventilated area. These safety directions were necessary to mitigate risk for products with higher concentrations (>10 per cent) of the chemical or for products that are spray-applied.

The critical health effects in the risk characterisation on which the NICNAS recommendation was based were the local effects (eye irritation and potential skin irritation following repeated exposure to the chemical). Reversible changes in the lungs have been observed in animals following exposure to >100 mg/m^3. The chemical does not appear to produce the haemolytic effects observed with the shorter chain ethylene glycol butyl ether, 2-butoxyethanol. Changes to haematological parameters were only noted following oral exposure to high doses (1 000 mg/kg bw/d).

The reason for referring this scheduling proposal to the ACCS was that DEGBE was last reviewed by the DPSC in 2004, at which time it was decided that its toxicological profile was more consistent with Schedule 5, rather than the generic Schedule 6 entry for ethylene glycol monoalkyl ethers and their acetates. Accordingly, the DPSC created a new Schedule 5 entry, with a cut-off to exempt at 10 per cent.

The chemical had been referred for re-consideration of scheduling as an outcome of the NICNAS IMAP process. A related chemical (hexyloxyethanol) had been referred to the July 2013 ACCS meeting, which recommended its listing in Schedule 6 as a separate entry from the generic entry for diethylene glycol monoalkyl ethers.) The NICNAS IMAP report on DEGBE includes recommendations for strengthening hazard statements and concentration restrictions on use in products such as cosmetics, domestic cleaners, paints and floor sealants. The advice of the ACCS was needed to implement any scheduling amendments.

The delegate sought the following specific advice from the ACCS:

- The NICNAS IMAP assessment particularly notes potential developmental toxicity with relatively high oral NOAELs, although somewhat lower dermal NOAELs. The report also notes risk assessments suggesting a relatively low margin of exposure (MOE) for some uses of DEGBE (particularly in cosmetics). Does the ACCS consider that Schedule 5 listing (with 10 per cent cut-off to exempt) remains appropriate for DEGBE?

- Is there a need to include an entry in Appendix C to prohibit the use of DEGBE in cosmetics (or other domestic products?) at concentrations above those listed in the NICNAS IMAP report?

- There are currently no First Aid statements, Warning Statements or Safety Directions for scheduled products containing DEGBE. Can the ACCS suggest suitable entries in Appendices E and F?

- Does the current entry for ethylene glycol monoalkyl ethers in Appendix I (Uniform Paint Standard) adequately address uses of DEGBE?

- What information would be needed to assess the regulatory impacts of any proposed changes to the scheduling of DEGBE (e.g. in AGVET products)?

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=195>.

Scheduling status

Preparations containing more than 10 per cent diethylene glycol monobutyl ether are listed in Schedule 5.

Scheduling history

In November 1984, the Poisons Scheduling Standing Committee (PSSC) included ethylene glycol monoalkyl ethers and their acetates in Schedule 6.

This scheduling was reaffirmed at the May 1992 NDPSC meeting.

At its June 2003 meeting the NDPSC confirmed that diethylene glycol monobutyl ether was included in Schedule 6 by virtue of the provisions of Part 1, paragraph 2(c) of the SUSMP.

In February 2004 the NDPSC decided to create a specific separate Schedule 5 entry for diethylene glycol monobutyl ether. The NDPSC also decided to exempt from scheduling, preparations containing 10 per cent or less of diethylene glycol monobutyl ether.

Public pre-meeting submissions

Two submissions were received.

The first submission indicated that it was unsure of the new first aid, warning and safety directions being proposed. The submission asserted that preparations containing 10 per cent of the substance already have appropriate statements on the label to enable safe use of their products, and that this was only to be expected for products carrying the "CAUTION" signal heading. If specific first aid, warning and safety directions are considered necessary, the submissions suggested that there needs to be further consultation with industry including the proposed specific statements to ensure that the impact on companies using this substance is minimised (need for new artwork/template, relabelling, etc.) The submission asserted that based on the IMAP report, there were no concerns with the current exemption of products containing 10 per cent or less of DEGBE.

The second submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that the current scheduling of diethylene glycol monobutyl ether remains appropriate.

The ACCS recommended that Appendix E and F statements are required.

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

Delegate's interim decision

The delegate accepts the ACCS advice that the current Schedule 5 entry for diethylene glycol monobutyl ether (DEGBE) remains appropriate, but that new Appendix E & F statements are required for products not exempted under that entry. The delegate also notes ACCS advice that the 10% cut-off to exempt also remains appropriate, having considered the relatively low MOE calculations for dermal application in cosmetics in the NICNAS report.

The delegate has decided that the implementation date is to be 1 June 2015.

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

The reasons for the recommendation comprised the following:

- First aid, warning statements and safety directions were not applied when diethylene glycol monobutyl ether was originally included in Schedule 5. Provision of such label statements address the potential hazards and should enhance consumer safety when using such products.
- The toxicity profile of diethylene glycol monobutyl ether is consistent with SPF factors for Schedule 5, with the 10% cut-off to exempt still appropriate.

Delegate's considerations

- The delegate considered the following in regards to this proposal:
- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[8];
- Other relevant information.

Submissions on interim decision

Two public submissions were received.

One submission noted that while it had no objections to delegate's interim decision to include the substance in Appendix E and F, an extended implementation period, i.e. 1 June 2016, may be required for the companies to adopt the labelling changes.

The other submission indicated that as the delegate's interim decision on the substance had no impact on therapeutic goods, it had no further comments regarding delegate's interim decision.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

APPENDIX E, PART 2

Poison	Standard Statements
Diethylene glycol monobutyl ether	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor E1 - If in eyes wash out immediately with water.

[8] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Poison	Standard Statements
	S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

APPENDIX F, PART 3

Poison	Warning Statements	Safety Directions
Diethylene glycol monobutyl ether	5. Irritant	1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist. 9. Use only in well-ventilated area.

1.9 ETHYLENE GLYCOL MONOMETHYL ETHER

ACCS advice to the delegate

The committee noted that the name of the substance should be diethylene glycol, monomethyl ether rather than ethylene glycol monomethyl ether as it was published on the public notice inviting public comments.

As the name of the substance was incorrectly published, the committee indicated that it was unable to provide a recommendation to the delegate owing to issues associated with transparency and natural justice. The committee decided not to proceed with this matter at this meeting and recommended the delegate include diethylene glycol, monomethyl ether on the next public notice inviting public comments.

Delegate's interim decision

The delegate agreed with this recommendation and referred the diethylene glycol, monomethyl ether to the July 2014 committee meeting.

Delegate's final decision

The delegate apologises for the error in the name ethylene glycol monomethyl ether as it was published on the public notice inviting public comments for the November ACCS meeting, and confirms that consideration of this chemical under its correct name, diethylene glycol, monomethyl ether (DEGME) will be referred to a future meeting of the ACCS (July 2014).

1.10 TETRAHYDROFURAN

Scheduling proposal

On 17 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, recommended to the delegate that for domestic uses, tetrahydrofuran (THF) be a new entry in Schedule 5 with possible exemptions at low concentration levels.

The NICNAS report recommended that further risk management was required for the chemical, believing that sufficient information was available to recommend the chemical be risk managed for public safety from its potential use in domestic products through scheduling, and occupational

health and safety through classification and labelling. Further assessment is recommended to examine the need for a hazard classification for potential carcinogenicity of the chemical.

The delegate's reason for referring this scheduling proposal to the ACCS is that the toxicological profile of the chemical warrants scheduling and that the toxicological profile appears to be consistent with the Scheduling Policy Framework for Medicines and Poisons (SPF, 2010) factors for listing in Schedule 5. The advice of the ACCS was requested to confirm this scheduling proposal.

This scheduling submission for THF is one of several NICNAS-referred chemicals from the IMAP program. THF is a solvent used at relatively low concentrations in a range of consumer products, including cleaners, adhesives and stain removers. A number of solvents with comparable toxicity have been included in Schedules 5 and 6, including the related furan 1,2-dioxane. The NICNAS IMAP report on THF includes recommendations for strengthening hazard statements for products such as householder cleaners.

The delegate sought ACCS advice to implement any scheduling amendments, specifically:

- The NICNAS IMAP assessment highlights the skin/eye irritancy potential for THF, in an otherwise relatively low toxicity profile. Does the ACCS support listing of THF in Schedule 5, with a cut-off to exempt at a yet to be determined per cent?
- Is THF the most appropriate name under which to list this chemical in the schedules? Is it necessary to cross-reference the IUPAC name (oxolane) or the abbreviation (THF) in the SUSMP index?
- Does the ACCS agree that the observed hepatocellular and renal carcinogenic responses seen in rats and mice are of little consequence from a scheduling perspective?
- Can the ACCS suggest suitable First Aid statements, warning statements and safety directions in Appendices E and F for scheduled products containing THF?
- What information would be needed to assess the regulatory impacts of any proposed scheduling of THF (e.g. in AGVET products)?

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=117>.

Scheduling status

THF is not specifically scheduled and is not captured by any entry in the SUSMP.

Scheduling history

Not applicable.

Public pre-meeting submissions

Three public submissions were received.

The first submitter indicated that it did not believe that THF or other organic solvents require scheduling controls. However, if any scheduling is considered necessary for THF, it would be necessary to consider all organic solvents for their irritation potential. This would also require further consultation and consideration of the impact on industry. Any scheduling consideration

should also be limited THF (and any other solvents) rather than to salts and derivatives to ensure that other substances are not inadvertently captured e.g. a number of fragrances are derivatives of THF.

The second submission indicated that it was unclear on what concentration cut-off had been proposed and requested that the committee to consider that while not all these ingredients appear on the TGA ARTG ingredient list, some of these substances may be included in proprietary ingredients that are used in therapeutic goods. The submission further requested that the committee consider existing usage within proprietary ingredients and to propose cut-off concentrations that will not impact existing use in proprietary ingredients and in therapeutic goods.

The final submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that THF does not require listing in the Schedules.

Delegate's interim decision

The delegate accepts the ACCS advice that there is no need to include tetrahydrofuran in any of the schedules of the SUSMP. Industrial uses are adequately regulated under other legislation. The toxicology profile of the chemical is relatively low, although it could meet SPF factors for listing in Schedule 5 based on its irritancy potential (a property common to many organic solvents that are not scheduled). However, its use in products available in the domestic retail market is generally at such low concentrations that do not warrant controls via poisons legislation and there is insufficient information to determine an appropriate cut-off to exempt should listing in Schedule 5 be made.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[9];
- Other relevant information.

Submissions on interim decision

Two public submissions were received.

One submission indicated that it supports delegate's decision not to list the substance in a schedule.

[9] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

The other submission noted that as the delegate's interim decision had no impact on therapeutic goods, it had no further comments on this issue.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.11 2-NITROTOLUENE

Scheduling proposal

On 13 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, requested that the delegate consider a proposal to include the substance in Appendix C. The basis for this recommendation is that the main critical effects to human health include genotoxicity, carcinogenicity and potential reproductive/fertility effects.

The delegate's reason for referring this scheduling proposal to the ACCS was that 2-nitrotoluene is prohibited as an ingredient of cosmetics in several international regulatory programs, and NICNAS is seeking similar controls over its use in cosmetics[10] in Australia. NICNAS suggests that the toxicological profile of the chemical warrants scheduling and that the toxicological profile appears to be consistent with the Scheduling Policy Framework for Medicines and Poisons (SPF, 2010) criteria for listing in either Schedule 6 or 7 (based on its mutagenicity and carcinogenicity profile). The advice of the ACCS was requested to confirm this scheduling proposal.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support listing of 2-nitrotoluene in Schedule 6 or 7?
- Is there likely to be any conflict with current Schedule 6 listings for nitrobenzene or nitrophenols?
- Is 2-nitrotoluene the most appropriate name for any listing, or is another name appropriate (e.g. o-nitrotoluene, 2-methyl-1-nitrobenzene)?
- Is there a need to include a specific listing in Appendix C to restrict its use in cosmetics, or is a Schedule 7 listing, with an appropriate Appendix J condition a sufficient level of control?
- Is there a need to develop specific Appendix E & F statements (and Appendix J if listed in S7)? If so, what does the ACCS suggest?

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=66>.

Scheduling status

2-nitrotoluene (also known as benzene,1methyl-2-nitro-) is not specifically scheduled.

The major chemical class, benzene, is listed in Schedule 7, Appendices E, F and J and the major chemical subclass, nitrobenzene is listed in Schedule 6, Appendices E and F.

[10] 2-nitrotoluene is likely to be a component of cleaning/washing agents, paints, lacquers and varnishes at concentrations up to 0.9 per cent in finished products

Scheduling history

Benzene

In February 1971, the Poisons Schedule Sub-Committee (PSSC) decided to include preparations containing more than 1 per cent benzene in Schedule 7. The PSSC decided to exclude motor fuels containing 5 per cent or less of benzene and motor fuels containing more than 5 per cent but not more than 20 per cent when packed in 5 gallons or less containers.

In November 1985, the Poisons Schedule Committee (PSC) decided to amend the Schedule 7 entry to exempt preparations containing 15 mL/L or less of benzene and petrol containing 50 mL/L or less of benzene from this listing.

Nitrobenzene

In May 1956, the Poisons Schedule Committee (PSC) decided to include nitrobenzene in Schedule 6. The PSC also decided to exempt nitrobenzene in solid or semi-solid polishes, in soaps containing 1 per cent or less of nitrobenzene and in other preparations containing 0.1 per cent or less of nitrobenzene.

There was no rationale given for these decisions. The Secretariat was unable to find a record of the decision to include these substances in Appendices E, F and J.

Public pre-meeting submissions

One public submission was received.

The submitter did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that that 2-nitrotoluene be included in Schedule 7.

The ACCS recommended an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- No essential use in Australia.
- Toxicological profile for reproductive, genotoxic and carcinogenicity consistent with Schedule 7.

Delegate's interim decision

The delegate accepts ACCS advice that 2-nitrotoluene be listed in Schedule 7. Features of its toxicological profile suggest a significant genotoxic, carcinogenic and reproductive toxicity potential that would be consistent with SPF factors for listing in Schedule 7. While there appear to be no essential uses of 2-nitrotluene in Australia, listing in Schedule 7 would provide for effective control over imported products (e.g. cosmetics).

The delegate notes and accepts ACCS advice that listing in Appendix C is not an appropriate means of controlling the possible use of 2-nitrobenzene in cosmetics, given the range of international restrictions already in place. There does not appear to be any conflict with existing (but rather old) Schedule 6 entries for related substances, nitrobenzene and nitrophenols.

The delegate agrees to the implementation date of 1 June 2014.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[11];
- Other relevant information.

Submissions on interim decision

One public submission was received. The submission indicated that as the delegate's interim decision on 2-nitrotoluene has no impact on therapeutic goods, it has no further comments regarding delegate's interim decision on the substance.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

SCHEDULE 7 – NEW ENTRY

2-NITROTOLUENE.

1.12 FURFURAL (ALSO KNOWN AS 2-FURANCARBOXALDEHYDE)

Scheduling proposal

On 17 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, recommended that the delegate consider including 2-furancarboxaldehyde in Schedule 6 with exemption at very low concentrations which may be applicable for specific uses. The basis for this was to mitigate risk from its use in cosmetics and domestic products.

The NICNAS report recommended risk management for public safety from its potential use in cosmetics and/or domestic products through scheduling, and occupational health and safety through classification and labelling.

The delegate referred a proposal to include 2-furancarboxaldehyde in Schedule 6 (with an appropriate cut-off to exemption) to mitigate risk from its use in cosmetics and domestic products.

[11] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

This scheduling submission for 2-furancarboxaldehyde (furfural) is one of several NICNAS-referred chemicals from the IMAP program, where the primary public exposure is likely to be via use of cosmetics, fragrances, flavourings and other domestic products (adhesives, cleaners) at very low concentrations. There are other possible uses as a solvent or component of pest control products and it may be found in food at levels up to 63 mg/kg. The primary purpose for this referral by NICNAS was to limit the concentration of furfural in cosmetics/flavouring, in accordance with EU restrictions on such uses.

The delegate sought ACCS advice on how best to manage the scheduling aspects of such submissions, specifically:

- Furfural has a moderately high toxicity profile, with an acute and chronic toxicity consistent with the SPF criteria for Schedule 6 (or possibly Schedule 7 if concerns about equivocal genotoxicity and/or carcinogenicity are relevant). However, public exposure is only likely to occur through the use as a fragrance ingredient (possibly up to 0.1 per cent), at which concentration adverse health effects are unlikely. Does the ACCS consider that listing in the SUSMP is appropriate? If so, should it be listed in Schedule 6 or Schedule 7, with an appropriate cut-off to exempt?

- If scheduled, what name should be used in the listing (2-furancarboxaldehyde or the more common name, furfural)?

- The EU Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP) is of the opinion that furfural can be safely used as a fragrance/flavour ingredient at a maximum concentration of 0.036 per cent in the fragrance compound. The maximum concentration of furfural that can be safely used as a fragrance/flavour ingredient in toothpaste is 0.002 per cent in the fragrance compound. Are these suitable cut-offs to exempt a Schedule 6 or Schedule 7 entry for furfural, or is a more generic cut-off (0.1 per cent?) more appropriate?

- Is there a need to develop Appendix E & F statements to cover products that would not meet schedule exemption concentrations? If so, please suggest such statements.

- Is scheduling furfural likely to have unintended consequences – e.g. capture of AGVET or other products where solvent use or residues may exceed cut-off levels?

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=116>.

Scheduling status

2-furancarboxaldehyde has not been specifically scheduled.

Scheduling history

2-furancarboxaldehyde has not been considered for scheduling previously; however, the following related chemicals have been considered. 2,3,4,5-bis-(2-butylene)-tetrahydro-2-furfuraldehyde; and butadiene furfural copolymer.

2,3,4,5-bis-(2-butylene)-tetrahydro-2-furfuraldehyde

At its meeting in February 1986, the DPSC directed that the Agricultural and Veterinary Chemicals Association (AVCA) be contacted for a list of products containing the above substance and that the

matter be placed on the agenda of its November 1986 meeting. However, this matter was not included in the November 1986 agenda.

Butadiene furfural copolymer

At its May 1974 meeting the PSSC was of the opinion that butadiene furfural copolymer should be exempted from the requirement of scheduling.

Public pre-meeting submissions

Three submissions were received.

The first submission indicated that the International Fragrance Association (IFRA) Standard sets the limit on furfural at 10 ppm for skin contact products and 500 ppm for non-skin contact products. While it may not be the role of the ACCS or the Delegate to decide whether to adopt the IFRA Code into the Australian cosmetics and consumer products regulatory framework, this was an issue that must be considered. It was suggested that it was not practical or efficient to reconsider all fragrances and flavours through the scheduling process. It was recommended that when there is an international body like IFRA that investigates issues surrounding flavours and fragrance in depth, it makes little sense to duplicate this work, particularly when most companies comply with the IFRA Code voluntarily. The New Zealand Cosmetic Products Group Standard has already adopted the IFRA Code. The submission further suggested a separate discussion, if possible, on the adoption of internationally accepted standards like the IFRA Code. The submission requested excluding furfural from scheduling when used as a fragrance or flavour in cosmetics, and that any scheduling consideration of furfural should ensure that other furan-based fragrances and indeed other furan-based chemicals for use other than as fragrances were not inadvertently caught in the scheduling of furfural.

The second submission indicated that it was unclear on what concentration cut-off had been proposed and requested that the committee consider that while furfural may not appear on the TGA ARTG ingredient list, it may be included in proprietary ingredients that are used in therapeutic goods. The submission further requested that the committee consider existing usage within proprietary ingredients and to propose a cut-off concentration that will not impact existing use in proprietary ingredients and in therapeutic goods.

The last submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on the delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that preparations containing furfural be included in Schedule 6 except in preparations containing 0.1 per cent or less of furfural.

The ACCS also suggested entries for furfural to be included in Appendix E and F.

The ACCS recommended an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- Appropriate use of the substance other than when used as a fragrance e.g. as a solvent in domestic products.
- Moderate to high toxicity profile, acute oral and inhalation toxicity consistent with the Scheduling Policy Framework for Schedule 6.

Delegate's interim decision

The delegate accepts the advice of the ACCS that a new Schedule 6 entry be created for furfural, based on a toxicological profile that is consistent with SPF factors for listing in Schedule 6. However, the delegate also notes that there were significant divisions within the ACCS on whether the use of this chemical as a component of fragrances requires scheduling, given the very low final concentrations likely to be present in consumer products. The delegate therefore accepts ACCS advice that a cut-off to exempt at 0.1% be included in the schedule entry, to accommodate its use in products where the public health hazard is insignificant. The delegate also accepts ACCS advice that new entries in Appendices E & F be created to provide appropriate labelling for products categorised via the Schedule 6 listing.

The delegate agrees to the implementation date of 1 June 2014.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[12];
- Other relevant information.

Submissions on interim decision

Two submissions were received.

One submission indicated that it tentatively supports the delegate's interim decision. The submission requested the proposed exemption from scheduling should exempt current Australian uses of furfural when used as a fragrance.

The other submission indicated that it supports the delegate's interim decision.

Delegate's final decision

The delegate has confirmed the interim decision, with a minor modification to the proposed SUSMP index cross-referencing, as no evidence has been received to alter the substance of the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Based on comments received, there should be no regulatory impact on products already in the Australian marketplace, so an early implementation date is considered appropriate.

[12] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Scheduling entry

SCHEDULE 6 – NEW ENTRY

FURFURAL **except** in preparations containing 0.1 per cent or less of furfural.

APPENDIX E, PART 2

Poison	Standard Statement
Furfural	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

Poison	Warning Statements	Safety Directions
Furfural	5. Irritant	1. Avoid contact with eyes 4. Avoid contact with skin

Note that the name used in the NICNAS report is 2-furancarboxaldehyde (also used in the pre-meeting publication inviting comment). The delegate proposes that cross references be included in the SUSMP index, as follows:

2-FURANCARBOXALDEHYDE

See FURFURAL

~~FURFURAL~~

~~See also 2-FURANCARBOXALDEHYDE~~

The delegate notes the comment in one of the submissions received following publication of the interim decision, that a second cross-referencing proposed for the SUSMP index is unnecessary, since there is no proposed schedule listing under the name 2-FURANCARBOXALDEHYDE. Accordingly, a second proposed cross-referencing has been deleted.

1.13 METHANOL

Scheduling proposal

On 17 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process recommended that the delegate consider amending the maximum authorised concentration in the finished cosmetic product to 5 per cent of methanol calculated as a percentage of ethanol and isopropyl, thereby bringing Australian regulations into line with EU Cosmetic Directive 76/768/EEC Annex III Part 1.

NICNAS recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of methanol in domestic products be managed through changes to poisons scheduling.

Management of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory control

The use of this chemical in domestic or cosmetic products is currently controlled by scheduling. The chemical is listed in the SUSMP under Schedule 5 or Schedule 6 based on its concentration in products/mixtures:

1) The chemical in preparations for domestic use is in Schedule 5 of the SUSMP if the concentration of methanol is over 2 per cent and equal to or less than 5 per cent (packaging with signal heading 'Warning'); and

2) Preparations containing over 5 per cent methanol are in Schedule 6 (packaging with signal heading 'Poison').

Preparations containing 2 per cent or less of methanol for domestic or cosmetic use are not scheduled.

For the purpose of revising concentration limits for scheduling, the delegate may wish to consider the form of restriction which exists in the EU Cosmetic Directive—'Maximum authorised concentration in the finished cosmetic product is 5 per cent calculated as a percentage of ethanol and isopropyl alcohol'.

The delegate's reason for referring this scheduling proposal to the ACCS was that, in accordance with section 4.2 of the Scheduling Policy Framework for Medicines and Chemicals (SPF, 2010)[13], advice was required to be obtained from an expert advisory committee for all rescheduling proposals. This scheduling submission for methanol is one of several NICNAS-referred chemicals from the IMAP program. Methanol is already included in Schedules 6 and Schedule 5 with appropriate cut-offs at 10 per cent and 2 per cent, respectively. The NICNAS IMAP report addresses the need to amend the current scheduling cut-offs to provide a new-cut-off for cosmetic preparations, consistent with EU Cosmetic Directive 76/768/EEC Annex III Part 1.

The delegate sought ACCS advice and asked the committee to consider the following:

- Does the ACCS support the need for new scheduling restrictions on cosmetics containing methanol, to bring Australian regulations into line with EU Cosmetic Directive 76/768/EEC Annex III Part 1?

- Is the best way to implement this to draft a new entry in Appendix C covering methanol in cosmetics, or should the existing Schedule 5 and Schedule 6 entries be amended to address this, with a consequent outcome that cosmetics containing more than the prescribed amounts would be captured by Schedule 5 or Schedule 6 controls?

[13] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

- Should the current Appendix E & F statements be applied to cosmetic products; in particular, is a new set of Appendix F Statements needed for cosmetic products, deleting reference to Safety Direction No. 4 'avoid contact with skin'.

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Tier II Human Health Assessment Report for methanol. This report is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=115>.

Scheduling status

Methanol is currently listed in Schedule 5 and Schedule 6 and included in Appendices E and F.

Scheduling history

In February 1985, the Poisons Schedule Committee (PSC) decided to amend the Schedule 6 methyl alcohol entry to include preparations containing 5 per cent or less of methyl alcohol in Schedule 5.

In August 1985, the PSC decided to amend the Schedule 5 entry to raise the maximum concentration to 10 per cent and to exclude preparations containing 2 per cent or less of methanol from schedule listing. The PSC also decided to change the name from methyl alcohol to methanol.

Public pre-meeting submissions

Three submissions were received.

The first indicated that methanol is used in Australia in both cosmetics and consumer products, but in most cases (particularly in cosmetics) is present as a denaturant in ethanol. It asserted there has been no significant new information put forward to suggest that the current scheduling controls are inappropriate. The submission did not support the proposed amendment to methanol scheduling.

The second submission indicated that although the delegate's proposal regarding methanol referred to cosmetic use, methanol is also used during manufacture of some therapeutic goods. The submission requested that the committee to confine any changes to cosmetics only so that therapeutic goods are not affected.

The last submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that the current scheduling for methanol remains appropriate.

Delegate's interim decision

The delegate accepts the advice of the ACCS that the current listings of methanol in Schedules 5 and 6 of the SUSMP remain appropriate. Noting that the presence of methanol in cosmetics is often as a component of denatured ethanol, the delegate agrees that there is no need to develop separate schedule entries for methanol purely to align with international regulatory controls over its use in cosmetics. There is no evidence that the controls requested by NICNAS would impact on the potential for products containing methanol to be abused.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* to be a) the risks and benefits of the use of the substance, b) the purposes for which a substance is to be used and the extend of use of a substance, c) the toxicity of the substance, e) the potential for abuse of a substance.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[14];
- Other relevant information.

Submissions on interim decision

Two public submissions were received. Both submissions support the delegate's interim decision on methanol.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.14 PENTANOIC ACID, 3-METHYL-2-OXO-, ETHYL ESTER

Scheduling proposal

On 17 September, the delegate received an application proposing the inclusions of pentanoic acid, 3-methyl-2-oxo-, ethyl ester in Schedule 5. The basis for this proposal was:

- Skin irritation data indicate the chemical is a slight skin irritant which meets the factors for Schedule 5.
- Eye irritation data indicate the chemical is a slight eye irritant which meets the factors for Schedule 5.
- Skin sensitisation data indicate the chemical is a slight skin sensitiser which meets the factors for Schedule 5.

A quantitative risk assessment for dermal sensitisation determined that the risk to the public is acceptable at concentrations of no more than 0.02 per cent in deodorants, 0.04 per cent in fine fragrances, 0.06 per cent in other leave on cosmetic products, 0.7 per cent in rinse-off cosmetic products and 0.9 per cent in household cleaning products. At these concentrations it is stated that the risk to the public from repeated exposure is expected to be acceptable.

The proposal provided to the delegate noted that 'accordingly, the strong warnings listed in Appendix F of the SUSMP and the use of distinctive packaging should apply'.

The delegate referred a proposal to schedule pentanoic acid, 3-methyl-2-oxo-, ethyl ester. The delegate's reason for referring this scheduling proposal to the ACCS was that the chemical is likely

[14] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

to be a component of fragrances, deodorants, cosmetics and household cleaning products (at concentrations up to 0.9 per cent in finished products). The toxicological profile of the chemical warrants scheduling (based mainly on limited acute toxicity data, including irritancy and sensitisation potential) and that the toxicological profile appears to be consistent with the SPF[15] factors for listing in Schedule 5. The advice of the ACCS is requested to confirm this scheduling proposal.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support listing of pentanoic acid, 3-methyl-2-oxo-, ethyl ester in Schedule 5?
- Is pentanoic acid, 3-methyl-2-oxo-, ethyl ester the most appropriate name for any listing, or is another name appropriate (e.g. 3-methyl-2-oxopentanoic acid ethyl ester)?
- Is there a need to schedule the chemical at all, given that public exposure is only likely to occur with products in which this chemical is a fragrance component, at such low concentrations that are unlikely to represent a health hazard?
- Is there a need to develop specific Appendix E & F statements? If so, what does the ACCS suggest?

Substance details

Pentanoic acid, 3-methyl-2-oxo-, ethyl ester is intended to be used as a component of fragrances for a variety of cosmetic and domestic products (proposed usage concentration: ≤1.15 per cent in fine fragrances, ≤2.5 per cent in other cosmetic products and ≤25 per cent in household cleaning products).

End-points of acute toxicity	Species	Pentanoic acid, 3-methyl-2-oxo, ethyl ester	SPF*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	-	No data	
Acute inhalation toxicity LC_{50} (mg/kg bw/4h)	-	No data	
Skin irritation	Rabbit	Slight irritant	
Eye irritation	Rabbit	Slight irritant	
Skin sensitisation**	Guinea pig	Evidence of sensitisation	
Mutagenicity	Bacterial reverse mutation	Non mutagenic	

[15] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

*Scheduling Policy Framework for Medicines and Chemicals (2010)
**Human skin repeated insult patch test (1and 5 per cent) studies show no evidence of skin sensitisation.

Repeated dose toxicity

No repeated dose toxicity data were provided for the notified chemical.

Mutagenicity

The notified chemical was not mutagenic in a bacterial reverse mutation study.

Public exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤25 per cent concentration) through the use of the household cleaning products and the rinse-off and leave-on cosmetic and personal care products. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

Scheduling status

Pentanoic acid, 3-methyl-2-oxo-, ethyl ester is not specifically scheduled.

Scheduling history

Not applicable.

Public pre-meeting submissions

Two submissions were received.

One submitter indicated that although this substance was assessed by NICNAS and added to the Australian Inventory of Chemical Substances (AICS) in April 2013, they had no further is information regarding this substance. The submission also indicated that it can be difficult for industry to identify chemicals used in their products, particularly for cosmetics, when the common name for the substance is not made available. While this substance may be an industrial chemical, if consideration of the substance includes its use in cosmetics and consumer products, the INCI name and common name of the substance would need to be made available for so that further comments could be made.

The other submitter did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that pentanoic acid, 3-methyl-2-oxo-, ethyl ester does not require a schedule listing.

Delegate's interim decision

The delegate accepts ACCS advice that this chemical does not require listing in the schedules of the SUSMP. The chemical has a low toxicity profile, with potential skin/eye irritancy and sensitisation potential the main features that would warrant control via scheduling. However, the ACCS noted that the use of the chemical as a fragrance ingredient would be at very low concentrations in consumer products, and advised that is was unconvinced that the risk assessments provided a suitable basis for setting possible (very low) cut-off concentrations for sensitisation.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[16];
- Other relevant information.

Submissions on interim decision

Two public submissions were received.

One submission supports the delegate interim decision of not to include the substance in a schedule.

The second submission indicated that as the delegate's interim decision had no impact on therapeutic goods, it had no further comments on the delegate's interim decision.

Delegate's final decision

The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.15 MERCAPTOACETIC ACID

Scheduling proposal

On 13 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, requested that the delegate consider a proposal to include the substance in Schedule 6. This recommendation was based on the main critical effects to human health namely, severe eye irritation, skin sensitisation and harmful effects through contact with skin during short term or acute exposure. Long-term exposure may cause carcinogenicity.

The delegate's reason for referring this scheduling proposal to the ACCS is that this was one of several NICNAS-referred chemicals where the primary public exposure is likely to be via use of cosmetic products. The delegate needed ACCS advice on how best to manage the scheduling aspects of such submissions.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support a Schedule 5 or 6 listing for this chemical with an appropriate cut-off (at 11 per cent or less with an exception to unscheduled or to Schedule 5?)?
- Does the ACCS recommend any additional scheduling controls, or specific references to, various cosmetic products (e.g. hair care and/or depilatory products)?
- Is there a need to specify different scheduling cut-off levels for different cosmetic products, as in the EU Directive?

[16] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

- Does the ACCS consider that the schedule entry for this compound be made under the name mercaptoacetic acid, or thioglycolic acid, and that such an entry would capture all the salts considered in the NICNAS IMAP report?
- Can the ACCS recommend suitable entries in Appendices E & F for this class of chemicals?

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=129>.

Scheduling status

Mercaptoacetate salts are not specifically scheduled.

Scheduling history

Not applicable.

Public pre-meeting submissions

Two public submissions were received.

One submission indicated that although mercaptoacetic acid (or thioglycolic acid) is not currently scheduled it is in Annex III (restricted use) of the EU Cosmetics Directive. The safety of mercaptoacetic acid has also been reviewed by the Cosmetic Ingredients Review (CIR) panel. The CIR conclusion was that mercaptoacetic acid is "safe for use in hair straighteners permanent waves, tonics, dressings, and so forth, wave sets, other non-colouring hair products, and hair dyes and colours, at concentrations up to 15.2 per cent; hairdressers should avoid skin contact and minimize consumer skin exposure; safe for use in depilatories when formulated to be non-irritating under conditions of recommended use". The submission tentatively supported scheduling of mercaptoacetic acid (with cross reference to thioglycolic acid in the index) as Schedule 6 with exemptions for cosmetic products containing 15.2 per cent or less of mercaptoacetic acid.

The other submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that mercaptoacetic acid in cosmetic products be included in Schedule 6 except when in Schedule 5 or in preparations containing 5 per cent or less of mercaptoacetic acid.

The committee, in addition to recommending when included in Schedule 6, also recommended that Appendix E and F statements were required.

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

The reasons for the recommendation comprised the following:

- Chemicals properties used in cosmetics but has a low to moderate toxicity at higher concentration levels. Is a skin irritant.
- Use in cosmetics can be unscheduled but higher concentrations needs to be regulated.

- Cut-off levels based on international regulatory approaches.

Delegate's interim decision

The delegate accepts ACCS advice that new entries be created for the strongly acidic substance mercaptoacetic acid (thioglycolic acid) in Schedules 6 (cosmetic preparations with concentrations above 20%) and Schedule 5 (cosmetic preparations between 5 and 20%), with an overall exemption from scheduling at 5%. The entries are specific for cosmetic products, based on the main expected sources of public exposure through use in hair care and depilatory products, with potential for skin/eye irritancy and sensitisation driving the scheduling and cut-offs for the chemical and its salts. The delegate also accepts ACCS advice relating to new entries in Appendices E & F, providing for appropriate First Aid Instruction, Safety Directions and Warning Statements.

The delegate agrees to the implementation date of 1 June 2014.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[17];
- Other relevant information.

Submissions on interim decision

Two public submissions were received.

One submission indicated that while it supports the delegate's decision to list cosmetic preparations containing mercaptoacetic acid in Schedules 5 and 6, the delegate should consider excluding mercaptoacetic acid's derivative from the proposed schedule listing. The submission asserted that mercaptoacetic acid is a simple molecule and inclusion of derivatives in the schedule entry can have unintended consequences of capturing a large number of substances that do not reflect the hazard and risk profile of the substance. The submission also indicated that the implementation time should be extended, i.e. 1 June 2016, to allow industry with sufficient time to either reformulate or even relabel products currently marketed in Australia.

The other submission indicated that as the delegate's interim decision on mercaptoacetic acid had no impact on therapeutic goods, it had no further comments on delegate's interim decision on this substance.

[17] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and agrees to minor clarifications to the proposed Schedule 5 and 6 entries, so that they cover the acid and its salts, but not derivatives. The delegate also notes the need to clarify the method of calculation of the proposed cut-offs. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Industry submissions indicate that a longer implementation period is needed to allow for the orderly re-labelling of affected products. Therefore a later implementation date (1 June 2015) is proposed. The delegate has not accepted industry proposals for an even longer implementation period, until 1 June 2016, in the interests of balancing industry compliance needs with the need to adequately inform the general public of the potential risks.

Scheduling entry

SCHEDULE 6 – NEW ENTRY

MERCAPTOACETIC ACID and its salts, but excluding its derivatives, in cosmetic preparations **except:**

a) when included in Schedule 5; or

b) in preparations containing 5 per cent or less of mercaptoacetic acid or its salts (as mercapturic acid).

SCHEDULE 5 – NEW ENTRY

MERCAPTOACETIC ACID and its salts, but excluding its derivatives, in cosmetic preparations containing 20 per cent or less of mercaptoacetic acid or its salts (as mercapturic acid), **except** in preparations containing 5 per cent or less of mercaptoacetic acid or its salts (as mercapturic acid).

When in Schedule 6 the following Appendix E and F statements.

APPENDIX E, PART 2

Poison	Standard Statements
Mercaptoacetic acid	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 washout immediately with water.

APPENDIX F, PART 3

Poison	Warning Statements	Safety Direction
Mercaptoacetic acid	5. Irritant 28. (Over) (Repeated) exposure may cause sensitisation.	1. Avoid contact with eyes. 31. Do not use on broken skin.

Appendix E and F statements when in Schedule 5.

APPENDIX E, PART 2

Poison	Standard Statements
Mercaptoacetic acid	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 washout immediately with water.

APPENDIX F, PART 3

Poison	Warning Statements	Safety Direction
Mercaptoacetic acid	5. Irritant	1. Avoid contact with eyes.

In addition to the above entries, the delegate proposes cross-referencing in the SUSMP index as follows:

~~MERCAPTOACETIC ACID~~

~~See also THIOGLYCOLIC ACID~~

THIOGLYCOLIC ACID

See MERCAPTOACETIC ACID

In response to submissions requesting that the new Schedule 5 and 6 entries not only specify that the scheduling relates only to use in cosmetics, that there is an additional need to exclude derivatives of thioglycolic acid. Accordingly, the delegate agrees to wording changes as set out above.

1.16 1,3-CYCLOHEXADIENE-1-CARBOXYLIC ACID, 4,6,6-TRIMETHYL-, ETHYL ESTER

Scheduling proposal

On 17 September 2013, the delegate received an application proposing the inclusion of 1,3-cyclohexadiene-1-carboxylic acid, 4,6,6-trimethyl-, ethyl ester in a schedule with exemption for scheduling for cosmetic products and fragrances containing less than 1 per cent of the substance. The basis for this recommendation is the results of the skin irritation and skin sensitisation tests.

Data also suggested that products containing the chemical at concentrations of 1 per cent or above available to the public must carry safety directions and warning statements on the label consistent with the following statement: ‘May cause allergy.’

The delegate considered the proposal for including 1,3-cyclohexadiene-1-carboxylic acid, 4,6,6-trimethyl-, ethyl ester in a schedule with exemption for cosmetic products and fragrances containing less than 1 per cent and referred the proposal to the Advisory Committee on Chemicals Scheduling (ACCS). This proposal is one of several chemicals where the primary public exposure is likely to be via use of cosmetic products. This issue therefore required ACCS advice on how best to manage the scheduling aspects of such submissions.

The delegate sought the following specific advice from the ACCS:

- Given the relatively low toxicity profile of this chemical, and the fact that public exposure is only likely to occur through the use of cosmetic products containing up to 0.025 per cent of this fragrance chemical (or in perfumes at up to 1 per cent) , does the ACCS consider that listing in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) is appropriate? If so, in which schedule should it be listed?
- If scheduled, what name should be used in the listing (1,3-Cyclohexadiene-1-carboxylic acid, 4,6,6-trimethyl-, ethyl ester or a trade name
- Is the potential for skin sensitization associated with its use in fragrances sufficient to warrant scheduling of such substances? If so, which schedule is suggested and what Appendix E & F statements should be applied?

Substance summary

The chemical will be used as a fragrance ingredient in a variety of cosmetic, toiletry and household products. It will be present at a maximum concentration of 1 per cent in fine perfumes, and a maximum of 0.025 per cent in other products.

nd-point of acute toxicity	Species	1,3-cyclohexadiene-1-carboxylic acid, 4,6,6-trimethyl-, ethyl ester	SPF*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute inhalational toxicity LC_{50}	No data	No data	Not determined
Skin irritation	Rabbit	Irritating	
Eye irritation	Rabbit	Slightly irritating with reversible effects.	
Skin sensitisation	Mouse	Evidence of sensitisation.	

**Scheduling Policy Framework for Medicines and Chemicals (2010)*

Repeat-dose toxicity

Repeated exposure to the notified chemical for 28 days was investigated in the rat at dose levels of 30, 300 and 1000 mg/kg bw/day. The effects in the liver and thyroid were observed at 1000 and 300 mg/kg bw/day. Centrilobular hepatocyte enlargement of the liver was evident in animals of both sex treated with 1000 and 300 mg/kg/day. Thyroid changes identified as follicular cell hypertrophy were evident in animals of either sex treated with 1000 mg/kg bw/day or males only treated with 300 mg/kg bw/day. These effects were considered as adaptive changes to the treatment. The no observed adverse effect level (NOAEL) was established as 1000 mg/kg bw/day, based on no adverse effects at this dose level.

Mutagenicity

The chemical was not mutagenic in a bacterial reverse mutation test and in a mammalian chromosome aberration test.

Genotoxicity

The chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.

Carcinogenicity

No data provided.

Public exposure

Public exposure to the notified chemical is expected to be widespread and frequent particularly through daily use of personal care products and household products containing the notified chemical. Exposure to the notified chemical will vary depending on individual use patterns. The principal route of exposure will be dermal and accidental ocular exposure may also occur. Inhalation exposure is also possible if products are applied by spray. Accidental ingestion from the use of these types of products is also possible from facial use. Considering the low concentrations used in personal care and household products (up to 0.025 per cent), significant exposure is not expected from using these product types.

Public exposure to the notified chemical in fine fragrances at 1 per cent was estimated using the Scientific Committee on Consumer Products' (SCCP's) Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation using a default 100 per cent dermal absorption factor for a 60 kg female (SCCP, 2006).

Scheduling status

1,3-Cyclohexadiene-1-carboxylic acid, 4,6,6-trimethyl-, ethyl ester is not specifically scheduled.

Scheduling history

Not applicable.

Public pre-meeting submissions

Three submissions were received.

The first submitter noted that the identity of many fragrance components are considered commercial-in-confidence by the suppliers, it is possible that the substance is being used in consumer products and cosmetics and disclosed on the label simply as "fragrance". The submission asserted that control of fragrances and flavour components through the scheduling system is unwieldy and inefficient. This is particularly true when an international scientific assessment and risk management body like International Fragrance Association (IFRA) publishes *Codes of Practice and Standards* that are specifically relevant for fragrance and flavours. The submission indicated that it would support a separate discussion on the controls of fragrance and flavours rather than through individual scheduling consideration of each fragrance and flavour.

The second submission indicated that it was unclear on what concentration cut-off had been proposed and requested that the committee to consider that while not all these ingredients appear on the Australian Register for Therapeutic Goods (ARTG) ingredient list, some of these substances may be included in proprietary ingredients that are used in therapeutic goods. The submission further requested that the committee consider existing usage within proprietary ingredients and to

propose cut-off concentrations that will not impact existing use in proprietary ingredients and in therapeutic goods.

The third submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The committee recommends that 1,3-cyclohexadiene-1-carboxylic acid, 4,6,6-trimethyl-, ethyl ester does not require a schedule listing.

Delegate's interim decision

The delegate accepts ACCS advice that it is not necessary to use the scheduling process to regulate fragrance chemicals when there is no evidence of a significant public health hazard associated with the very low concentrations likely to be found in consumer products in Australia. Industrial uses are adequately regulated under other legislation, and there is an international scientific assessment and risk management body that publishes *Codes of Practice and Standards* that are specifically relevant for fragrance and flavours. Accordingly, the interim decision of the delegate is to NOT include this chemical in the SUSMP.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the Therapeutic Goods Act 1989;
- Scheduling factors[18];
- Other relevant information.

Submissions on interim decision

Two submissions were received.

One submission indicated that as the delegate's interim decision on the substance had no impact on therapeutic goods, it had no further comments in relation to the delegate's interim decision.

The other submission supported the delegate's interim decision.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

[18] *Scheduling Policy Framework for Medicines and Chemicals (2010)* [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

1.17 3,7-DIMETHYL-2,6-OCTADIENAL ISOMERS (CITRAL, GERANIAL AND NERAL)

Scheduling proposal

On 29 August 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, recommended that the delegate consider creating a new Schedule 6 entry for citral and its related compounds.

The delegate considered the proposal for including 3,7-dimethy-2,6-Octadienal (citral, geranial and neral) in Schedule 5.

The delegate reason for referring this scheduling proposal to the Advisory Committee on Chemicals Scheduling (ACCS) was that this scheduling submission relating to three isomers of 3,7-dimethy-2,6-Octadienal (citral, geranial and neral) is one of several NICNAS-referred chemicals where the primary public exposure is likely to be via use of cosmetics, fragrances and other domestic products (polishes, paints, washing and cleaning products, finger paints and modelling clay). There are other possible uses as a component of pest control products, flavourings and disinfectants. The delegate needed the ACCS advice on how best to manage the scheduling aspects of such submissions.

The delegate sought the following specific advice from the ACCS:

- The relatively low toxicity profile of these chemicals suggests consistency with the SPF factors for Schedule 5. However, public exposure is only likely to occur through the use of products with concentrations ranging up to 5 per cent, at which concentration adverse health effects are unlikely. Does the ACCS consider that listing in the SUSMP is appropriate? If so, should they be listed in Schedule 5, with an appropriate cut-off to exempt (5 per cent)?
- If scheduled, what name should be used in the listing (3,7-dimethy-2,6-Octadienal, with indexing cross references to the three isomers citral, geranial and neral)?
- Although it is not known whether any of these isomers is present in geranium oil, is there any potential ambiguity with the current listing of geranium oil in Appendix B?
- There are quite low concentration limits (0.001 per cent and 0.01 per cent) in EU Cosmetic Directive 76/768/EEC Annex III Part 1 specifying the highest concentrations permitted in cosmetic and personal care products without labelling. Is it feasible to include these limits in any scheduling proposal?

Is it feasible to include concentration limits in other types of products in the schedules, based on the calculations in the dermal sensitisation Quantitative Risk Assessment (QRA) of the International Fragrance Association (IFRA), as reported in the NICNAS IMAP report?

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=92>.

Scheduling status

Citral, geranial and neral are not currently scheduled.

Scheduling history

As the isomers of 3,7-dimethy-2,6-Octadienal are not scheduled, scheduling history is not available.

Public pre-meeting submissions

Four public submissions were received.

The first indicated that there are other fragrance compounds that are closely related to citral that may also be used widely (e.g. citrol) and the submission focus on citral due to the short timeframe for comments and the large number of agenda items. The organisation requested that any scheduling decisions made should reflect the fact that industry may not have had sufficient time to consider the impact of scheduling decisions on all derivatives of citral and other substances on the agenda. They indicated that in the EU and the USA citral must be disclosed on the label of cosmetic products when used in rinse-off products at concentrations greater than 0.01 per cent and in leave on products at concentration greater than 0.001 per cent. The submitter suggests that these criteria recognise that citral can cause allergic reactions in some individuals. They also stated that there appeared to be no restrictions on neral or geranial, or citral when used in consumer products. It was highlighted that the International Fragrance Association (IFRA) Standard restricts the use of citral in some consumer products and cosmetics and therefore the use of the scheduling process for fragrances and flavours would be inefficient. The submission therefore requested a separate discussion on the controls of fragrance and flavours rather than commenting on each individual fragrance and flavour.

The second submission indicated that it was unclear on what concentration cut-off had been proposed and requested that the committee to consider that while not all these ingredients appear on the Australian Register for Therapeutic Goods (ARTG) ingredient list, some of these substances may be included in proprietary ingredients that are used in therapeutic goods. The submission further requested that the committee consider existing usage within proprietary ingredients and to propose cut-off concentrations that will not impact existing use in proprietary ingredients and in therapeutic goods.

The third submitter indicated that citral should remain unscheduled as the safety of the ingredient when used in fragrances has been established by IFRA. Citral has been used in fragrances contained in their cosmetic products for many years with no known safety issues. Additionally no other market restricts the use of citral in cosmetic products. If a Schedule 5 entry is adopted we strongly urge the committee and the delegate to exempt the use of citral in fragrances and flavours contained in cosmetic products.

The final submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommends that a new Schedule 5 entry for 3,7-dimethyl-2,6-octadienal isomers be created. However, there was insufficient information available to finalise the recommendation. The committee recommends that the delegate seeks further information on

- the extent of use and concentrations of this material in commercial products in Australia
- the possible regulatory impacts of scheduling
- the basis for any possible cut-off concentrations to be applied to the Schedule
- an implementation date suitable for this Schedule.

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

The reasons for the recommendation comprised the following:

- The ubiquity in products in the public domain containing these isomers resulting in extensive potential exposure.
- The potential for perceived public health concerns associated with these fragrances in domestic products.
- The extensive use of these isomers in products in Australia.
- The toxicological profile of these isomers being consistent with SPF factors for S5.

Recommendations for other action by delegate:

- Committee recommends that this substance should be listed in Schedule 5 but is unable to provide advice on whether a cut-off to exempt from scheduling is warranted and if so at what level due to lack of data provided to the committee.

Delegate's interim decision

The delegate has noted that this is not a straightforward scheduling matter. Ostensibly, the toxicity profile of the three isomers of 3,7-dimethy-2,6-Octadienal (citral, geranial and neral) appear to satisfy SPF factors for inclusion in Schedule 5, based on relatively low acute systemic toxicity, and mild skin irritancy potential. Sensitisation potential appears to be a driving force behind the NICNAS recommendation to include these substances in Schedule 5, with appropriate warning statements for those likely to suffer allergic reactions. Factors complicating the interim scheduling decision are:

- The lack of information on the extent of use of the three isomers in fragrances used in Australian products.
- The fact that some of these isomers (especially citral) may be components of essential oils that are already included in Appendix B (e.g. lemongrass oil, geranium oil), and therefore exempt from scheduling.
- If they were to be included in Schedule 5, what cut-off concentration(s) to exempt would be appropriate, and should this be driven by overseas (e.g. EU) regulations on permitted concentrations in cosmetics and/or fragrances.

The interim decision of the delegate is to defer this scheduling matter, pending the receipt of further information from industry on product types, concentrations used and the likely presence of these isomers in various essential oils. When available, this information will be referred back to the ACCS for further consideration.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;

- Scheduling factors[19];
- Other relevant information.

Submissions on interim decision

Four public submissions were received.

Two submissions supported the delegate's interim decision to defer scheduling of the substance.

The third submission indicated that as some of the 3,7-dimethyl-2,6-octadienal isomers may be components of essential oils, which may be found in therapeutic goods, future scheduling matters relating to the isomers should be considered by the joint ACCS & ACMS to ensure the cut-off limit, route of administration, function of the ingredient and possible impact on the therapeutic goods have been considered.

The fourth submission noted that there are about 20 essential oils or absolutes containing >1% citral. Many of the essential oils are used in aromatherapy and other complementary medicines and marketed or sold as pure oil products or in blends in quantities of between 0.5 to 12%w/w. The submission therefore requested the delegate consider these facts while scheduling the substance.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the decision to defer scheduling of these three chemicals, pending further consideration by the advisory committees. The delegate will refer information received on product types, concentrations used and the likely presence of these isomers in various essential oils to the advisory committees, including consideration of the potential for any scheduling actions to impact on therapeutic goods and essential oils used in aromatherapy.

The delegate has confirmed that the reasons for deferral of a scheduling decision at this time are in keeping with those for the interim decision.

1.18 ZINC LACTATE

Scheduling proposal

On 13 September 2013, NICNAS under the New Chemicals Assessment scheme has requested that the delegate consider a proposal to include the preparations containing more than 2.5 per cent zinc lactate in Schedule 6 with strong warnings listed in Appendix F of the SUSMP and use of distinctive packaging. The basis for this recommendation is that it has moderate to high acute oral toxicity and eye irritancy. The maximum permitted concentration of the chemical in any product intended for human use (or in toothpastes) should not exceed 2.5 per cent.

The delegate considered the proposal for inclusion of zinc lactate to Schedule 6.

The delegate's reason for referring this scheduling proposal to the ACCS was that zinc lactate is a chemical referred by NICNAS following evaluation as a new chemical. Its proposed use is as an ingredient in toothpastes. Other potential uses that could result in public exposure have not been identified. The NICNAS recommendation is that inclusion in Schedule 6 is warranted on the basis of its acute toxicity profile, particularly its irritancy potential, but notes that use in toothpastes at up to 2.5 per cent should not produce adverse health effects. The NICNAS notes that this conclusion

[19] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

also applies to chronic exposure to absorbed zinc from the use of toothpastes. ACCS advice is needed on how to use scheduling to limit the use and concentration of this chemical in toothpastes.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support inclusion of zinc lactate in Schedule 6, based on its acute toxicity profile, including its irritancy potential, with a cut-off to exempt at 2.5 per cent when an ingredient of toothpastes?
- Since this chemical is a complex of zinc with lactic acid, is zinc lactate the most appropriate name for listing in the schedule (there are precedents for specifically listing other inorganic and organic zinc compounds)?
- Is there a need to include a specific entry in Appendix C to limit its use in toothpastes, or is the Schedule 6 entry sufficient to control this use?
- What Appendix E & F statements should be applied to scheduled products containing zinc lactate (if any, given that a secondary notification and NICNAS assessment would be required if other uses are contemplated)?
- Are there likely to be any uses of zinc lactate inadvertently captured by the Schedule 6 entry, and should the 2.5 per cent exemption for toothpastes be a general exemption (in all products) at and below this concentration? If the exemption applies only to toothpastes, should it also specify the age range (adults and children over 12) to which the risk assessment applies?
- Is there any need for a consequential amendment to the current Schedule 4 entry for zinc compounds (it currently applies only to preparations for internal human use)?

Substance details

Zinc lactate is used as a component of toothpaste. It can also be used as a dietary supplement[20] and can be found in mouthwash, facial cleansers, breath fresheners, body wash and liquid hand soaps.[21] However, it cannot be established that such products are available in Australia or what the concentration of zinc lactate is in these products, though it is expected to be minimal[22].

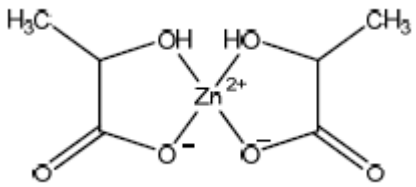

Figure 5. Structural formula of zinc lactate.

End-point of acute toxicity	Zinc lactate	SPF*
Acute oral toxicity LD_{50} (mg/kg bw)	500 – 2000	Moderate to high

[20] http://www.jostchemical.com/chemicals/2963.html
[21] http://www.goodguide.com/ingredients/111051-zinc-lactate
[22] NICNAS's Public Report on Zinc lactate. STD/1388 [http://www.nicnas.gov.au/chemical-information/new-chemical-assessments]

End-point of acute toxicity	Zinc lactate	SPF*
Acute dermal toxicity LD_{50} ((mg/kg bw)	No data	
Acute inhalational toxicity LC_{50} (mg/L/4h)	No data	
Skin irritation	Not irritant	
Eye irritation	Irritant	
Skin sensitisation	No data	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

Repeated dose toxicity

No repeated dose toxicity studies on the notified chemical were provided. Several studies on zinc compounds have been conducted *via* the oral route, in both humans and animals. In the EU report of zinc distearate (EC, 2004), a NOAEL of 50 mg Zn2+/day (0.83 mg/kg bw/day) from human studies was chosen for risk assessment purposes, based on noted effects at higher dosage levels, in particular disruption of copper homeostasis.

The Recommended Dietary Intake (RDI) for zinc is 12 mg (4.5 mg for children aged 1-3 years). Zinc lactate is a permitted form (FSANZ, 2000).

Mutagenicity

No data on the mutagenicity potential for the notified chemical was provided.

Carcinogenicity

Limited studies on the carcinogenicity potential of zinc compounds are available. It is noted in the EU report (EC, 2004) that zinc deficiency or supplementation may influence carcinogenesis, but that there is no evidence for a direct carcinogenic action of zinc.

Reproductive toxicity

In the EU report (EC, 2004), a NOAEL of >19.9 mg Zn2+/kg bw/day was adopted for developmental toxicity in animals. It is noted that a zinc deficiency results in an impairment of fertility and foetal development. Therefore, zinc was determined not to be of concern with respect to reproductive toxicity in humans.

This risk to the public associated with the use of zinc lactate at concentrations of 2.5 per cent or less when used by adults and children aged 12 years or older is not considered to be unreasonable.

Scheduling status

Zinc lactate is not currently scheduled. A Schedule 4 entry exists for Zinc compounds for human internal use, however as the use for this substance is not for human internal use this entry does not apply.

Scheduling history

There is no scheduling history for zinc lactate.

Public pre-meeting submissions

Three public submissions were received.

The first submission indicated that currently medicines containing zinc compounds for human internal use are excluded from scheduling requirements if the recommended daily dose in preparations is 25 mg or less of zinc. If the recommended daily dose is between 25 mg and 50 mg, the preparations are exempted when compliant with the requirements of the Required Advisory Statements for Medicine Labels (RASML). The product notified to the NICNAS contained 2.5 per cent of zinc lactate, or approximately 0.75 per cent of zinc. At this concentration level, even if dilution factors are not taken into account, i.e. the full average daily amount of toothpaste used (2.75 g) is ingested, the zinc intake would be below 25 mg (approximately 20 mg). Medicines containing zinc compounds that are intended to be ingested are unscheduled when the daily dose of zinc is 25 mg or less of zinc (based on the information above). The submission indicated that zinc lactate as an ingredient in cosmetics does not require scheduling.

The second submitter indicated that there are some inconsistencies with the Australian Register of Therapeutic Goods (ARTG) entry restrictions for this ingredient when used in toothpastes. The ARTG entry for the ingredient also proposes a usage limit of 2.0 per cent or less of zinc lactate for dermal use.

The third submission did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The committee recommends that zinc lactate be included in Schedule 6 with an exception cut-off to unscheduled for a) preparations containing 2.5 per cent or less of zinc lactate; and b) if in tooth paste labelled 'not recommended for children under 12 years of age', with an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- Maintaining stability in relevant products, e.g. preservatives. Risk of ingestion of excessive amount of zinc.
- Toxicity risk related to children's use of adult toothpaste. Ocular toxicity of zinc lactate.

Delegate's interim decision

The delegate partially accepts the advice of the ACCS. The delegate notes that the primary purpose behind the recommendation in the NICNAS report on zinc lactate was to restrict the concentration in toothpastes to 2.5% and, based on risk assessment calculations of daily zinc systemic intake, to limit the use of toothpastes exceeding 2.5% to adults and children aged >12 years. The Schedule 6 proposal is also partly based on the imprecise estimate of the acute lethal dose of zinc lacate, and an uncertain characterisation of its eye irritancy potential. The delegate disagrees with ACCS advice that the Schedule 6 entry be generic, with exemptions for toothpastes <2.5%. There is insufficient evidence of its potential uses and public health hazards other than in toothpastes, and unknown implications for restricting use in a broader range of products. Therefore, the delegate has decided

to limit the Schedule 6 entry to toothpastes containing 2.5% or more of zinc lactate and to apply an age exemption to products labelled with the warning '*not recommended for children under 12 years of age*'.

The delegate agrees with the implementation date of 1 June 2014.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[23];
- Other relevant information.

Submissions on interim decision

Three public submissions were received. One of the submitter (indicated below as the third submission) did not submit a public submission for the delegates' proposal inviting public comments.

The first submission indicated that the proposed concentration cut-off for toothpaste preparations containing 2.5% or less of zinc lactate was lower than orally ingested complementary medicines which do not require RASML statements. The submission therefore requested the delegate consider either increasing exemption cut-off from 2.5% to 3% or not scheduling zinc lactate for use in toothpastes. The submission also indicated that the exemption from the proposed Schedule 6 entry age exemption to products labelled with the warning '*not recommended for children under 12 years of age'* was not clear and this needs to be amended.

The second submission noted that it had no further comments on delegate's interim decision on zinc lactate.

The third submission indicated that the delegate's interim decision on zinc lactate appears to be that toothpastes containing more than 2.5% zinc lactate is in Schedule 6, and that toothpastes containing 2.5% or less of zinc lactate should be labelled "Not recommended for children under 12 years of age". The submission noted that the Schedule 6 entry would be clearer if it were to read along the following lines:

ZINC LACTATE in toothpastes **except** in toothpaste preparations containing 2.5 per cent or less of zinc lactate and labelled with the statement:

> Not recommended for children under 12 years of age.

[23] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

The submission also noted that including an entry in Appendix F Part 1 along the lines "Not recommended for children under 12 years of age", and an entry in Part 3 for zinc lactate in toothpastes.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and has determined to set aside the interim decision and refer the matter back to the Advisory Committee on Chemicals Scheduling for further advice. Issues raised in the consultation process that need further consideration include:

- Estimates of zinc intake associated with toothpaste use and the basis for the risk assessments for systemic zinc exposure in relation to other sources of zinc, including therapeutic uses.

Clarification of the basis for labelling toothpastes as '*not recommended for children under 12 years of age*' and an appropriate schedule wording to achieve this objective.

Since a final decision has been deferred, the delegate reserves further consideration of reasons under Section 52E(1).

Scheduling entry

SCHEDULE 6 – NEW ENTRY

ZINC LACTATE in toothpastes **except**

a) in toothpaste preparations containing 2.5 per cent or less of zinc lactate; and

b) when in toothpaste labelled 'not recommended for children under 12 years of age'.

In response to submissions requesting clarification of the proposed Schedule 6 entry, the delegate has withdrawn the proposed schedule entry. The matter will be referred back to the Advisory Committee on Chemicals Scheduling for further advice.

1.19 TRIETHANOLAMINE

Scheduling proposal

On 13 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, requested that the delegate consider a proposal to reschedule triethanolamine listed in Schedule 5 to provide a cut-off to except cosmetic leave-on preparations containing 2.5 per cent or less of triethanolamine.

NICNAS recommendation for public health

The NICNAS in their IMAP report recommended that an amendment to the current listing of the chemical in the SUSMP be considered. Matters to be taken into consideration include:

- a concern for irritation with leave on cosmetic products where the product contains ≥2.5 per cent of triethanolamine;

- a concern for nitrosamine formation with use of the chemical in cosmetic products under certain conditions such as when used with nitrosating systems, particularly for leave-on cosmetic products;

- pH of the cosmetic product and concentration of triethanolamine salts affecting free triethanolamine levels; and the intradermal application of the chemical is more likely to result in skin irritation, such as when used in certain tattoo removal procedures requiring intradermal

administration. Therefore, it is recommended that regulatory controls to prevent the use of intradermal application of the chemical in certain tattoo removal cosmetics be considered.

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=427>.

The delegate's reason for referring this scheduling proposal to the ACCS was that, in accordance with section 4.2 of the Scheduling Policy Framework for Medicines and Chemicals[24] (SPF, 2010), advice is required to be obtained from an expert advisory committee for all rescheduling proposals. The NICNAS IMAP report is a public document and it contains sufficient information for ACCS to provide advice. Furthermore, its recommendations would be known to industry.

Triethanolamine is already included in Schedule 5 with a cut-off to exempt for preparations containing less than 5 per cent. The NICNAS IMAP report addresses the potential for skin irritation to occur at concentrations above 2.5 per cent and recommends amending the Schedule 5 entry to include such preparations in the Schedule 5 entry (i.e. add an additional sub-clause to the exemption specific for leave-on (and other?) cosmetic preparations.

The NICNAS IMAP report also requests consideration of scheduling action to restrict preparations used by intradermal injection for tattoo removal.

The delegate sought the following specific advice from the ACCS:

- Does the ACCS support the proposed amendment to the Schedule 5 cut-off for cosmetic preparations containing more than 2.5 per cent of triethanolamine?
- Should this amended cut-off apply only to leave–on cosmetic preparations, or all cosmetic preparations?
- Is the 5 per cent cut-off for other triethanolamine preparations (e.g. cleaners) still appropriate?
- Should the current Appendices E & F statements be applied to the new clause; in particular, is a new set of Appendix F Statements needed for cosmetic products, deleting reference to Safety Direction No. 4 'avoid contact with skin'.
- What scheduling actions could best give effect to the NICNAS recommendation to restrict the use of triethanolamine applied intradermally for tattoo removal? Would this be a specific listing in Appendix C, or a new entry in Schedule 4 (similar to that for ethanolamine)?
- Does the ACCS have concerns about the potential for triethanolamine to promote the formation of nitrosamines, and is there any control that could be placed on this via scheduling?

Substance details

Use of triethanolamine

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of 1 000 – 9 999 tonnes. The following Australian uses were reported under previous mandatory and/or voluntary calls for information:

[24] National Coordinating Committee on Therapeutic Goods, 2010, *Scheduling Policy Framework for Medicines and Chemicals*

- Cosmetic use i.e. pH control and neutralising agent or in tattoo removal cream
- Domestic use i.e. neutralising and emulsifying agent in laundry detergents and household cleaning products
- Commercial use i.e. in solvents, construction material, corrosion inhibitor and in paint and printing inks
- Site-limited use i.e. manufacturing other chemicals, explosives manufacture and in waste oil treatment

The identified international uses of triethanolamine include:

- Domestic use i.e. detergents (laundry powders), cleaning and polishing products (bathroom cleaners, leather and car waxes) and disinfectants (in aerosol disinfectant air fresheners).
- Commercial use i.e. lubricants, corrosion inhibitors and paints
- Site-limited use i.e. extracting hydrogen sulphide gas, producing other chemicals (piperazine) and as a chelating agent.

Toxicity end-points

The NICNAS IMAP report notes that the critical health effects for risk characterisation of triethanolamines include acute toxicity (oral, dermal, inhalation, eye, skin and respiratory irration) and harmful effects following repeated oral exposure.

End-point of acute toxicity	Triethanolamine	SPF*
Acute oral toxicity LD_{50} (mg/kg bw)	5200 – 11 300	Low
Acute dermal toxicity LD_{50} (mg/kg bw)	>2000	Low
Acute inhalational toxicity LC_{50} (mg/L/4 h)	1800	Moderate to high
Skin irritation	Not irritant	
Skin irritation (humans)	Irritant	
Eye irritation	Irritant	
Skin sensitisation (Maximisation test and Lymph node assay)	Not a sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

Respiratory irritation

Based on the available information a classification for respiratory irritation is warranted (refer to Repeat dose toxicity—inhalation).

Observation in humans

The CIR (2013) reported that, in clinical provocative tests using 5–10 'hyperreactors,' 100 per cent triethanolamine produced an irritant reaction on non-scarified skin, 10 per cent triethanolamine was a marked irritant on scarified skin and 5 per cent triethanolamine in ethanol was slightly irritating to scarified skin (CIR, 2013).

In studies testing formulations containing 0.45–2.4 per cent of the chemical, no irritation was observed (CIR, 2013). According to the CIR expert panel, formulations containing 0.83–20.04 per cent triethanolamine were irritating. However, given the absence of detailed information regarding the formulations, this opinion is difficult to interpret.

Repeat dose toxicity

Oral

In the only available well reported study, the no observed adverse effect level (NOAEL) was >1000 mg/kg bw/day. Based on the available data, the chemical does not meet the factors for classification for repeated dose toxicity through the oral route.

Dermal

The chemical is reported to cause local (acanthosis, inflammation and ulceration of the skin) and systemic (increased kidney weights and nephropathy in female rats) effects following repeated dermal exposure.

The NOAEL for systemic renal effects was 250 mg/kg bw/day in female rats only (NTP, 1999). The systemic effects were observed at concentrations that do not warrant a hazard classification.

Inhalation

Based on the available information, no hazard classification for repeated dose inhalation toxicity is recommended. However, a classification for respiratory irritation is warranted.

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

Considering the animal studies conducted, there is no evidence of carcinogenicity through the oral route and equivocal evidence of carcinogenicity through the dermal route. The available data do not warrant hazard classification.

The International Agency for Research on Cancer (IARC) has classified the chemical as 'not classifiable as to its carcinogenicity to humans' (Group 3), based on inadequate evidence for carcinogenicity in humans and experimental animals (IARC, 2000).

The Cosmetic Ingredient Review (CIR) Expert Panel reported that while the chemical does not directly react with N-nitrosating agents to form nitrosamines, the chemical could undergo hydrolytic cleavage that results in diethanolamine. This in turn can be N-nitrosated to chemicals that may be carcinogenic. Therefore, the chemical should not be used in consumer products where N-nitroso compounds could be formed (CIR, 2013).

Reproductive and developmental toxicity

The chemical does not show specific reproductive or developmental toxicity through the dermal route and is equivocal through the oral route. The available data do not warrant a hazard classification.

International restrictions include

European Union (EU) cosmetic restriction III/62[25]: Authorised use in leave-on products at a maximum concentration of 2.5 per cent in the finished product. Furthermore, for both leave-on and rinse-off products the following restrictions apply:

- do not use with nitrosating systems;
- minimum purity: 99 per cent;
- maximum secondary amine content: 0.5 per cent (applies to raw materials);
- maximum nitrosamine content: 50 microgram/kg; and
- keep in nitrite-free containers.

Scheduling status

This chemical (excluding its salts and derivatives, except in preparations containing 5 per cent or less of triethanolamine) is listed in Schedule 5 of the SUSMP.

Triethanolamine is included in Appendix E with standard statement of A 'For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once),' G3 'If swallowed, do NOT induce vomiting', E1 'If in eyes was out immediately with water' and S1 'If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water' and in Appendix F with a warning statement 'Irritant' and safety directions of 'Avoid contact with eyes' and 'Avoid contact with skin'.

Scheduling history

The toxicological information relating to triethanolamine, and other ethanolamines (diethanolamine and monoamine) have been considered by the NDPSC over several meetings in 1995, 1996 and 2000.

Public pre-meeting submissions

Four submissions were received.

One submitter indicated that the main concern for triethanolamine is the irritation potential. Based on the information in the NICNAS IMAP report on triethanolamine, irritation is likely to be induced by chemical reaction between triethanolamine and the skin and eyes rather than through other mechanisms e.g. TRPV1 receptor agonist. The irritation potential should therefore relate to the un-neutralised triethanolamine and not the salts of the triethanolamine, which could also the rationale for the current schedule entry. The submission indicated that re-scheduling of triethanolamine is unwarranted. The submission further noted that it was unaware of any concerns raised with consumer or cosmetic products containing triethanolamine with the current scheduling controls. This may be partly due to triethanolamine being used at levels lower than allowed by current scheduling.

[25] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on Cosmetic Products (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:en:PDF)

Another submission did not provide comments regarding the delegates' proposal and indicated that it will provide comments, if required, based on the delegates' interim decision.

A third submission supported that the scheduling of triethanolamine remains as per the current schedule, and that the current allowable concentration in unscheduled products of up to 5 per cent remains unchanged. This submission commented that the regulatory restriction on concentration of triethanolamine in cosmetics was not consistent across overseas jurisdictions with restrictions in the European Union but not in the US or Canada.

The fourth submitter noted that some therapeutic goods contain triethanolamine salicylate as an active ingredient and requested that any scheduling amendment should exclude salts and derivatives from scheduling. The current Schedule 5 entry for the substance excludes salts and derivatives therefore for consistency, the proposed amendment should also excludes salts and derivatives of the substance.

ACCS advice to the delegate

The committee recommends that the current scheduling of triethanolamine remains appropriate, except when used for tattoo removal.

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

- the risks and benefits of the use of a substance.

The reasons for the recommendation comprised the following:

- evidence of significant adverse health effects when use in tattoo removal. This use potentially requires medical supervision.

Delegate's interim decision

The delegate accepts ACCS advice that the current listing of triethanolamine in Schedule 5 remains appropriate and that there is insufficient evidence of a public health concern to lower the exemption threshold from 5% to 2.5%. The delegate notes concerns raised about the potential for adverse effects associated with the use of chemical products containing triethanolamine in tattoo removal. While listing such preparations in Schedule 4 may be the most appropriate way to control this use, the delegate accepts ACCS advice such use be referred for advice from a joint meeting of the ACCS and ACMS before taking any scheduling action.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;

- Scheduling factors[26];
- Other relevant information.

Submissions on interim decision

Three public submissions were received.

Two submissions indicated that they support the delegate's decision of not to amend the current schedule triethanolamine listing. Both submissions indicated that it would be appropriate to refer this proposal either to the joint ACCS & ACMS or to the ACMS.

One submission indicated that as the delegate's interim decision on this item had no effects on therapeutic goods, it had no further comments on this issue.

Delegate's final decision

The delegate notes the submissions received in response to publication of the interim decision and confirms the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.20 TRISILOXANE, 1,1,1,3,5,5,5-HEPTAMETHYL-3-[(TRIMETHYLSILYL)OXY]-

Scheduling proposal

On 17 September, NICNAS under the New Chemicals Assessment process has recommended that the delegate consider including trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]- in Schedule 6 except when in make-up, face care products and rinse-off products at or below 34 per cent and in lip products at or below 20 per cent in which case the chemical should be included in Schedule 5.

The basis for this recommendation is:

- The chronic, carcinogenicity and reproductive toxicity data indicate the chemical has a moderate risk of producing irreversible toxicity which meets the scheduling factors for Schedule 6.
- A quantitative risk assessment based on repeat dose toxicity potential of the analogue substances (D4 and D5), indicated that body lotion should be excluded from the possible product types and the concentration of the chemical in lip products should be no more than 20 per cent.

The delegate's reason for referring this scheduling proposal to the ACCS was that this is one of several NICNAS-referred chemicals where the primary public exposure is likely to be via use of cosmetic products. The delegate requested the Advisory Committee on Chemicals Scheduling (ACCS) advice on how to best manage the scheduling aspects of such submissions.

The delegate sought the following specific advice from the ACCS:

- Given the relatively low toxicity profile of this chemical, and the fact that public exposure is only likely to occur through the use of cosmetic products containing up to 34 per cent of this organosilane chemical, does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed?

[26] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

- If scheduled, what name should be used in the listing (1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]-trisiloxane or methyl trimethicone)?
- If scheduled, what is an appropriate cut-off to a lower schedule or to exempt? Should this be 34 per cent for all cosmetic uses, or different cut-offs for different product types?
- Can the ACCS advise on whether it is possible to implement, through scheduling, the NICNAS recommendation that the chemical should not be used in body lotions or aerosols?
- Is there a need for Appendices E and F statements, given that public exposure to the pure chemical is unlikely to occur, and cosmetic products containing 34 per cent or less would not appear to warrant warning statements?
- While there is no indication cosmetic products containing this organosilane will be injected or implanted, is there any need to amend the current Appendix C entry that prohibits such use for silicones?

Substance details

Organosilicones, such as trisiloxane, has been used in various industrial applications due to their unique active surface properties. In aqueous systems, hydrophilically substituted trisiloxane derivatives function as excellent wetting agents. Trisiloxane surfactants have been used as adjuvants in agricultural applications for a long time[27].

Trisiloxane is used in the manufacture of various products, including resin, synthetic rubber, artificial synthetic fibers and filaments, pharmaceuticals and medicines, paints, coatings, adhesives, soap, cleaning compounds, toilet preparations, and household appliances[28].

Trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]- will be used at ≤34 per cent concentration in a range of cosmetics, including facial cleansers, shampoos, conditioners, shower gels, make-up removers and lip products[29].

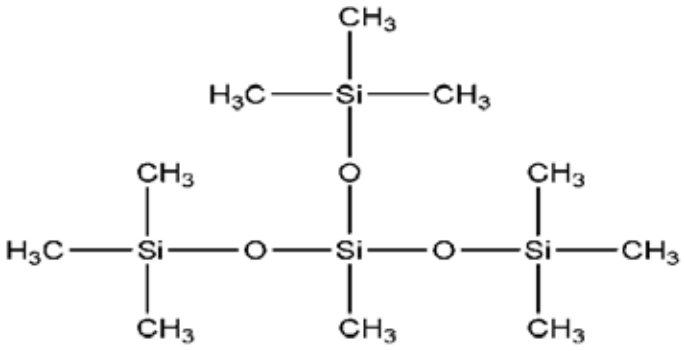

Figure 6. Structure of trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]

[27] Trisiloxane Surfactants – Mechanisms of Spreading and Wetting . Venzmeir et al

[28] Trisiloxane, 1,1,1,5,5,5-hexamethyl-3,3-bis[(trimethylsilyl)oxy]- (M4Q). Available at http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=2F7C2533-1

[29] NICNAS's Public Report on Trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]-(INCI Name: Methyl Trimethicone). LTD/1637 [http://www.nicnas.gov.au/chemical-information/new-chemical-assessments]

End-points of acute toxicity	Species	Trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]-	SPF*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Acute dermal toxicity**	Not provided	Not provided	Not provided
Acute inhalational toxicity**	Not provided	Not provided	Not provided
Skin irritation	Rabbit	Non-irritant	
Eye irritation	Rabbit	Non-irritant	
Skin sensitisation	Guinea pig	Non-sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)
**Based on studies conducted on analogue substances, namely octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5), low acute dermal and inhalation toxicity is expected for the notified chemical.

Repeat-dose toxicity

A 28-day repeat-dose oral toxicity study was conducted on the notified chemical in rats. No deaths or clinical effects were recorded for this study. While this study established a no observed effect level (NOEL) of 1 500 mg/kg bw/day, only one dose of the test substance was administered and no haematological or clinical chemistry measurements were made.

Mutagenicity

Trisiloxane was not mutagenic in a bacterial reverse mutation study and was not clastogenic in an *in vitro* mammalian chromosome aberration test.

Genotoxicity

Trisiloxane was not a genotoxic.

Reproductive toxicity

No reproductive toxicity studies were provided on trisiloxane. Studies on an analogue substance (D4) have been conducted and this chemical is classified under category 3 for reproductive toxicity (R62 Possible risk of impaired fertility; HSIS). Reproductive toxicity effects were noted in rats following inhalation. These included an increase in pre-implantation loss, increased post-implantation loss suppression of luteinising hormone surge, reductions in corpora lutea and in the number of pups born to exposed dams. While the relevance of these findings to humans and to the notified chemical is uncertain, the possibility of chronic effects following repeated, long term exposure to the notified chemical via inhalation cannot be ruled out.

Carcinogenicity

No carcinogenicity studies on trisiloxane were provided. In chronic/carcinogenicity studies conducted on analogue chemicals (D4 and D5) in rats via inhalation, endometrial adenomas were

observed at the highest dose level and were concluded to be due to threshold effects on the rat endocrine system (which was also supported by the lack of genotoxic potential). However, the relevance of these effects to humans and to the notified chemical is uncertain.

Public health

At the proposed use concentration of ≤34 per cent notified chemical in cosmetic products, acute toxicity effects are not expected. The repeated dose toxicity effects of the notified chemical have not been determined. However, based on the observation of adverse effects in analogue chemicals, D4 and D5, particularly with respect to reproductive toxicity and carcinogenicity, similar effects in the notified chemical cannot be ruled out.

Repeat dose toxicity potential was estimated by calculation of the margin of exposure (MOE) of the notified chemical using the worst case exposure scenario of 0.52 mg/kg bw/day and the no observed adverse effect level (NOAEL) of 17.8 mg/kg bw/day, which was established in toxicity studies involving the analogues D4 and/or D5. A MOE value ≥100 is considered acceptable to account for intra- and inter-species differences. Using the abovementioned NOAEL, a MOE of 34 was estimated. Thus, the risk to the public from use of the notified chemical at 34 per cent concentration in cosmetic products, including facial cleansers, shampoos, conditioners, shower gels, make-up removers and lip products is considered to be unreasonable.

In the exposure estimate, the greatest contributors were body lotion (based on the large daily exposure amount and large skin surface area) and lipstick (based on ingestion of the notified chemical). Exclusion of body lotion from the possible product types and reduction of the concentration of the notified chemical in lipstick products from 34 per cent to 20 per cent, allows recalculation of the combined internal dose to 0.182 mg/kg bw/day. A MOE of 98 is then estimated.

In light of the conservative parameters used, the risk to the public associated with the use of the notified chemical at ≤34 per cent concentration in make-up, face care products and rinse off products and ≤20 per cent in lip products is not considered to be unreasonable.

Scheduling status

Trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]- is not specifically scheduled.

Scheduling history

Not applicable.

Public pre-meeting submissions

Two public submissions were received.

One submission raised concerns with a number of aspects of the NICNAS assessment of methyl trimethicone and the scheduling proposal from scientific assessment and risk management viewpoints. The human health assessment, particularly the setting of the MOE was based on the NOAEL of "analogues" D4 (octamethylcyclotetrasiloxane) and/or D5 (Decamethylcyclopentasiloxane). It was NICNAS' decision to assign D4 and D5 as "analogues" of methyl trimethicone. The submission indicated that it failed to see the structural similarity between methyl trimethicone and D4/D5. All of these substances are silicone based and are similar in molecular weight [mass], however this is where the similarities appear to end. Without providing scientific justification for assigning D4/D5 as analogues of methyl trimethicone (e.g. mode of action for D4/D5 is known and it is likely, based on scientific logic that can be explained, that methyl trimethicone will also trigger the same toxicological response as D4/D5), the use of D4/D5 data for risk assessment of methyl trimethicone is inappropriate. There is no scientific justification in the public reports of NICNAS assessments. The only justification NICNAS put forward for the use of

D4/D5 as analogues is that the three substances have similar molecular weight [mass], water solubility, partition co-efficient and vapour pressure. The submission did not support scheduling of methyl trimethicone, D4 or D5 based on all available information on these substances.

The other did not provide comments regarding the delegate's proposal and indicated that it will provide comments, if required, based on delegate's interim decision.

ACCS advice to the delegate

The committee recommends that trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy]- does not require a schedule listing.

Delegate's interim decision

The delegate accepts ACCS advice that trisiloxane, 1,1,1,3,5,5,5-heptamethyl-3-[(trimethylsilyl)oxy] does not require scheduling, either under this name, or its INCI name, methyl trimethicone. The toxicity profile of this chemical suggests sufficiently low acute toxicity to not warrant scheduling. However, the delegate notes and agrees with concerns raised by both the ACCS and in an industry submission, that inferring a reproductive toxicity potential for this chemical, based on 'read-across' from studies with cyclic siloxanes of similar molecular weight, provides insufficient evidence of relevant toxicity for this to be considered in the scheduling process.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[30];
- Other relevant information.

Submissions on interim decision

Two public submissions were received.

One submission indicated that it supports the delegate's decision of not to include the substance in a schedule.

The other submission noted that as the delegate's decision had not impact on therapeutic goods, it had no further comments on this issue.

[30] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

1.21 C11-C15-SECONDARY, ETHOXYLATED, OXIRANE AND OXIRANE, ETHYL (OXIRANE)

Scheduling proposal

On 29 August 2013, the delegate received an application proposing the inclusion of C11-C15-secondary, ethoxylated, oxirane and oxirane, ethyl in Schedule 6. The basis for this recommendation is that the substance's high acute oral toxicity and the slight to moderate eye irritancy. The acute oral LD_{50} for the neat chemical was 550 – 2000 mg/kg in rats. Eye irritation was slight to moderate in rabbits based on the level of corneal opacity, iritis and conjunctival irritation observed.

The delegate's reason for referring this scheduling proposal to the ACCS was that although substance's proposed uses are mainly industrial and there is little likelihood that any products containing a high enough concentration to warrant scheduling would appear in the retail marketplace, it would be useful to have ACCS's advice.

The delegate sought the following specific advice from the ACCS:

- While the toxicity profile of this polymer appears to be consistent with Schedule 6 factors in the Scheduling Policy Framework, is this sufficient reason to consider including it in the SUSMP, given that the proposed use pattern is mainly industrial and there appears to be limited likelihood that products entering the domestic retail market would have concentrations high enough to warrant scheduling?
- If scheduling is warranted, is there sufficient information on acute toxicity and/or irritancy potential to determine a cut-off to a lower schedule or to exempt?
- If inclusion in Schedule 6 is supported by the ACCS, please indicate wording that would identify this specific polymeric chemical in the schedules, and suggest appropriate Appendix E (First Aid) and Appendix F (warning statements and safety directions) statements?

Substance details

The polymer contains alcohols, C11-C15-secondary, ethoxylated, oxirane and oxirane, ethyl (the polymer). The polymer is a non-ionic surfactant that will be used at up to 1 per cent concentration in products for a range of applications, including coatings (40 per cent of total import volume), industrial hard surface cleaners (25 per cent), food and non-dairy beverage cleaning (25 per cent), inks (5 per cent), and adhesives (5 per cent).

End-points of acute toxicity	Species	C11-C15-secondary, ethoxylated, oxirane and oxirane, ethyl (oxirane)	SPF*
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	550-2000;	Moderate to high toxicity
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000;	Low toxicity

End-points of acute toxicity	Species	C11-C15-secondary, ethoxylated, oxirane and oxirane, ethyl (oxirane)	SPF*
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2000	Low toxicity
Skin irritation	Rabbit	Slightly irritating	
Eye irritation	Rabbit	Irritating	
Skin sensitisation*	Human	No evidence of sensitisation	

*Scheduling Policy Framework for Medicines and Chemicals (2010)
**Study performed on an analogue polymer.

Acute oral toxicity study

In the main study 3/4 animals treated at 2000 mg/kg bw died within 1-day of dosing, with notable signs of toxicity in these animals including hypoactivity, hunched posture and/or ano-genital staining. Red discolouration of the intestines was noted at necropsy in the animals that died during the observation period. No abnormalities were noted at necropsy in animals treated at the lower doses (550 and 175 mg/kg bw).

In a second acute oral toxicity study, the notified polymer was determined by the study authors to have an LD_{50} >2000 mg/kg bw. However, it is noted that 2/5 animals tested at 2000 mg/kg bw died within 1-day of dosing, with hypoactivity and/or ano-genital staining noted in these animals prior to death. Red discolouration of the intestines or lungs was noted at necropsy in the animals that died during the observation period.

Repeated dose toxicity

No repeated dose toxicity data were submitted for the notified polymer. However, reports from three studies (90-day feeding studies) conducted on an analogue polymer in rats (treated at 62.5, 125, 250 and 500 mg/kg bw/day) and dogs (treated at 82, 154 and 354 mg/kg bw/day) were submitted.

While limited details were provided (and/or limited parameters were tested), the results indicated statistically significant mean body weight gain reductions in male and female rats dosed with the test substance at ≥125 mg/kg bw/day. The absolute liver and kidney weights were statistically significantly decreased in rats dosed with the test substance at 500 mg/kg bw/day; however, the relative weights were not significantly reduced. The no observed adverse effect level (NOAEL) in rats was established by the study authors as between 62.5 and 125 mg/kg bw/day.

In dogs, doses of 354 mg/kg bw/day resulted in severe mean body weight losses and the subsequent halting of treatment at week 6. These animals re-gained weight on the control diet by the study completion. Statistically significantly reduced haemoglobin was noted in one dog receiving the test substance at 354 mg/kg bw/day. Hydrocephalus was noted in 1 male and 2 female dogs treated with the test substance at 354 mg/kg bw/day, however, this was considered to be non-treatment related by the study authors, on the basis that it is a common lesion in dogs (although in this study, control group dogs did not have any evidence of hydrocephalus). The NOAEL in dogs, for the notified polymer has been estimated to between 150 and 350 mg/kg bw/day.

Genotoxicity

The notified chemical was not mutagenic in a bacterial reverse mutation study and was not clastogenic in an *in vitro* mammalian chromosome aberration test.

Toxicity for reproduction

No reproductive and developmental toxicity data were submitted for the notified polymer. A reproductive and developmental toxicity study that was conducted on an analogue polymer in rats (treated at 60, 168 and 470 mg/kg bw/day) was submitted. The results of the study indicated that there were no adverse effects in foetuses, but there was some systemic toxicity in male and female adults (reductions in mean body weight, food consumption and clinical signs were noted) at doses ≥168 mg/kg bw/day. Therefore, a no observed effect level (NOEL) for parental toxicity of 60 mg/kg bw/day was established and a NOAEL for reproductive/developmental toxicity was established as ≥470 mg/kg bw/day.

Public health

The public may be exposed to the notified polymer when applying the paint containing <1 per cent notified polymer by brush or roller. Spray application is not anticipated, as this requires the use of special tools. DIY use is expected to be infrequent and users may wear some PPE to minimise exposure. In addition, painting is expected to occur in ventilated environments.

The public may come into contact with products to which the coatings, adhesives and inks containing the notified polymer have been applied. However, the polymer will be bound in a matrix and will be unavailable for exposure.

Therefore, under the proposed use scenarios, the risk to public health is not considered to be unreasonable.

Scheduling status

The polymer is not specifically scheduled.

Scheduling history

Not applicable.

Public pre-meeting submissions

Two public submissions were received.

One submission indicated that the substance name [C11-C15- secondary, ethoxylated, oxirane and oxirane, ethyl (oxirane)] did not appear to represent a chemical structure. Firstly, “ethoxylated” means reacted with oxirane (synonym for oxirane is ethylene oxide). It was noted in the submission that oxirane may have been accidentally repeated but noticed that “oxirane, ethyl” which is assumed to refer to butylene oxide, is not referenced in the substance name (e.g. butoxylated). Further the word “secondary” should refer to an alkyl chemical structure such as alcohols e.g. secondary ethoxylated alcohol – this does not appear to be the case. The submitter will be interested in any scheduling proposals for ethoxylated alcohols or scheduling amendment proposals for ethylene oxide.

The second submission did not provide comments regarding the delegate’s proposal and indicated that it will provide comments, if required, based on delegate’s interim decision.

ACCS advice to the delegate

The committee recommends that a polymer which contains alcohols, C11-C15-secondary, ethoxylated, oxirane and oxirane, ethyl- does not require a schedule listing.

Delegate's interim decision

The delegate accepts ACCS advice that this polymer does not need to be included in any schedules of the SUSMP. While the polymer itself may have toxicological properties that appear to satisfy SPF factors for inclusion in Schedule 6, the likelihood is low that the public could be exposed to concentrations high enough to constitute a health hazard when it is used as a component of paints and coatings.

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

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[31];
- Other relevant information.

Submissions on interim decision

Two public submissions were received.

One submission indicated that it supported the delegate's interim decision of not to include the substance in a schedule.

The other submission indicated that as the delegate's interim decision on this polymer had no impact on therapeutic goods, it had no further comments regarding delegate's interim decision on this polymer.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

[31] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

2. Scheduling proposals referred to the November 2013 meeting of the joint Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee on Medicines Scheduling (ACMS) – ACCS & ACMS # 7

2.1 INTERPRETATION

Scheduling proposal

The Chemicals and Medicines Scheduling Delegates (the delegates) considered a proposal to include definitions, such as cosmetic use and/or personal care use, in Part 1 of the SUSMP to better define these terms and their intent and purpose.

The delegates' reasons for referring this proposal to the joint committee of the Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee on Medicines Scheduling (ACMS) include:

- Does the joint meeting of the ACCS and ACMS advise that definitions for the terms cosmetic use and personal care preparations be included in Part 1 of the SUSMP?
- If so, does the joint meeting of the ACCS and ACMS concur that the definition of cosmetic adequately covers products that could be included under the definition personal care preparations (e.g. soaps, baby wipes), thus obviating the need for a separate definition for personal care products?
- If so, does the joint meeting of the ACCS and ACMS agree that references to personal care preparations in current schedule entries be deleted as delegate-initiated editorial amendments?
- Does the joint meeting of the ACCS and ACMS agree that a definition based on the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) *Industrial Chemicals (Notification and Assessment) Act 1989* (ICNA) may have stronger legislative backing in Australia, and should form the basis for the SUSMP Part 1 entry? Please advise whether the full wording or a simple cross-reference to the NICNAS ICNA is suitable for the Part 1 entry.
- Alternatively, is a form of words based on the European Union (EU), Unites States (US) Food and Drugs Administration (FDA), US National Sanitation Foundation (NSF) or Canadian FDA products descriptions a better approach?

Substance details

The following definitions were considered by the committees and the delegates:

Definition of a cosmetics/cosmetic product

- EU - European Cosmetic Regulations – 'cosmetic product' means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours.
- USA - Federal Food, Drug and Cosmetic Act (FFDCA) - defines cosmetics by their intended use, as 'articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance'.

- Canada - Food and Drugs Act – 'cosmetic' includes any substance or mixture of substances manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth, and includes deodorants and perfumes.

- Australia - *Industrial Chemicals (Notification and Assessment) Act 1989 (ICNA)* - (modified on 1 August 2013) cosmetic means:

    (a) a substance or preparation intended for placement in contact with any external part of the human body, including:

        (i) the mucous membranes of the oral cavity; and

        (ii) the teeth;

        with a view to:

        (iii) altering the odours of the body; or

        (iv) changing its appearance; or

        (v) cleansing it; or

        (vi) maintaining it in good condition (also see Part C of the ICNA) ; or

        (vii) perfuming it; or

        (viii) protecting it; or

    (b) a substance or preparation prescribed by regulations made for the purposes of this paragraph;

    but does not include:

    (c) a therapeutic good within the meaning of the *Therapeutic Goods Act 1989*; or

    (d) a substance or preparation prescribed by regulations made for the purposes of this paragraph.

Personal care products

A search of various overseas government websites, including the US, EU and Canada, was unable to locate a specific definition for 'personal care use' or 'personal care product'.

The NSF, an independent, non-profit, standards development testing/certification organisation located in the United States, defines that:

'Personal care product: A non-medicinal consumable product that is intended to be used in the topical care and grooming of the body and hair and that is rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to a body, human or animal, for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions. Personal care products are specifically for use in such activities as cleansing, toning, moisturizing, hydrating, exfoliating, conditioning, anointing, massaging, colouring/decorating, soothing, deodorizing, perfuming, and styling.'

Cosmetic: (1) an article intended to rubbed, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) an article, other than soap, intended for use as a component of any such articles.

The document is available at:
<http://standards.nsf.org/apps/group_public/download.php/1055/Comments%20on%20Definition%20section.pdf>.

Scheduling status

There is no definition for cosmetic use in the SUSMP.

Scheduling history

There is no history to be considered as the proposal is for a new entry to be included in Part 1, Interpretation of the SUSMP.

Public pre-meeting submissions

Six submissions were received.

One submission indicated that the term 'cosmetic' is used more than 50 times in the SUSMP. It therefore supports a move to better define common terms in an unambiguous way and offered the following suggestion for cosmetic use: 'A treatment or therapeutic substance whose primary effect is to enhance the appearance of a patient without any functional benefit'.

Another submission indicated that it favours setting the definition for 'cosmetic' and not for 'personal care'.

A separate submission requested that other definitions such as human or therapeutic use and extern use should also be included in the SUSMP. The submission noted that *in vitro* diagnostic materials are now regulated as 'medical devices' and as such are 'for therapeutic use'. As a result chemical reagents typically used in basic laboratory techniques that previously did not require scheduling controls now do require (sometimes very stringent) scheduling and in recent cases new facility licensing considerations. This is causing significant difficulty particularly at state government poisons licensing level, whereas industrial chemicals these substances do not require facility specific poisons licensing but as constituents of Class I *in vitro* diagnostic materials they now do. There are likely to be numerous other examples of substances that are routinely used in diagnostic materials that are now subject to (potentially excessive) scheduling.

The fourth submission supported defining the term 'cosmetic' in the SUSMP. The submission indicated that the terms 'personal care' and 'personal care use' are not currently used in the SUSMP therefore indicated that these terms need not to be included in the SUSMP.

The fifth submission indicated that it agreed that a clear definition for 'cosmetic' should be included in the Poisons Standard, since this is a term currently used within the standard.

The last submission did not provide comments regarding the delegates' proposal and indicated that it will provide comments, if required, based on delegates' interim decision.

ACCS-ACMS advice to the delegates

The joint committee of the ACCS-ACMS recommended that a definition of 'cosmetic' be included in Part 1 of the SUSMP.

The ACCS-ACMS recommended an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- The committee agreed to include the definition in the SUSMP to avoid confusion and interpretation of the standard. The proposed definition is consistent with those in *the Industrial Chemicals (Notification and Assessment) Act 1989* and the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations 1991*.

Delegates' interim decision

The delegates note that there is a large number of current entries in the SUSMP that refer to 'cosmetic use', but that there is currently no definition in Part 1 that clarifies the types of products to which these entries refer. The delegates agree with the recommendation of the joint ACMS-ACCS, that a definition consistent with that currently used in the *Industrial Chemicals (Notification and Assessment) Act* 1989 and the Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations 1991 be included in the relevant list of definitions in Part 1, INTERPRETATION to provide clarity to existing and future SUSMP entries that use this term.

The delegates agree with the implementation date being 1 June 2014.

The delegates made their decision in accordance with subsection 52E (1) of the *Therapeutic Goods Act 1989,* clause f) – any other matters that the Secretary considers necessary to protect public health.

Delegates' considerations

The delegates considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS/ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[32];
- Other relevant information.

Submissions on interim decision

Three submissions were received. Two submissions supported the delegates' interim decision. The third submission supported the decision to include a cosmetic definition, but suggested that the full ICNA definition be included, as clause (c) (that a cosmetic is not a therapeutic good) should be included. Should the delegates decide not to include the full definition in Part 1 – Interpretation, then the submitter suggests to at least include clause that states cosmetics do not include therapeutic goods as provision (b) on the grounds that it is important for clarity.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Delegates' final decision

The delegates note the submissions received in response to publication of the interim decision and **confirm** the interim decision, as the comments received do not provide sufficient evidence to alter the interim decision. The delegates note there is support for using a definition of 'cosmetic' that is consistent with definitions already in use in the *Industrial Chemicals (Notification and Assessment)*

[32] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Act 1989 and the Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations 1991. However, the delegates do not accept the proposal to add the sub-clause in these definitions that exclude therapeutic goods, because there are several existing entries in Schedules 2 and 4 where the intention is to **include** cosmetic use.

The delegates have confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

PART 1 INTERPRETATION – New entry

"Cosmetic" means:

(a) a substance or preparation intended for placement in contact with any external part of the human body, including:

(i) the mucous membranes of the oral cavity; and

(ii) the teeth;

with a view to:

(iii) altering the odours of the body; or

(iv) changing its appearance; or

(v) cleansing it; or

(vi) maintaining it in good condition; or

(vii) perfuming it; or

(viii) protecting it.

2.2 ETHANOL, 2-(DIMETHYLAMINO) – OR DEANOL

Scheduling proposal

On 13 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, requested the chemicals and medicines scheduling delegates (the delegates) consider a proposal to include ethanol, 2-(dimethylamino)- in Schedules 5 or 6 and to make relevant amendments to the current Schedule 4 entry for deanol.

The delegates' reasons for referring this proposal to the joint committee of the Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee on Medicines Scheduling (ACMS) include:

- Does the ACCS-ACMS support the separate listing of 2-diethylaminoethanol in either Schedule 5 or Schedule 6, based on its acute toxicity potential (including irritancy)?
- If so, please recommend consequential edits for the current Schedule 4 listing.
- Is 2-diethylaminoethanol the preferred listing name rather than any of the other names included in the NICNAS IMAP report?
- Is there sufficient information on the comparative toxicity profiles of 2-diethylaminoethanol and other ethanolamines currently listed in Schedule 5 and Schedule 6 to inform the scheduling of 2-diethylaminoethanol, including possible cut-offs and entries in Appendices E & F?

- Given that consumer products (including cosmetics) are unlikely to have sufficiently high concentrations of 2-diethylaminoethanol to warrant risk-based scheduling, is there sufficient information to recommend a scheduling cut-off to exempt?
- Is it necessary to apply scheduling to enable alignment of Australian cosmetic product regulation with that of the EU, which places a limit of 2.5 per cent in leave-on cosmetics?
- If the ACCS/ACMS advice is to include 2-diethylaminoethanol in either Schedule 5 or Schedule 6, is there sufficient information to determine any scheduling impacts on AGVET or other commercial products containing this chemical as an ingredient?

Substance summary

Please refer to the NICNAS IMAP Tier II Human Health Assessment Report for ethanol, 2-(dimethylamino)-. This report is available on the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=50>.

Two-dimethylaminoethanol (DMAE), a precursor of choline, may enhance central acetylcholine formation. It has been employed as a central stimulant in the treatment of hyperactive children but its efficacy has not been substantiated33.

DMAE has been used as an ingredient in skin care, and in cognitive function and mood enhancing products. It is marketed as a free base or salt, and in theory, the two forms should be equally effective and able to substitute for each other in pharmaceutical formulations[34].

The NICNAS notes that the substance will be used for various purposes, including:

- cosmetic (as a buffering agent in cosmetic products);
- domestic (in paints, lacquers and varnishes and in cleaning/washing agents); and
- site-limit use (as a catalyst in the production of flexible and rigid polyurethane foams and polyurethane lacquers, reactant in the manufacture of ion exchange resins and pharmaceuticals and component of corrosion inhibitor formulations).

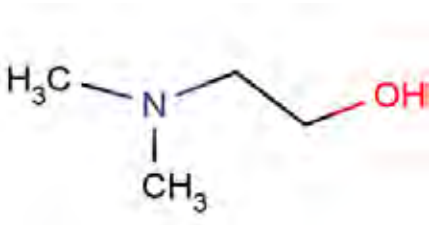

Figure 8. Structural formula of deanol.

End-point of acute toxicity	DMAE	SPF*
Acute oral toxicity LD_{50} (mg/kg	1183 (1203 mg/kg bw in males and 1220 mg/kg bw in	Moderate to high toxicity

[33] Martindale. Thirty-second edition.

[34] Structural characterization and stability of dimethylaminoethanol and dimethylaminoethanol bitartrate for possible use in cosmetic firming. Clares et al. Available at http://www.ncbi.nlm.nih.gov/pubmed/20716435.

End-point of acute toxicity	DMAE	SPF*
bw)	females)	
Acute dermal toxicity LD_{50} (mg/kg bw)	1220 - 3135	Low to moderate toxicity*
Acute inhalational toxicity LC_{50} (mg/L)	6.5	
Skin irritation	Irritant	
Eye irritation	Irritant	
Skin sensitisation	Sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

[**Secretariat's Note:** if the acute dermal toxicity LD_{50} value is between 200 mg/kg and 2000 mg/kg, it is considered to be a Schedule 6 substance (moderate to high toxicity) and if the value is above 2000 mg/kg, it meets the Schedule 5 factors (low toxicity).]

Repeat-dose toxicity

Oral

No data is available.

Dermal

No data is available.

Inhalation

Apart from decreased body weight gain and lesions in exposed areas due to the corrosive nature of the chemical, no other adverse systemic effects were reported in the single study available. Groups of 20 rats/sex were exposed to the chemical vapour at 0, 8, 24 or 76 ppm for six hours/day, five days/week for 13 weeks. Decreased body weight gain and histopathological lesions of the eye, respiratory and olfactory epithelium was observed at 76 ppm. Transient corneal opacity occurred at the end of each of the exposure periods at 24 and 76 ppm. This reversible effect is likely to be due to the corrosive properties of the undiluted substance. The study included histopathological examination of the testes—no adverse effects were reported for this organ. The no observed adverse effect concentration (NOAEC) for systemic effects was 24 ppm, but the NOAEC was 8 ppm for local effects on the eye (OECD, 2001).

Genotoxicity

Based on the data available, the chemical is not considered genotoxic.

Carcinogenicity

No data is available.

Reproductive/developmental toxicity

Based on the limited data available, the chemical is not considered to have reproductive or developmental toxicity.

Public exposure

Considering that the chemical is used in cosmetics and domestic products, the main public exposure is expected to be through the dermal route. Inhalation and accidental ingestion may also be possible.

However, as the chemical is expected to be used only as a buffering agent in cosmetics, high concentrations of the chemical as the free amine are not expected to be present in cosmetic formulations or products.

Duration of exposure to the chemical will depend on the type of product (i.e. a rinse-off or a leave-on cosmetic product). No data on the Australian use pattern are available for cosmetic use and there are no restrictions for using this chemical in Australia. The EU has restrictions on the use of this chemical in cosmetics (2.5 per cent maximum in leave-on products).

The irritant and corrosive properties of the chemical can be attributed to its strong alkaline nature. When used as a buffering agent in cosmetic products, extremes of pH are not expected and no irritation risk is likely.

The chemical is used as a dispersant aid and a neutralising agent in waterborne paint products (OECD, 2001). Although up to 5 per cent concentration is used in industrial products, only a fraction of a per cent is used in consumer products (OECD, 2001). Therefore, the chemical at very low concentrations (<1 per cent) in consumer products is not expected to cause unreasonable risk to the public.

International regulations

The NICNAS indicates that under EU regulation this chemical is restricted under 'trialkylamines, trialkanolamines, and their salts' where the maximum concentration allowed in leave-on products is 2.5 per cent.

Scheduling status

Deanol is listed in Schedule 4.

Other amines such as ethanolamine, diethanolamine and triethanolamine are listed in Schedule 5 and Appendices E and F. Apart from Schedule 5 listing, ethanolamine is also listed in Schedules 4 and 6. Diethanolamine is also listed in Schedule 6.

Scheduling history

Deanol is listed in Schedule 4.

Other amines such as ethanolamine, diethanolamine and triethanolamine are listed in Schedule 5 and Appendices E and F. Apart from Schedule 5 listing, ethanolamine is also listed in Schedules 4 and 6. Diethanolamine is also listed in Schedule 6.

Scheduling history

Deanol

Deanol is first listed in Schedule 4 in February 1971 by the Poisons Schedule Sub-Committee (PSC). No reasons were given for this decision.

Ethanolamine

In May 1993, the Drugs and Poisons Schedule Sub-Committee decided to include ethanolamine for therapeutic use in preparations for injections in Schedule 4. In November 1999, the NDPSC decided to delete 'therapeutic use' from ethanolamine's Schedule 4 entry based on a recommendation from the Trans-Tasman Harmonisation Working Party.

In May 1995, the NDPSC decided to include preparations containing more than 5 per cent and up to 20 per cent ethanolamine (excluding its salts and derivatives) in Schedule 5 and all other preparations (except when included in Schedules 4 and 5) in Schedule 6. The NDPSC also decided to include ethanolamine in Appendices E and F. This decision was based on ethanolamine's potential for corrosive injury to eyes and skin.

Diethanolamine and triethanolamine

In May 1974, the PSC decided to include triethanolamine in Appendix B. No rationale was given for this decision. In May 1995, the NDPSC decided to remove triethanolamine from Appendix B entry.

In February 1997, the NDPSC decided to include preparations containing more than 5 per cent and up to 20 per cent diethanolamine (excluding its salts and derivatives) in Schedule 5 and all other preparations in 6. The NDPSC also decided to include preparations containing more than 5 per cent triethanolamine (excluding its salts and derivatives) in Schedule 5. Moreover, the NDPSC decided to include diethanolamine and triethanolamine in Appendices E and F.

Public pre-meeting submissions

Three public pre-meeting submissions have been received. One submission states that for deanol for therapeutic use, the current Schedule 4 entry remains appropriate. However, to accommodate non-therapeutic uses of the substance, the Schedule 4 entry could be amended to state deanol for therapeutic use. The submission did not provide comment on the suggestion of Schedule 5 or Schedule 6 entries.

The second submission noted no reports of deanol being used in Australia for industrial purposes, but did provide a list of industrial uses internationally. The submission also noted that salts and derivatives of deanol being used in cosmetics and topical therapeutics like sunscreens. Based on this, the submitter suggested amending the Schedule 4 entry to read 'deanol for therapeutic use excluding topical therapeutic use'.

The third submission did not provide comment at this time, but wished to be advised of the committees' recommendations and the delegates' interim decision so to provide a further submission if appropriate.

ACCS/ACMS advice to the delegates

The committees recommend that the current entry in Schedule 4 for deanol be amended to include 'for therapeutic use'. In addition, the committee recommends that a cross-reference with IUPAC and INCI names is appropriate.

The implementation date will be 1 June 2014.

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

The reasons for the recommendation comprised the following:

- When used therapeutically it needs to remain in Schedule 4. There are other legitimate uses that are regulated by other means.
- Potential for misuse.

Delegates' interim decision

The delegates accept the advice of the joint ACMS/ACCS that there is insufficient evidence of a public health risk to consider regulating the use of this chemical in cosmetics and household products by inclusion in Schedule 5. However, it is necessary to edit the current Schedule 4 to ensure that it regulates only products for therapeutic use. The delegates also agree that cross-referencing the DEANOL entry in the index under other commonly used names (DMEA, dimethyl MEA and 2-(dimethalamino)ethanol will assist interpretation of the entry.

The delegates agree with the implementation date being 1 June 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegates included: b) the purpose for which a substance is to be used and the extent of use and f) – any other matters that the Secretary considers necessary to protect public health.

Delegates' considerations

The delegates considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS/ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[35];
- Other relevant information.

Submissions on interim decision

Two submissions were received. Both submissions supported the delegate's interim decision.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Delegates' final decision

The delegates note the submissions received in response to publication of the interim decision and **confirm** the interim decision as no evidence has been received to alter the interim decision. The delegates have confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Schedule 4 – Amendment

DEANOL for therapeutic use.

[35] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Index – cross-reference

DEANOL

See 2-(dimethylamino)ethanol, DMEA, DIMETHYL MEA

2-(dimethylamino)ethanol

See DMEA, DIMETHYL MEA, DEANOL

DMEA

See DIMETHYL MEA, DEANOL, 2-(dimethylamino)ethanol

DIMETHYL MEA

See DEANOL, 2-(dimethylamino)ethanol, DMEA

2.3 SALICYLIC ACID

Scheduling proposal

On 13 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, requested the chemicals and medicines scheduling delegates (the delegates) consider a proposal to amend the current Schedule 3 and Schedule 4 entries for salicylic acid and possibly create a new Schedule 5 entry to align with the restrictions of European Union (EU) on the use of salicylic acid in cosmetics to a maximum concentration of 3 per cent.

The delegates' reasons for referring this proposal to the joint committee of the Advisory Committee on Chemicals Scheduling (ACCS) and the Advisory Committee on Medicines Scheduling (ACMS) include:

- Does the joint meeting of the ACCS and ACMS support the creation of a separate schedule entry for salicylic acid to conform with European Union (EU) restrictions on its use in cosmetics?
- Can the joint meeting of the ACCS and ACMS suggest any justification for a schedule entry that is so restrictive of dermal use in cosmetics, when use for therapeutic purposes is unrestricted for dermal preparations containing up to 40 per cent salicylic acid?
- Which schedule is the more appropriate for a cosmetic entry for salicylic acid (if needed), with what cut-offs, and with what Appendix E and F entries?
- Please suggest any necessary consequential amendments to the current Schedule 3 and Schedule 4 entries.

Substance details

Please refer to the NICNAS IMAP Human Health Tier II Assessment Report, which is available on the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=138>.

Scheduling status

Salicylic Acid is listed in Schedule 3 in preparations for dermal use except in preparations containing 40 per cent or less of salicylic acid.

Sodium Salicylate (Benzoic acid, 2-hydroxy-, monosodium salt) is listed in Schedule 4 in preparations for injection for the treatment of animals.

Scheduling history

In February 1974, the Poisons Standard Sub-committee reviewed the scheduling of analgesics after reports of bleeding from gastric ulcers and renal damage were received. The committee decided that all non-narcotic analgesics should be scheduled to limit availability to the public and to seek the opinion on limitation of pack size from the States' Poisons Advisory Committees. The recommended scheduling for salicylic acid was Schedule 3.

At the February 1974 meeting, the committee received correspondence from the Chiropody Board of South Australia which highlighting adverse effects of preparations containing caustic substances, mainly salicylic acid. The Board suggested products should carry warning labels. Again the committee sought the opinion of the State Poisons Advisory Committees. It was last mentioned in the meeting minutes of February 1975 after being deferred in previous meetings, where the committee was still waiting for the opinion of the Australasian College of Dermatologists.

In November of 1998, the NDPSC decided to include sodium salicylate in Schedule 4 in preparations for injection for the treatment of animals, as sodium salicylate would be expected to have a similar toxicity profile to that of aspirin (Schedule 4 for injection) and that veterinary supervision was needed to ensure appropriate use of the injectable form.

The Schedule 3 entry for salicylic acid appeared in the 2007 publication of the SUSMP. The entry was referred to in the June 2006 NDPSC meeting in relation to Trans-Tasman Harmonisation – asking New Zealand to consider amending its entry from 'external use' to 'dermal use' in line with Australian Scheduling. However, the decision for the Schedule 3 entry cannot be located.

Public pre-meeting submissions

Four public pre-meeting submissions have been received. One submission believes the current scheduling of salicylic acid is appropriate, however if there is a need to set a limit for cosmetic preparations, the wording should be carefully considered so only to apply cosmetics.

The second and the third submission do not support the proposal and has provided evidence from the 2001 Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNRP), which the submitter believes the NICNAS IMAP report for salicylic acid is based on.

The fourth submission did not provide comment at this time, but wished to be advised of the committees' recommendations and the delegates' interim decision so to provide a further submission if appropriate.

ACCS-ACMS advice to the delegates

The committees recommend that the current salicylic acid listing in the Schedules remains appropriate.

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

The reasons for the recommendation comprised the following:

- No evidence for failure in the existing control system being used therapeutically at concentrations higher than the proposed cut-off.

Delegates' interim decision

The delegates accept the advice of the joint committee of ACMS and ACCS that there is no need to amend the current schedule entries for salicylic acid, simply to align with overseas regulation of its

use in cosmetics. The delegates note that the current Schedule 3 entry, regulating the dermal use of salicylic acid in therapeutic goods, exempts preparations containing less than 40%.

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

Delegates' considerations

The delegates considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- ACCS-ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[36];
- Other relevant information.

Submissions on interim decision

Three submissions were received. All 3 submissions supported the delegates' interim decision.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Delegates' final decision

The delegates have confirmed the interim decision as no evidence has been received to alter the interim decision. The delegates have confirmed that the reasons for the final decision are in keeping with those for the interim decision.

3. Scheduling proposals referred to the November 2013 meeting of the Advisory Committee on Medicines Scheduling (ACMS) – ACMS # 10

3.1 ESOMEPRAZOLE

Scheduling proposal

The medicines scheduling delegate considered a proposal for a new Schedule 3 entry for esomeprazole in oral preparations containing 20 mg or less of esomeprazole per dosage unit for the relief of symptoms for gastro-oesophageal reflux (heartburn) and symptoms of gastro-oesophageal reflux disease in packs containing not more than 14 days supply.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Substance details

Esomeprazole is the S-isomer of the proton pump inhibitor omeprazole and is used similarly in the treatment of peptic ulcer disease and nonsteroidal anti-inflammatory drug (NSAID)-associated ulceration, in gastro-oesophageal reflux disease and the Zollinger-Ellison syndrome. It is given as

[36] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

the magnesium or sodium salt but doses are calculated in terms of esomeprazole. Esomeprazole magnesium 22.2 mg and esomeprazole sodium 21.3 mg are each equivalent to about 20 mg of esomeprazole.

In the United Kingdom, the dose for treatment of severe (erosive) gastro-oesphageal reflux disease is 40 mg once daily for 4 weeks, extended for a further 4 weeks if necessary; in the USA, where doses of 20 to 40 mg daily are permitted for initial treatment, a further 4 to 8 weeks of treatment may be considered for patients who do not heal after 4 to 8 weeks. For maintenance, or for symptomatic disease without erosive oesophagitis, doses equivalent to 20 mg of esomeprazole daily may be used in both countries.

Scheduling status

Esomeprazole is currently listed in Schedule 4 of the Poisons Standard.

Scheduling history

Esomeprazole

In November 2000, at the request of the New Zealand Ministry of Health, the National Drugs and Poison Scheduling Committee (NDPSC) considered scheduling esomeprazole to harmonise with New Zealand's inclusion of the substance in Schedule 1, Part 1 (equivalent to Schedule 4 of the SUSMP). Noting the benefit to public health, the committee supported harmonisation and made the decision to include esomeprazole in Schedule 4.

Omeprazole

Omeprazole was first considered by the Drugs and Poisons Scheduling Committee (DPSC) in May 1989 as the first in a new class of drug that was useful for the treatment of duodenal ulcers, reflux and Zollinger-Ellison syndrome. The committee recommended it be entered in Schedule 4.

It was then reconsidered in November 2001 for veterinary use, which was captured by its Schedule 4 entry.

Omeprazole and other Proton Pump Inhibitors (PPIs) (pantoprazole and lansoprazole) were considered for a Schedule 3 entry in February 2010. Members supported a limit of 20 mg per dosage unit and limited pack size to no more than 14 days supply after considering the mode of action, safety profile and intended use. The committee decided to create a new Schedule 3 entry for omeprazole in oral preparations containing 20 mg or less of omeprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days of supply.

In the same meeting in February 2010, the committee discussed including esomeprazole in their consideration, however felt that consideration should only be given to the substance mentioned in the proposal.

Public pre-meeting submissions

Three public submissions were received. All 3 submissions supported the proposal due to esomeprazole having similar benefit/risk profile to other Schedule 3 PPIs and for the consistency in PPI scheduling.

ACMS advice to the delegate

The ACMS recommended inclusion of a new Schedule 3 entry for esomeprazole in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms

of gastro-oesophageal reflux disease, in packs containing not more than 14 days supply and amending the current Schedule 4 entry.

The ACMS recommended an implementation date of 1 June 2014.

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

The reasons for the recommendation comprised the following:

- Safety profile is consistent with other PPIs and appropriate for a Schedule 3 entry.
- Consistent with other PPIs for short-term use for symptomatic relief on the advice of a pharmacist.

Delegate's interim decision

The interim decision is to amend the SUSMP by including a new Schedule 3 entry for esomeprazole in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days supply and to amend current Schedule 4 entry to reflect the new Schedule 3 entry.

The delegate agrees with the implementation date being 1 June 2014.

The delegate decided that the relevant matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* include: 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 of a substance, and c) the toxicity of a substance.

The reasons for the interim decisions are:

- The well-established safety profile of the substance was supported by good clinical trial evidence and is appropriate for a Schedule 3 entry.
- The first-line use of PPIs in general, and esomeprazole in particular, for typical symptoms of gastro-oesophageal reflux disease (GORD) is recognised and supported by good clinical trial evidence and meta-analyses (Cochrane reviews).
- That esomeprazole was the only Protein Pump Inhibitor (PPI) not listed in Schedule 3 and that the safety profile of esomeprazole is comparable to those PPIs listed in Schedule 3.
- As supported by the evidence, there should be consistency of scheduling with the other PPIs for short-term use for symptomatic relief on the advice of a pharmacist

Delegate's consideration

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- Public submissions received;
- The evaluation report (no publically available);
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;

- Scheduling factors[37];
- Other relevant information.

Submissions on interim decision

Two submissions were received, both supporting the delegate's interim decision.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

Schedule 3 – New entry

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

Schedule 4 –Amendment

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

3.2 MACROGOLS

Scheduling proposal

The medicines scheduling delegate considered a proposal to either amend the current Schedule 3 entry or create a new Schedule 2 entry for macrogols when in liquid concentrate preparations for oral use in adults and children over 12 years of age for laxative use, with a potential inclusion of a concentration cut-off and/or limited pack size.

The delegate referred the proposal to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Substance details

Macrogol 3350 (macrogols) is the Australian approved name for polyethylene glycol (PEG). It is typically inert and a non-immunogenic chemical that confers greater water solubility to proteins. Macrogol is used as a laxative medicine and to treat constipation. It works by increasing the stool volume, which triggers colon motility via neuromuscular pathways. The consequence is an improved propulsive colonic transportation of the softened stools through the bowel to be emptied.

Scheduling status

Macrogols, in both liquid concentrate form (the product currently undergoing product review) and in powder form (product currently on the market), is unscheduled for laxative use.

[37] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Scheduling history

At the May 2000 National Drugs and Poisons Scheduling Committee (NDPSC) meeting, Macrogol 3350 in preparations for bowel cleansing was first scheduled in Schedule 3.The decision was based on the available toxicity profile of Macrogol 3350 comparable to sodium phosphate, which was in Schedule 3.

In August 2000, the NDPSC declined a proposal to include Macrogol 3350 in Appendix H, for the reasons that there was no clear benefit from advertisement. At this meeting the NDPSC also noted that Macrogol 3350 was indicated for bowel cleansing *prior to surgery or investigative procedures*.

In October 2002, the NDPSC noted that the Schedule 3 entry for sodium picosulphate *oral preparations for bowel cleansing prior to diagnostic, medical and surgical procedures* was harmonised with New Zealand. The NDPSC was of the view that it would be appropriate to amend the entries for sodium phosphate and Macrogol 3350 to be consistent with the entry for sodium picosulphate. The scheduling entry for Macrogol 3350 was amended from 'in preparations for bowel cleansing' to 'in oral preparations for bowel cleansing prior to diagnostic, medical and surgical procedures'.

In October 2006, as a result of the Trans-Tasman Harmonisation Working Party recommendations, the NDPSC decided to adopt the New Zealand class entry 'macrogols' and delete the Australian entry Macrogol 3350.

Public pre-meeting submissions

Two public submissions were received.

One submission seemed in favour of the proposal provided that the scheduling proposal was based on a recommended daily dosage, with a pack size consistent with short-term use. Access to a health care professional was advisable.

The other submission did not support the proposed scheduling and believed that the current status of being unscheduled is appropriate as the presentation of the product makes it clear that the substance contained in the product requires dilution prior to use. They also commented that the risk/benefit of macrogol in liquid form has been shown to be no different to that of macrogol powder for solution.

ACMS advice to the delegate

The ACMS recommended creating a new Schedule 2 entry for macrogols in preparations for oral use as a liquid concentrate for laxative use.

The ACCS recommended an implementation date of 1 June 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the committee included: a) the risks and benefits of the use of a substance and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the recommendation comprised the following:

- The need for diluted form justifies a Schedule 2 entry.
- Supply to the consumer needs to be in an environment where professional advice is available.

Delegate's interim decision

The delegate accepts the advice of the ACMS and the interim decision is to include a new Schedule 2 entry in the SUSMP being:

MACROGOLS in preparations for oral use as a liquid concentrate for laxative use.

The delegate agrees with the implementation date being 1 June 2014.

The delegate decided that the relevant matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* include: a) the risks and benefits of the use of a substance and d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for this decision are:

- The need for dilution of the concentrated liquid justifies a Schedule 2 entry.
- Due to concerns regarding the potential for misuse of the liquid concentrate, supply to the consumer needs to be in an environment where professional advice is available.

Delegate's consideration

- Scheduling proposal;
- Public submissions received;
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[38];
- Other relevant information.

Submissions on interim decision

A submission was provided, informing the delegate that the reasons for decision was being considered and that further comment may be provided at a later date. The submission did mention that liquid macrogols was currently in the supply chain to Australia and that the delegate's final decision may impact on product artwork and shipping.

Edited versions of these submissions are available at Public submissions on scheduling matters.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

Scheduling entry

SCHEDULE 2 – New entry

MACROGOLS in preparations for oral use as a liquid concentrate for laxative use.

[38] Scheduling Policy Framework for Medicines and Chemicals (2010) [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

Part B - Final decisions on matters not referred to an expert advisory committee

4. Chemicals

4.1 AFOXOLANER

The Chemicals Scheduling Delegate (the delegate) considered a proposal to include afoxolaner in Schedule 5.

The delegate decided to make a delegate-only decision. The Advisory Committee on Chemicals (ACCS) was not consulted.

Scheduling status

Afoxolaner, an isoxazoline group of chemical, is not specifically listed in the SUSMP. Another isoxazoline chemical, namely isoxaflutole is listed in Schedule 5.

SCHEDULE 5

ISOXAFLUTOLE.

Scheduling history

Isoxaflutole was first considered in May 1997 by the National Drugs and Poisons Schedule Committee (NDPSC). The NDPSC, based on its acute toxicity profile decided to include isoxaflutole in Schedule 5.

Substance summary

Afoxolaner, a member of the isoxazoline family, binds at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA)[39]. Afoxolaner, a new ectoparasiticide, is systemically active against ticks and fleas. The benefits of a product containing afoxolaner are its efficacy in the treatment of flea and tick infestations on dogs. The product is in general well tolerated at the recommended dose, adverse reactions (gastrointestinal effects) were only observed in overdoses[40].

[39] 4-Azolylphenyl isoxazoline insecticides acting at the GABA gated chloride channel. Lahm et al March 2013. Bioorganic and Medicinal Chemistry Letters 2013 May 15;23(10):3001-6. Available at http://www.ncbi.nlm.nih.gov/pubmed/23566518

[40] Committee for Medicinal Products for Veterinary Use Summary of opinion (initial authorisation) NexGard International non-proprietary name (INN): Afoxolaner. European Medicines Agency. Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/medicines/002729/smops/Positive/vet_smop_000124.jsp&mid=WC0b01ac058008d7aa]

Toxicity of the technical grade active constituent

The summary of acute toxicity studies is shown in the table below.

End-point of toxicity	Species	Afoxolaner	SPF* classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	>1,000 (no deaths)	Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	>2000 (no deaths)	Low toxicity
Inhalational	-	No study submitted	Not applicable
Skin irritation	Rabbits	Non-irritant	[redacted]
Eye irritation	Rabbits	Non-irritant	
Skin sensitisation	Mice (local lymph node assay)	Non-sensitiser	

**SPF – Scheduling Policy Framework for Medicines and Chemicals (2010)*

Repeat-dose toxicity potential

In repeat-dose toxicity studies, the most sensitive species was the rat, with reduced body weight gain and food consumption at 50 mg/kg bw/d in a 90-day study, with effects noted as early as week 2 of treatment. The NOEL for this study was 10 mg/kg bw/d.

Across repeat-dose toxicity studies, treatment-related reductions in body weight gain and/or body weight loss, as well as reduced food consumption were commonly found effects in all species tested. In most studies, a cascade of adaptive metabolic effects were noted and considered secondary to treatment-related decreased food consumption and decreased body weight gain.

Carcinogenic potential

No carcinogenicity studies were submitted in support of afoxolaner. In this case, noting the use pattern of substance in the product as a once-monthly treatment in a non-food-producing use situation, carcinogenicity studies were not required for the purposes of this risk assessment. The OCS notes that there was no evidence that afoxolaner would be an *in vivo* genotoxicant.

Genotoxicity potential

There was no evidence of a mutagenic and/or genotoxic potential *in vitro* with and without metabolic activation or *in vivo*.

Developmental and reproductive toxicity potential

Studies in rats and rabbits did not show any evidence of afoxolaner being a reproductive or developmental toxicant.

Neurological toxicity potential

No specific neurotoxicity studies were submitted, though in the single- and repeat-dose toxicity studies conducted, no evidence of neurotoxicity was observed.

Toxicity of the product

No acute studies were submitted on the formulated product. The potential acute toxicity was extrapolated from data on the excipients.

The summary of acute toxicity studies on the product is shown in the table below.

End-point of toxicity	Toxicity of the product
Acute oral toxicity LD_{50}	Low toxicity*
Acute dermal toxicity LD_{50}	Low toxicity*
Inhalational	No studies submitted**
Skin irritation	Non-irritant
Eye irritation	Non-irritant*
Skin sensitisation	Not sensitising

* based on the toxicological profile of all ingredients in the product.
** expected to be low exposure by this route, due to nature of formulation.

Delegate's consideration

The delegate considered the following in regards to this application for re-scheduling.

- evaluation report (not publically available);
- section 52E of the Therapeutic Goods Act 1989;
- scheduling factors[41]; and
- other relevant information.

Delegate's interim decision

Afoxolaner had low acute toxicity profile to be consistent with the Scheduling Policy Framework for Medicines and Chemicals factors for listing in Schedule 5. More significant toxicity would be expected with repeated dosage, due to accumulation of active drug.

The acute poisoning risk to humans (in particular children) is low, partly associated with the proposed packaging of only six tablets in blister packaging.

The delegate also considered whether a Schedule 4 listing for afoxolaner could be more appropriate, providing for oversight of treatment by a veterinarian. The delegate indicated that because the

[41] *Scheduling Policy Framework for Medicines and Chemicals (2010)* [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

treatment instructions are sufficiently clear that pet owners should be able to manage the required dosage regimen without a veterinarian's oversight.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

An early implementation date is proposed to facilitate marketing of the product when registered by the APVMA. The delegate therefore proposes an implementation date of 1 June 2014.

Scheduling entry

SCHEDULE 5 - NEW ENTRY

AFOXOLANER for the treatment and prevention of flea infestations and control of ticks in dogs in oral divided preparations each containing 140 mg or less of afoxolaner per dosage unit.

4.2 FLUENSULFONE

Scheduling proposal

The Office of Chemical Safety (OCS) evaluated the data provided in support of an application for the approval of a new active constituent fluensulfone. The OCS recommended that fluensulfone be included in Schedule 6 in the S*tandard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

The delegate decided to make a delegate-only decision. The Advisory Committee on Chemicals (ACCS) was not consulted.

Scheduling status

Fluensulfone is not specifically scheduled.

Scheduling history

As fluensulfone is not specifically scheduled, the scheduling history is not available.

Substance summary

Fluensulfone is a novel nematicide developed for agricultural use (soil incorporation) for the control of root knot nematodes in cucurbits and fruiting vegetables. Fluensulfone belongs to a new chemical class, namely fluoroalkenyle (-thioether).

Toxicity

Acute toxicity of the technical grade active constituent

The summary of acute toxicity studies is shown in the table below.

End-point Toxicity	Species	Fluensulfone	SPF* Classification
Oral LD_{50} (mg/kg bw)	Rats	671	Moderate to high
Dermal LD_{50} (mg/kg bw)	Rats	>2,000	Low toxicity

End-point Toxicity	Species	Fluensulfone	SPF* Classification
Inhalational LC_{50} (mg/m^3/4h)	Rats	>5,100	Low toxicity
Skin irritation	Rabbits	Slight	
Eye irritation	Rabbits	Non-irritant	
Skin sensitisation	Guinea pigs	Sensitiser	

**Scheduling Policy Framework for Medicines and Chemicals (2010)*

Acute toxicity of the product

The summary of the acute toxicity studies on the product containing fluensulfone are listed in the below table.

Toxicity	Species	fluensulfone	SPF* Classification
Oral LD_{50} (mg/kg bw)	Rats	>300 - < 2000 mg/kg bw	Moderate to high
Dermal LD_{50} (mg/kg bw)	Rats	>2,000	Low toxicity
Inhalational LC_{50} (mg/L)	Rats	> 6.0 (equates to 6,000 mg/m^3)	Low toxicity
Skin irritation	Rabbits	Moderate	
Eye irritation	Rabbits	Moderate eye irritant	
Skin sensitisation	Guinea pigs	Sensitiser	

**Scheduling Policy Framework for Medicines and Chemicals (2010)*

Short-term toxicity

Oral toxicity

In a 4-week dietary study, mice (5/sex/dose) were fed with 0, 100, 500 and 2000 ppm (equivalent to 0/0, 30/41, 101/155, and 375/353 mg/kg bw/day in males/females, respectively). Food intake was decreased at 500 ppm (28-33%) and 2000 ppm (34-63%) in both sexes. Water consumption was slightly increased at 2000 ppm in females. Body weight loss was observed at 2,000 ppm in the first week of treatment in both sexes. At the end of treatment the mean body weight difference from the controls was -13% in males at 2000 ppm.

Dermal toxicity

In a dermal toxicity study, 10/sex/dose rats were exposed (for 6 hours each day for 5 consecutive days per week) to 0, 80, 400 or 2000 mg/kg bw/day.

No mortality occurred, and no clinical signs of toxicity were observed. Transient reductions in food consumption were noted in males at 400 mg/kg bw/day and in both sexes at 2000 mg/kg bw/day. A slight reduction in body weight gain, driven by a decrease in body weight gain during week 1 of the study, was noted in males at the 2,000 mg/kg bw/day dose level. In females dosed with 2000 mg/kg bw/day fluensulfone, slight alterations in haematological (increased red cell volume distribution width, decreased mean corpuscular haemoglobin concentration, and increased reticulocytes) and clinical chemistry (increased cholesterol, reduced serum ALAT) parameters were observed.

Sub-chronic toxicity

Oral toxicity

In a 90-day dietary toxicity study, 12/sex/dose mice received diets containing 0, 60, 300 and 1500 ppm (equivalent to 0/0, 11/18, 51/68 and 228/252 mg/kg bw/day in males/females, respectively) of fluensulfone for a period of 13 weeks.

There were several mortalities during the study: 2, 2, 4 and 4 males and 3, 0, 0 and 5 females for the control and treated groups in order of ascending doses. Apart from the death of a single female of the highest dose group, which was also the only animal in which clinical signs (piloerection, squatting position, poor general condition, and emaciation) were recorded, all mortalities were related to blood sampling.

Inhalational toxicity

In a 90-day inhalation toxicity study, groups of 10 male and 10 female rats were exposed nose-only to fluensulfone for 6 hours/day, 5 days/week for 13 consecutive weeks (resulting in 65 and 66 exposure days for males and females, respectively) to target concentrations of 0, 0.04, 0.2 or 1.0 mg/L.

Potentially adverse changes which were present at the lowest concentration consisted of weight loss on exposure days in males, prolonged prothrombin time in females, decreased thymus weight in males (without histopathological effects) and histopathological changes in the epiglottis (squamous metaplasia, epithelial hyperplasia, focal mononuclear cell infiltrate) in both sexes and in the nasal cavity (squamous epithelial hyperplasia) in males.

Long-term toxicity

In a 1-year oral toxicity study, fluensulfone was administered in the diet to groups of 4/sex/dose dogs at 0, 5, 50 100 and 500 ppm (0.0, 0.1/0.1, 1.5/1.5, 3.1/3.3. 16.0/16.2 mg/kg bw/day in male/females) for a period of 52 weeks.

Oral administration of fluensulfone dogs in the diet at a dose of 500 ppm resulted in transient changes in consistency of faeces, reductions in food intake in females and lower body weight gains, mean body weights and terminal body weights, effects on haematology and biochemistry parameters and on the liver.

Carcinogenicity

In an oral oncogenicity study, 4 groups of 50 male and 50 female mice (allocation a) were treated for 78 weeks with 0, 30, 200 or 1200 ppm of fluensulfone in their feed. Additionally, 6 males and 6 females were exposed to the same dietary concentrations and used for liver enzyme determination after 13 weeks of treatment. The average daily intakes of test material were 0, 4.2, 27.6 or 152.3 mg/kg bw/day for males and 0, 6.4, 39.0 or 188.4 mg/kg bw/day for females.

Absolute and relative (to brain weight) prostate weights were observed in males in the 200 and 1,200 ppm dose groups. Changes in other organ weights at 1,200 ppm (increased relative kidney, adrenal gland, epididymal, testes, heart, and brain weight in males; decreased absolute kidney

weight in females, and increased relative liver weight in females) were likely secondary to the effect of fluensulfone exposure on body weight.

Neurotoxicity

In a subchronic dietary neurotoxicity study, groups of 12 male and 12 female rats received fluensulfone in their diet at concentrations of 0, 100, 500 and 2500 ppm (equivalent to 0/0, 6/7, 31/34, and 153/162 mg/kg bw/day in males/females) for at least 90 days.

All animals scheduled for neurohistological examination survived the scheduled study period. Treatment-related effects included lower food consumption and body weight gain in males and females at 2500 ppm, as well as reduced body weight in males.

Reproductive/Developmental toxicity potential

There were no treatment related effects on reproductive performance in a dietary 2-generation rat study up to and including dose levels producing parental toxicity.

Fluensulfone was not a developmental toxicant in oral gavage studies in the rat and rabbit.

Genotoxicity

Fluensulfone is non-mutagenic/genotoxic in *in vitro* studies with and without metabolic activation and non-genotoxic in *in vivo* studies.

Immunotoxicity

Fluensulfone was not an immunotoxicant in mice in an immunotoxicity study that evaluated anti-sheep red blood cell response.

Delegate's consideration

The delegate considered the following in regards to this application for re-scheduling.

- Evaluation report (not publically available);
- Section 52E of the *Therapeutic Goods Act 1989*;
- Scheduling factors[42]; and
- Other relevant information.

Delegate's final decision

The toxicological profile of fluensulfone is consistent with the SPF criteria for listing in Schedule 6, with the estimated lethal dose in the range 50-2000 mg/kg and some potential for skin/eye irritation and sensitisation. The systemic toxicity on repeated exposure to fluensulfone provides additional support for Schedule 6 listing. The evaluation report discusses, in some detail, the human significance of the lung alveolar/bronchiolar carcinogenic responses seen in female mice. While the proposed mode of action (MoA) and human relevance of these tumours is not established beyond reasonable doubt, there is no evidence of genotoxic potential and the MoA evidence is sufficiently strong that the observed carcinogenesis could be a response specific to female mice and have no human relevance. Therefore, listing in a more restrictive schedule (Schedule 7) is not warranted.

[42] *Scheduling Policy Framework for Medicines and Chemicals (2010)* [http://www.tga.gov.au/pdf/scheduling-policy-framework.pdf]

While the evaluation report did not supported the registration of a product for home garden use, this is not an issue that would negate listing in Schedule 6. However, the decision to NOT include a scheduling cut-off for the proposed product supports the OCS recommendation.

An early implementation date is proposed to facilitate marketing of the product when registered by the APVMA. The delegate therefore proposes an implementation date of 1 June 2014.

Schedule entry

SCHEDULE 6 – NEW ENTRY

FLUENSULFONE.

4.3 IRON SALT AND CALCIUM SALT OF CHROMATES (INCLUDING DICHROMATES)

Scheduling proposal

On 17 September 2013, NICNAS under the Inventory Multi-tiered Assessment Prioritisation (IMAP) Tire II human health assessment process, recommended that the delegate consider a proposal to amend the current Schedule 6 chromates entry to add the iron and calcium salts to the list of chromate salts exempt from scheduling when included in paints and tinters at 5 per cent or les and to also amend the current Appendix I (Uniform Paint Standard) chromates entry to include additional chromate salts namely iron and calcium.

The delegate decided to make a delegate-only decision. The Advisory Committee on Chemicals (ACCS) was not consulted.

Scheduling status

Chromates are listed in Schedule 6, Appendices E, F and I (listed as chromium).

SCHEDULE 6

CHROMATES (including dichromates) except in paints or tinters containing 5 per cent or less of chromium as the ammonium, barium, potassium, sodium, strontium or zinc chromate calculated on the non-volatile content of the paint or tinter.

APPENDIX E

Poisons	Standard statements
Chromates	A For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). G3 If swallowed, do NOT induce vomiting. E2 If in eyes, hold eyelids apart and flush the eyes 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 I

The First Schedule	
The proportion of a substance for the purpose of this section Schedule is calculated as a percentage of the element present in the non-volatile content of the paint.	
Substance	**Proportion**
CHROMIUM as chromates of ammonia, barium, potassium, sodium, strontium or zinc	more than 5 per cent

Scheduling history

In April 1963 the Poisons Advisory Panel decided to list chromates in Schedule 6. No reasons were given for this decision.

In August 2000, the National Drugs and Poisons Schedule Committee decided to amend the chromate entry to read: chromates (including dichromates) except in paints or tinters containing 5 per cent or less of chromium as ammonium, barium, potassium, sodium, strontium or zinc chromate calculated on the non-volatile content of the paint or tinter.

Substance details

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report, which is available on from the NICNAS website: <http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=411>.

Delegate's consideration

The delegate considered the following in regards to this application for re-scheduling.

- Evaluation report (not publically available);
- Section 52E of the *Therapeutic Goods Act 1989*;

- Scheduling factors; and
- Other relevant information.

Delegate's final decision

The delegate has decided to amend the current Schedule 6 and Appendix I (Uniform Paint Standard) entries for chromates to include additional chromate salts (iron and calcium) that might be present in paints sold in Australia. The toxicological profile of these salts is expected to be related to the valence state (VI) of the chromate component and comparable to those salts already listed in the Schedule 6 paint/tinter exemptions and Appendix I (Schedule 1) restrictions. The delegate has decided on an implementation date of 1 June 2014.

Scheduling entry

Schedule 6 - AMENDMENT

CHROMATES (including dichromates) **except** in paints or tinters containing 5 per cent or less of chromium as the ammonium, barium, calcium, iron, potassium, sodium, strontium or zinc chromate calculated on the non-volatile content of the paint or tinter.

Appendix I - AMENDMENT

Substance	**Proportion**
CHROMIUM as chromates of ammonia, barium, calcium, iron, potassium, sodium, strontium or zinc	more than 5 per cent

4.4 SODIUM 5- NITROGUAIACOLATE

Scheduling proposal

The Chemicals Scheduling Delegate (the delegate) considered a proposal to include sodium 5-nitroguaiacolate (Na-5NG), sodium o-nitrophenolate (Na-oNP) and sodium p-nitrophenolate (Na-pNP) in Schedule 6. As sodium ortho-nitrophenolate and sodium para-nitrophenolate are sodium salts of o-nitrophenol and p-nitrophenol respectively, the current Schedule 6 ortho- and para-nitrophenols entries may capture these substances.

The delegate decided to make a delegate-only decision. The Advisory Committee on Chemicals (ACCS) was not consulted.

Scheduling status

Sodium 5-nitroguaiacolate is not specifically scheduled.

Other nitrophenolates, such as sodium ortho-nitrophenolate and sodium para-nitrophenolate, are listed in Schedule 6.

SCHEDULE 6

NITROPHENOLS, ortho-, meta-, and para-, **except** when separately specified in these schedules.

Scheduling history

Ortho-, meta- and para-nitrophenols were first considered by the Committee on Poisons Schedules (CPS) in May 1956. The CPS decided to include these substances in Schedule 1 (substances which are extremely dangerous to human life) and Schedule 2 (substances which are dangerous to human life if misused or carelessly handled). No rationale was given for this decision.

In November 1990, the National Drugs and Poisons Schedule Committee (NDPSC) considered translocating Schedule 1 entries appropriately in different schedules. In February 1991, the NDPSC decided to move some substances, including ortho-, meta- and para-nitrophenols, from Schedule 1 to other appropriate schedules. The translocation of Schedule 1 substances to other Schedules was completed in November 1994. Since February 1995 no substance is listed under Schedule 1.

Information on when and why nitrophenols entry was transferred from Schedules 1 and 2 to Schedule 6 was not available.

Substance details

Sodium 5-nitroguaiacolate, a nitrophenolate, is a plant growth regulator[43]. The substance is naturally found in plants and stimulate plant growth by altering the activity of specific antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT) and peroxidase (POX)[44].

Acute toxicity

The summary of acute toxicity studies is shown in the table below.

End-point of toxicity	Species	Sodium 5-nitroguaiacolate	SPF* classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	723 (Males) 706 (Females)	Moderate to high
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbits	>2000	Moderate to high
Acute inhalational toxicity LC_{50} (mg/m^3)	Rats	> 2380 (no deaths)	Moderate to high
Skin irritation	Rabbits	Non-irritant	
Eye irritation	Rabbits	Severe irritant	
Skin sensitisation	Guinea pigs	Non-sensitiser	

**SPF – Scheduling Policy Framework for Medicines and Chemicals (2010)*

[43] Sodium 5- Nitroguaiacolate, Sodium o-Nitrophenolate and Sodium p-Nitrophenolate Fact Sheet. Available at [http://www.epa.gov/pesticides/chem_search/reg_actions/registration/fs_G-10_01-Aug-01.pdf]

[44] Field Evaluation of Nitrophenolate Plant Growth Regulator (Chaperone) for the Effect on Cotton Lint Yield. Bynum et al (2007) Available at: [http://www.cotton.org/journal/2007-11/1/upload/jcs11-20.pdf]

Repeat-dose toxicity

Sodium 5-nitroguaiacolate was of low toxicity in a 90-day oral toxicity study in dogs, with a NOEL established at the highest dose tested of 60 mg/kg bw/day.

Carcinogenicity

No evidence of carcinogenicity was observed in long-term studies.

Neurotoxicity

No evidence of neurotoxicity in acute and repeat-dose toxicity studies.

Reproductive/Developmental toxicity

Sodium 5-nitroguaiacolate was not a reproductive toxicant in rats, or a developmental toxicant in rats and rabbits.

Genotoxicity

Sodium 5-nitroguaiaicolate was found to be positive in *Saccharomyces cerevisiae* cells for both aneuploidy and recombination. Sodium 5-nitroguaiacolate is likely to induce mitotic aneuploidy and mitotic recombination in *S.cerevisiae* cells, suggesting that sodium 5-nitroguaiaicolate may have genotoxic potential in mammalian cells. The long-term *in vivo* studies in rodents did not indicate a carcinogenic effect. The OCS report therefore notes that, overall the weight of evidence indicates that sodium 5-nitroguaiacolate is unlikely to be genotoxic.

Delegate's consideration

The delegate considered the following in regards to this application for re-scheduling.

- evaluation report (not publically available);
- section 52E of the *Therapeutic Goods Act 1989*;
- scheduling factors; and
- other relevant information.

Delegate's final decision

The toxicological profile of sodium 5-nitroguiaicolate is consistent with Scheduling Policy Framework for Medicines and Chemical's factors for Schedule 6 listing. Accordingly, the delegate decided to include 2-methoxy-5-nitrophenol (the IUPAC name for this chemical), with no cut-off, in Schedule 6. The delegate also decided to create a cross-reference in the Index for sodium 5-nitroguiaicolate to 2-methoxy-5-nitrophenol. The implementation date for this decision is 1 October 2014.

Schedule entry

SCHEDULE 6 - NEW ENTRY

2-METHOXY-5-NITROPHENOL.

INDEX – NEW ENTRY

SODIUM 5-NITROGUAIACOLATE.

See 2-METHOXY-5-NITROPHENOL

5. New chemical entities – medicines for human therapeutic use

5.1 COLLAGENASE CLOSTRIDIUM HISTOLYTICUM

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of collagenase *Clostridium histolyticum*, a new chemical entity for a human therapeutic medicine.

Collagenase *Clostridium histolyticum* is indicated for the treatment of Dupuytren's contracture [a fixed flexion contracture of the hand where the fingers bend towards the palm and cannot be fully straightened] in adult patients with palpable cord.

Collagenase *Clostridium histolyticum* is an enzyme produced by the bacterium *Clostridium histolyticum* that dismantles excessive collagen by disrupting its chemical structure. Reducing the accumulation of collagen improves movement of the affected fingers.

The delegate decided to make a delegate-only decision to include this in Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Collagenase *Clostridium histolyticum* is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Collagenase C*lostridium histolyticum* is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include collagenase C*lostridium histolyticum* in Schedule 4, with an implementation date of 27 March 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of; (b) the purpose and the extent of use of; (c) the toxicity of; (d) the dosage, formulation, labelling, packaging and presentation of; and (e) the potential for abuse of collagenase C*lostridium histolyticum.*

The delegate decided that the reasons for the final decision comprise of the following.

- Collagenase Clostridium histolyticum is a new biological entity with no clinical experience in Australia.
- It is indicated for the treatment of Dupuytren's contracture in adult patients with a palpable cord.

- Experience of its use is limited.
- The use of Collagenase Clostridium histolyticum requires medical intervention by doctors who are experienced in the diagnosis and surgical management of Dupuytren's disease and who have undergone a prescriber education and training program.
- Toxicity is mainly confined to the treated limb but there is potential for distal effects.
- It is only to be administered in a setting with the ability to monitor vital signs and treat allergic reactions.
- It is presented as 0.9 mg lyophilised powder for injection by local administration into the cord.
- It does not appear to produce dependency.
- There is potential for usage beyond the approved indication.

Schedule 4 – New Entry

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM.

5.2 EMPAGLIFLOZIN

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of empagliflozin, a new chemical entity for a human therapeutic medicine.

Empagliflozin is a selective inhibitor of sodium—glucose co-transporter 2.

Ronjoli (empagliflozin) tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Empagliflozin is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Empagliflozin is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include empagliflozin in Schedule 4, with an implementation date of 8 April 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of; (b) the purpose and the extent of use of; (c) the toxicity of; d) the dosage, formulation, labelling, packaging and presentation of; and (e) the potential for abuse of empagliflozin.

The delegate decided that the reasons for the final decision comprise the following:

- It is a new chemical entity with no clinical or marketing experience in Australia.

Schedule 4 – New Entry

EMPAGLIFLOZIN.

5.3 FEBUXOSTAT

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of febuxostat, a new chemical entity for a human therapeutic medicine.

Febuxostat is a non-purine selective inhibitor of xanthine oxidase that inhibits the formation of uric acid from xanthine and therefore decreases serum uric acid.

Febuxostat is proposed to be used in adults with chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of tophus and/or gouty arthritis).

The delegate decided to make a delegate-only decision to include febuxostat to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Febuxostat is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Febuxostat is classified as a prescription medicine in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include febuxostat in Schedule 4, with an implementation date of 27 March 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of; (b) the purpose and the extent of use of; (c) the toxicity of; d) the dosage, formulation, labelling, packaging and presentation of; and (e) the potential for abuse of febuxostat.

The delegate decided that the reasons for the final decision are comprised of the following.

- Febuxostat is a new chemical entity with no clinical experience in Australia.
- The risks and benefits are outlined in the Product Information, Delegate's Request for ACPM advice and the TGA evaluation reports.
- It is proposed to be used in adults with chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of tophus and/or gouty arthritis).
- Experience of its use is limited in Australia but it has been used overseas since 2008.
- The drug has potential for cardiovascular effects, hypersensitivity reactions and hepatic safety.
- Medicine is packed as film-coated tablets in blister packs.
- It does not appear to produce dependency and the abuse potential appears to be low.

Schedule 4 – New Entry

FEBUXOSTAT.

5.4 NORMAL HUMAN IMMUNOGLOBULIN

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of **Normal Human Immunoglobulin (NHIG)**, a new chemical entity for a human therapeutic medicine.

Normal Human Immunoglobulin is a human immunoglobulin G.

Normal Human Immunoglobulin is indicated in adults and children for replacement therapy in:

- Primary Immunodeficiency Disease (PID) and
- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Normal Human Immunoglobulin is not specifically scheduled in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP), but is captured by the following group/class entry:

> **SCHEDULE 4**
>
> IMMUNOGLOBULINS for human parenteral use **except** when separately specified in these Schedules.

Normal Human Immunoglobulin is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The TGA evaluation report.

- The advice of the Advisory Committee on Prescription Medicines.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include Normal Human Immunoglobulin in Schedule 4, with an implementation date of 8 April 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of; (b) the purpose and the extent of use of; (c) the toxicity of; d) the dosage, formulation, labelling, packaging and presentation of; and (e) the potential for abuse of Normal Human Immunoglobulin.

The delegate decided that the reasons for the final decision comprise the following:

- Normal Human Immunoglobulin is a new biological entity with no clinical/marketing experience in Australia.
- The product is used to treat serious medical conditions: Primary Immunodeficiency Disease (PID) and Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.
- The possible side effects include hypersensitivity, embolic and thrombolic events, aseptic meningitis syndrome etc.
- Hizentra should only be administered subcutaneously.
- The dose may need to be individualised for each patient dependent on the clinical response and serum IgG trough levels.
- No potential for abuse of a substance.

Schedule 4 – New Entry

NORMAL HUMAN IMMUNOGLOBULIN.

5.5 SERELAXIN

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of serelaxin, a new chemical entity for a human therapeutic medicine.

Serelaxin is a recombinant human relaxin-2, a vasoactive peptide hormone.

Serelaxin is proposed for use in patients with acute heart failure.

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Serelaxin is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Serelaxin is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- The TGA evaluation report.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include serelaxin in Schedule 4, with an implementation date of 8 April 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of; (b) the purpose and the extent of use of; (c) the toxicity of; d) the dosage, formulation, labelling, packaging and presentation of; and (e) the potential for abuse of serelaxin.

The delegate decided that the reasons for the final decision comprise the following:

- Serelaxin is a new biological entity with no clinical experience in Australia.
- The risks and benefits are outlined in the Product Information and the TGA evaluation reports.
- A significant risk is hypotension.
- Serelaxin is proposed for use in patients with acute heart failure.
- The use of serelaxin requires medical intervention, adjunctive therapy and evaluation.
- The use of serelaxin requires monitoring by a medical practitioner to minimize the risk of using it.
- It has no previous experience of use in Australia or overseas. It is proposed for hospital only use.
- The medicine's main toxicity is hypotension.
- It is presented as a pack containing 1 single-use vial containing 3.5 mg serelaxin in 3.5 mL of solution.
- It does not appear to produce dependency and the abuse potential appears to be low.

Schedule 4 – New Entry

SERELAXIN.

5.6 SIMEPREVIR

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of simeprevir, a new chemical entity for a human therapeutic medicine.

Simeprevir is hepatitis C virus NS3/4A protease inhibitor.

The proposed indication for simeprevir for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus-1 (HIV-1) co-infection who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Simeprevir is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Simeprevir is not classified/is classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The TGA evaluation report.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include simeprevir in Schedule 4, with an implementation date of 8 April 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of; (b) the purpose and the extent of use of; (c) the toxicity of; d) the dosage, formulation, labelling, packaging and presentation of; and (e) the potential for abuse of simeprevir.

The delegate decided that the reasons for the final decision comprise the following:

- Simeprevir is a new chemical entity with no clinical/marketing experience in Australia.
- Simeprevir is for the treatment of chronic hepatitis C (CHC) genotype 1 or genotype 4 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease.
- As simeprevir is to be used in combination with peginterferon and ribavirin, extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not

receive ribavirin unless they are using effective contraception (two reliable forms) during treatment with ribavirin and for 6 months after treatment.

- Use with Ribavirin and Peginterferon Alfa: Ribavirin may cause birth defects and fetal death and animal studies have shown interferons have abortifacient effects; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least two effective methods of contraception during treatment, and undergo monthly pregnancy tests.
- Photosensitivity: Serious photosensitivity reactions have been observed during combination therapy with Simeprevir, peginterferon alfa and ribavirin. Use sun protection measures and limit sun exposure.
- Rash has been observed during combination therapy with Simeprevir, peginterferon alfa and ribavirin.
- It is capsule form and to be taken once daily with food.
- The potential for abuse of this substance is unlikely.

Schedule 4 – New Entry

SIMEPREVIR.

5.7 SOFOSBUVIR

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of sofosbuvir, a new chemical entity for a human therapeutic medicine.

Sofosbuvir is hepatitis C virus nucleotide analogue NS5B polymerase inhibitor.

The proposed indication for sofosbuvir (SOVALDI) is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults. The proposed use is to be used with ribavirin for Genotype 2 and 3 hepatitis C and to be used with peginterferon alfa and ribavirin for Genotype 1 and 4 hepatitis C.

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Sofosbuvir is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

In the Medsafe committee meeting held on 18 December 2013: Sofosbuvir should be classified as Prescription Medicine (see http://www.medsafe.govt.nz/profs/class/mccMin12Nov2013.htm).

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The TGA evaluation report.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include sofosbuvir in Schedule 4, with an implementation date of 8 April 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of; (b) the purpose and the extent of use of; (c) the toxicity of; d) the dosage, formulation, labelling, packaging and presentation of; and (e) the potential for abuse of sofosbuvir.

The delegate decided that the reasons for the final decision comprise the following:

- Sofosbuvir is a new chemical entity with no clinical/marketing experience in Australia.
- Sofosbuvir (SOVALDI) is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults As sofosbuvir is to be used in combination with peginterferon and ribavirin, extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive ribavirin unless they are using effective contraception (two reliable forms) during treatment with ribavirin and for 6 months after treatment.
- Use with Ribavirin and Peginterferon Alfa: Ribavirin may cause birth defects and fetal death and animal studies have shown interferons have abortifacient effects; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least two effective methods of contraception during treatment, and undergo monthly pregnancy tests.
- Drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir. Rifampin and St. John's wort should not be used with sofosbuvir.
- It is a tablet.
- The recommended dose of SOVALDI tablets is 400 mg once daily taken orally with or without food.
- The potential for abuse of this substance is unlikely.

Schedule 4 – New entry

SOFOSBUVIR.

5.8 UMECLIDINIUM

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of umeclidinium, a new chemical entity for a human therapeutic medicine.

Umeclidinium (as bromide) is a long-acting muscarinic receptor antagonist.

Anoro Ellipta containing umeclidinium (as bromide) and vilanterol (as trifenatate) is indicated as a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The delegate decided to make a delegate-only decision to include this to Schedule 4. The Advisory Committee on Medicines Scheduling was not consulted.

Scheduling status

Umeclidinium (as bromide) is not specifically scheduled and is not captured by any entry in the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

Umeclidinium (as bromide) is not classified in New Zealand.

Delegate's consideration

The delegate considered the following in regards to this application for scheduling.

- The new drug application.
- Subsection 52E(1) of the *Therapeutic Goods Act 1989*.
- The *Scheduling Policy Framework* scheduling factors.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the SUSMP to include umeclidinium in Schedule 4, with an implementation date of 8 April 2014.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of umeclidinium.

The delegate decided that the reasons for the final decision comprise the following:

- Umeclidinium is a new chemical entity with no clinical/marketing experience in Australia.

Schedule 4 – New Entry

UMECLIDINIUM.

6. Editorials and errata