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

August 2014

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

A delegate of the Secretary to the Department of Health hereby gives notice of the 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 Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect (implementation date) of the decision.

The delegates' final decisions and reasons relate to:

- scheduling proposals initially referred to the March 2014 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#10);
- 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

A 'pre-meeting' public notice inviting submissions on the scheduling proposals referred to the expert advisory committees was published on 30 January 2014 at http://www.tga.gov.au/newsroom/consult-scheduling-accs-1403.htm**,** respectively.

Edited versions of these public submissions received in response to this invitation were published on 27 June 2014 at http://www.tga.gov.au/industry/scheduling-submissions.htm.

Interim decisions

The delegate's interim decisions on recommendations by the ACCS#10 were published on 27 June 2014 at http://www.tga.gov.au/industry/scheduling-decisions-1406-interim.htm. 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.

Edited versions of valid public submissions received in response to the interim decisions are available at 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 proposal to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer a matter to a committee, the delegate considers the scheduling guidelines as set out in the *Scheduling Policy Framework for Chemicals and Medicines* (SPF, 2010), available at http:www.tga.gov.au/industry/scheduling-spf.htm.

Publishing of the amendments to the Poisons Standard

The amendments to the Schedules, Appendices or other parts of the Poisons Standard are published electronically on ComLaw as amendments to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) prior to the date of effect (implementation date) of the final decisions. Further information, including links to the Poisons Standard on ComLaw, is available 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
CAS	Chemical Abstract Service

Abbreviation	Name
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
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
IMAP	Inventory Multi-tiered Assessment Prioritisation

Abbreviation	Name
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

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

1. Scheduling proposals referred to the March 2014 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#10)

1.1 1-BUTANOL

Scheduling proposal

On 29 August 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process requested that the delegate consider a proposal to include spray preparations containing 5 per cent or more of 1-butanol in Schedule 5. This proposal was first notified to the delegate in September 2013 at which time it was determined that expert advisory committee advice may not be required for this proposal. However, due to the complexity of the proposal, expert advice on this substance is being sought.

The delegate considered the proposal in the NICNAS IMAP report which focuses on the potential for eye damage and inhalation toxicity associated with the use of 1-butanol in cosmetics and various spray-on products used in a domestic setting. The issues raised have much in common with those in the 1-propanol IMAP report, and they could be considered together. In view of the potential impact on existing products, the delegate considers that advice is needed from the ACCS, with an appropriate public notice alerting the industry to the proposed scheduling action. Since the advice from the TGA is that 1-butanol is used as an excipient (in printing ink only) there is no need to refer the matter to a joint ACCS/ACMS meeting. The inclusion of 1-butanol (as an excipient) in one AgVet product should be considered by the ACCS.

The delegate asked the following specific questions:

- The principal issue raised by the NICNAS IMAP report is the potential for eye irritancy associated with concentrations of 1-butanol above 5 per cent, with more serious eye damage expected at 10 per cent and above. The Report also notes the potential for skin damage at higher concentrations and effects on the CNS associated with inhalation of vapours. The NICNAS report notes relevant exposure scenarios associated with the use of 1-butanol in cosmetics, domestic cleaners and in particular, spray-on products.

- The skin-eye toxicity can be attributed to the solvent and de-fatting effects of 1-butanol, and this would be expected of any short-chain alkyl alcohol, including ethanol. It is noted that ethanol is currently included in Appendix B for all uses.

- Does the ACCS consider that the toxicity potential for 1-butanol and its potential use in the listed products warrants inclusion in Schedule 6, with exemptions to Schedule 5 at x? per cent, and exempt below y? per cent?

- If scheduling is recommended, should this be limited to certain specific product types in the retail market? If so, what wording is recommended to achieve such limitations?

- If scheduling is recommended, is the preferred nomenclature 1-butanol, n-butanol or butyl alcohol (consistent with the naming style for ethyl alcohol used in the Appendix B entry)? Should any of these names be cross-referenced in the SUSMP index (as per ethyl alcohol)?

- What Appendix E & F statements are recommended for any scheduled products?

- What regulatory impacts on existing products would be expected for any of the above scheduling options, and to what extent should this be considered in setting an implementation date?

Substance summary

Please refer to the NICNAS IMAP Human Health Tier II Assessment Report for 1-butanol. This report is available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=85.

Scheduling status

1-butanol is not specifically scheduled.

Scheduling history

1-butanol has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

Four public submissions were received.

The first submission indicated that 1-butanol is listed in the TGA's ARTG ingredient list as n-butyl alcohol BP, indicating that it may have uses in therapeutic goods, although specific uses are not defined. This ingredient may have been used as a propellant in certain aerosol dosage forms for medicines. The submission noted that the delegate's proposal was not limited to cosmetic or industrial preparations containing 1-butanol, and no cut-off is proposed. It is concerned about the possibility that including 1-butanol in a schedule may have some impact on therapeutic goods, and requested that consideration should be given to exempt from scheduling for therapeutic goods containing 1-butanol.

The second submission indicated that it did not support scheduling of 1-butanol. If, however, 1-butanol is considered for inclusion in a schedule, it should be considered by the joint ACMS & ACCS consideration to ensure that therapeutic use of 1-butanol is not inadvertently affected. The submission asserted the Cosmetic Ingredient Review (CIR) found that that cosmetic preparations containing 1- butanol are safe therefore cosmetics preparations containing 1-butanol be exempted from scheduling.

The third submission noted that 1-butanol is currently used in therapeutic and cosmetic products, therefore the proposal should be considered by the joint ACCS & ACMS. The submission asserted that it is not aware of any issues using 1-butanol in aerosol products intended for cosmetic or therapeutic use. Based on the CIR Ingredient Status Report and publically available data, 1-butanol has been classified as safe for use in various cosmetic products. These types of products therefore should be exempted from the proposed Schedule 5 and/or 6 entry/s.

The fourth submission noted that 1-butanol is also used in therapeutic goods therefore the scheduling proposal should be considered by the joint ACCS and ACMS. The submission indicated that publically available data has shown that 1-butanol is recognized as safe for use in cosmetic products. If a Schedule 5 and/or Schedule 6 entry is considered appropriate, the entry should exempt from scheduling for cosmetic and therapeutic products containing 1-butanol. If a concentration cut-off is applied, the cut-off should be set at a concentration where current cosmetic and therapeutic products in the market will not be impacted.

ACCS advice to the delegate

The ACCS recommended that preparations containing 1-butanol at concentrations greater than 10 per cent be included in Schedule 6 except when in Schedule 5 and except for preparations containing 5 per cent or less of 1-butanol. Cosmetics and therapeutics to be exempted. The committee also recommends appropriate Appendix E and F statements for 1-butanol.

The ACCS recommended an implementation date of 12 months.

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

The reasons for the recommendation comprised the following:

- Potential for moderate to severe eye damage or respiratory irritation consistent with the SPF factors for Schedule 5 or Schedule 6 depending on concentration and use.

Delegate's interim decision

The delegate accepts the advice of the ACCS to include 1-butanol in Schedules 5 and 6. The critical toxicological endpoints driving this categorisation (potential for inhalation toxicity, skin irritancy and severe eye irritancy) are consistent with SPF criteria for listing in Schedule 6, with the public health risk sufficiently ameliorated for products between 5 and 10 per cent to be included in Schedule 5, and to be exempt from scheduling when less than 5 per cent. The delegate notes, but does not accept, the ACCS recommendation that cosmetics and therapeutic products be specifically exempted. There appear to be no therapeutic goods or cosmetics where the concentration of 1-butanol would be likely to exceed the 5 per cent cut-off to exempt, and if there are any such products, the warnings associated with the proposed schedule entries would be applicable and suitable.

The delegate agrees with the implementation date being 1 July 2015. The ACCS suggested that at least twelve months may be needed to implement the required label changes.

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 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[1];
- Other relevant information.

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

Public submissions on the interim decision

One submission was received. The submission indicated that 1-butanol does not require a schedule listing and requested the delegate to defer the final decision to seek reconsideration from the ACCS.

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

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 to seek further advice.

The delegate notes that the potential for eye irritation/damage at high concentrations is the principal driver for scheduling. Moreover, consistent with advice from the ACCS, the delegate has now formed the view that scheduling controls over the use of 1-butanol in cosmetics and therapeutic goods are unnecessary, given the safety evaluation profiles that have been undertaken for the existing range of products in these classes (or would be in the case of new therapeutic goods). If 1-butanol is to be scheduled, these products should be specifically exempt, as originally recommended by the ACCS.

The delegate also notes the apparent inconsistency of current and past committee advice relating to the need to schedule solvent-type materials with low toxicity profiles, but with properties that could result in similar eye irritation (e.g. ethanol, tetrahydrofuran). The delegate has therefore decided to refer the matter back to the ACCS to consider a range of product types containing 1-butanol that would specifically warrant scheduling to protect against eye damage, and whether these should include such products as aerosol or spray products (except in therapeutic goods), and/or arts & craft materials, where there may be a greater risk of being taken into the eye.

The matter is to be referred back the ACCS for further consideration. A new and appropriate implementation time can be determined after reconsideration of the scheduling proposal by the ACCS.

1.2 1-PROPANOL

Scheduling proposal

On 29 August 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process requested that the delegate consider a proposal to include cosmetics and domestic preparations, such as arts, craft and hobby material, containing 1-propanol in an appropriate schedule. This proposal was first notified to the delegate in September 2013 at which time it was determined that expert advisory committee advice may not be required for this proposal. However, due to the complexity of the proposal, expert advice on this substance is being sought.

The delegate noted that the NICNAS IMAP report focuses on the potential for eye damage associated with the use of 1-propanol in cosmetics and other products used in a domestic setting. It proposes inclusion in Schedule 6, with cut-offs to Schedule 5 and exempt. In view of the potential impact on existing products, the delegate considered that advice was needed from the ACCS, with an appropriate public notice alerting the industry to the proposed scheduling action. Since the advice from the APVMA and TGA was that 1-propanol had not been used in products they regulate, there was no need to refer the matter to a joint ACCS/ACMS meeting.

The delegate asked the following questions:

- The principal issue raised by the NICNAS IMAP report is the potential for eye irritancy associated with concentrations of 1-propanol above 5 per cent, with more serious eye damage

expected at 10 per cent and above. The Report also notes the potential for skin damage at higher concentrations and effects on the CNS associated with inhalation of vapours. The NICNAS report notes relevant exposure scenarios associated with the use of 1-propanol in cosmetics, domestic cleaners and in particular, arts, craft and hobby materials.

- The skin-eye toxicity can be attributed to the solvent and de-fatting effects of 1-propanol, and this would be expected of any short-chain alkyl alcohol, including ethanol. It is noted that ethanol is currently included in Appendix B for all uses.
- Does the ACCS consider that the toxicity potential for 1-propanol and its potential use in the listed products warrants inclusion in Schedule 6, with exemptions to Schedule 5 at x? per cent, and exempt below y? per cent?
- If scheduling is recommended, should this be limited to certain specific product types in the retail market? If so, what wording is recommended to achieve such limitations?
- If scheduling is recommended, is the preferred nomenclature 1-propanol, n-propanol or propyl alcohol (consistent with the naming style for ethyl alcohol used in the Appendix B entry)? Should any of these names be cross-referenced in the SUSMP index (as per ethyl alcohol)?
- What Appendix E & F statements are recommended for any scheduled products?
- What regulatory impacts on existing would be expected for any of the above scheduling options, and to what extent should this be considered in setting an implementation date?

Substance summary

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report for 1-propanol. This report is publically available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=47.

Scheduling status

1-Propanol is not specifically scheduled.

Scheduling history

1-Propanol has not been considered previously therefore scheduling history is not available.

Pre-meeting public submissions

Four public submissions were received.

The first submission indicated that 1-propanol is listed in the ARTG as propan-1-ol BP, and is allowed in therapeutic goods in products for dermal use up to a maximum concentration of 18 per cent w/v. The submission indicated that the delegate's proposal was not restricted to cosmetic or industrial products, and no cut-off was proposed. The submission was concerned about the possibility that there may be some impact on therapeutic goods, and requested that consideration should be given to exempt from scheduling for therapeutic goods containing 1-propanol.

The second submission indicated that NICNAS did not provide any evidence to suggest that current uses of some preparations containing up to 60 per cent of 1-propanol were causing public health and safety concerns. The submissions indicated that it did not support scheduling of 1-propanol, however, if a schedule listing for 1-propanol was considered appropriate, the proposal should be considered by the joint ACMS & ACCS to ensure that therapeutic uses of 1-propanol were not inadvertently captured.

The third submission indicated that 1-propanol is currently used in therapeutic and cosmetic products therefore the proposal should be considered by the joint ACCS & ACMS. The submission asserted that based on the CIR Ingredient Status report and publically available data, 1-propanol had been considered safe for use in various cosmetic products as currently used.

The fourth submission indicated that as therapeutic goods may contain 1-propanol, the scheduling proposal should be considered by the joint ACCS & ACMS. The submission asserted that the CIR Expert Panel has assessed the safety profile of certain cosmetic preparations containing 0.002 to 100 per cent of 1-propanol and concluded that 1-propanol was considered to be safe. The submission requested that if 1-propanol was to be included in Schedule 5 and/or Schedule 6, cosmetic and therapeutic products containing 1-propanol be exempted from the scheduling. If a concentration cut-off was applied, the cut-off should be set at a concentration where current cosmetic and therapeutic products in the market would not be impacted.

ACCS advice to the delegate

The ACCS recommended that preparations containing 1-propanol at concentrations greater than 10 per cent be in Schedule 6, between 5 and 10 per cent in Schedule 5, and exempt for preparations containing 5 per cent or less of 1-propanol. Cosmetics and therapeutics are to be exempted.

The ACCS recommended an extended implementation period of 12 months.

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

The reasons for the recommendation comprised the following:

- Potential for moderate to severe eye damage consistent with Schedule 5 or Schedule 6 depending on concentration and use.

Delegate's interim decision

The delegate accepts the advice of the ACCS to include 1-propanol in Schedules 5 and 6. The critical toxicological endpoints driving this categorisation (potential for inhalation toxicity, skin irritancy and severe eye irritancy) are consistent with SPF criteria for listing in Schedule 6, with the public health risk sufficiently ameliorated for products between 5 and 10 per cent to be included in Schedule 5, and to be exempt from scheduling when less than 5 per cent. The delegate notes, but does not accept, the ACCS recommendation that cosmetics and therapeutic products be specifically exempted. There appear to be no therapeutic goods or cosmetics where the concentration of 1-propanol would be likely to exceed the 5 per cent cut-off to exempt, and if there are any such products, the warnings associated with the proposed schedule entries would be applicable and suitable.

The delegate agrees with the implementation date being 1 July 2015. The ACCS suggested that at least twelve months may be needed to implement the required label changes.

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 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[2];
- Other relevant information.

Public submissions on the interim decision

One submission was received. The submission indicated that 1-butanol 1-propanol does not require a schedule listing and requested the delegate to defer the final decision to seek reconsideration from the ACCS.

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

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 to seek further advice.

The delegate notes that the potential for eye irritation/damage at high concentrations is the principal driver for scheduling. Moreover, consistent with advice from the ACCS, the delegate has now formed the view that scheduling controls over the use of 1-propanol in cosmetics and therapeutic goods are unnecessary, given the safety evaluation profiles that have been undertaken for the existing range of products in these classes (or would be in the case of new therapeutic goods). If 1-propanol is to be scheduled, these products should be specifically exempt, as originally recommended by the ACCS.

The delegate also notes the apparent inconsistency of current and past committee advice relating to the need to schedule solvent-type materials with low toxicity profiles, but with properties that could result in similar eye irritation (e.g. ethanol, tetrahydrofuran). The delegate has therefore decided to refer the matter back to the ACCS to consider a range of product types containing 1-propanol that would specifically warrant scheduling to protect against eye damage, and whether these should include such products as alcohol-based handrubs, and/or arts & craft materials, where the 1-propanol concentrations are likely to be substantively higher than the proposed scheduling cut-offs.

The matter is to be referred back the ACCS for further consideration. A new and appropriate implementation time can be determined after reconsideration of the scheduling proposal by the ACCS.

1.3 2,4-DIAMINOPHENOXYETHANOL SULFATE

Scheduling proposal

On 29 August 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) under its New Chemicals Assessment process, requested that the delegate consider a proposal to include 2,4-diaminophenoxyethanol sulfate in Schedule 6 and Appendix F entries. This proposal was first notified to the delegate in September 2013 at which time it was determined that expert advisory committee advice may not be required for this proposal. However, due to the complexity of the proposal, expert advice on this substance is being sought.

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

The delegate considered the proposal that the toxicity profile of 2,4-diaminophenoxyethanol sulphate includes moderate to high acute toxicity, moderate skin irritancy, severe eye irritancy and potential genotoxicity. Its proposed use is as a component of oxidative hair colouring products at up to 4 per cent. Its toxicity and use profiles are similar to an oxidative hair dye considered at the November 2013 ACCS meeting (2-amino-5-ethylphenol). ACCS advice is required to determine whether a similar scheduling approach should be used for 2,4-diaminophenoxyethanol sulfate (Schedule 6 with exempt cut-off with reverse scheduling label statements for exempt products) and are Appendix E & F statements required?

Substance summary

2,4-diaminophenoxyethanol sulfate is used as an ingredient of oxidative hair colouring products at a maximum final (on-head) concentration of 2.0 per cent, after mixing the hair dye formulation with a hydrogen peroxide preparation typically in 1:1 proportions[3].

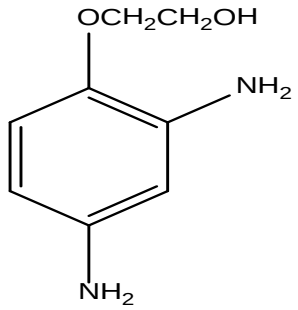

Figure 1. Structure of 2,4-diaminophenoxyethanol sulfate

The delegate noted that the NICNAS report indicated that the main analogue used in the assessment of 2,4-diaminophenoxy ethanol sulfate is ethanol, 2-(2,4-diaminophenoxy)-, dihydrochloride; CAS number: 66422-95-5 (INCI name: 2,4-diaminophenoxyethanol HCl). This differs from 2,4-diaminophenoxyethanol sulfate only in the counter ion of the salt, with the free base of the analogue and the notified chemical being identical. The structure of ethanol, 2-(2,4-diaminophenoxy)- is provided below (Figure 2). The water solubility and partition coefficient of the notified chemical and the analogue chemical are within similar ranges and thus absorption of the two chemicals across biological membranes is not expected to be significantly different. The NICNAS report concluded that it is reasonably considered that the analogue and 2,4-diaminophenoxyethanol sulfate will have comparable physical/chemical and toxicological properties.

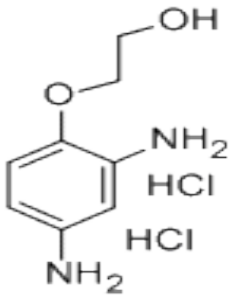

Figure 2. Structure of ethanol, 2-(2,4-diaminophenoxy)-, dihydrochloride

[3] Opinion on 2,4-diaminophenoxy ethanol dihydrochloride and sulfate. European Commission's Scientific Committee on Consumer Safety. Available at [http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_035.pdf]

Acute toxicity

The acute toxicity end-points for the chemical are listed in the below table.

Toxicity	Species	2,4-diaminophenoxyethanol sulfate	SPF* classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1 000- 1 113	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Mouse	1 160-1 745	Schedule 6
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not supplied	Not supplied	Unable to assess
Skin irritation	Rabbit	Slight irritant	
Eye irritation	Rabbit	Irritant	
Skin sensitisation (adjuvant test)	Guinea pig	Sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

Repeat-dose toxicity

In a 90-day oral repeat dose study, both male and female rats were exposed to the analogue chemicals at 0, 4, 20 and 100 mg/kg bw/day. At 100 mg/kg bw/day, excessive salivation was observed in both males and females and lower body weight gains were noted for males. The presence of urinary bilirubin, nitrites and glucose in the coloured urine (marked coloration from yellow to yellow-brown in both males and females) was detected at the end of the treatment period. The presence of these chemicals in the urine may have been due to an analytical interference, as there were no changes observed in the plasma levels of these chemicals. An increase in relative kidney weights was observed in males and females dosed with 100 mg/kg bw/day.

Deposition of brownish pigment in the thyroid (mainly in follicular epithelial cells) as well as brownish colouration of the thyroid was observed in all animals given 100 mg/kg bw/day. An augmented degree of spleen haemosiderosis (deposition of haemosiderin, a protein that stores iron) was also observed for most animals given 100 mg/kg bw/day. The microscopic changes to the thyroid and spleen were still observed at the end of the recovery period.

Plasma levels of the test substance were determined from samples taken on day 1 and week 13 of the study. Systemic exposure was found to increase proportionally with the dose level.

A no observed adverse effect level (NOAEL) of 20 mg/kg bw/day was established.

Mutagenicity

Based on these studies the analogue chemical is considered to be an *in vitro* mutagen/genotoxin. However, the results obtained from tests conducted *in vivo*, which explored the endpoints found to be positive *in vitro*, indicate that the test substance cannot be classified as an *in vivo* mutagen or genotoxin.

Bacterial gene mutation assay positive in one strain (Salmonella typhimurium) in the presence of S9 metabolic activation.

Genotoxicity

Several genotoxicity studies on the analogue chemical had been conducted. These include a number of bacterial cell assays, with some positive results in certain strains and/or conditions/concentrations, as well as negative results. There are also *in vitro* assays with some positive and some negative results, and *in vivo* assays, with negative results.

Carcinogenicity

In a 2-year study, rats exposed to 0, 0.05 and 0.1 per cent (corresponding intake levels: 0, 20.9 and 35.5 mg/kg bw/day for male rats and 0, 27.8 and 60.9 mg/kg bw/day for female rats) to the analogue chemical. Body weight gain was decreased for males and females in both treatment groups. Tumour incidences in control and treated groups were generally the same. Pigment deposition in the epithelial cells of thyroid follicles of both males and females was observed in the highest dose groups, though their distribution did not correlate with the occurrence of tumours. An increase in the C-cell adenoma was observed in the thyroid gland of male rats. The NICNAS report noted that the study authors indicated that this increase was not toxicologically significant as C-cell adenomas are common in old F344 rats. However, historical control values were not provided. The NICNAS report indicated that no conclusion regarding the carcinogenicity of the analogue chemical could be made on the basis of this study.

The NICNAS report noted that there was no sufficient evidence of carcinogenicity therefore no conclusion can be drawn from this study.

In another 2-year study, mice were exposed to 0, 0.04 and 0.07 per cent in water, ad libitum (corresponding intake levels: 0, 35.8 and 62.8 mg/kg bw/day for male mice and 0, 44.6 and 81.4 mg/kg bw/day for female mice). Tumour incidences in control and treated groups were the same. Pigment deposition in the epithelial cells of thyroid follicles of both males and females was observed in the highest dose groups. The distribution of the deposits did not correlate with the tumour occurrence.

Reproduction and developmental toxicity

In a reproductive toxicity study, rats were exposed to 0, 4, 20, 125 mg/kg bw/day of the analogue chemical. Clinical signs of maternal toxicity, such as salivation, reduced body weight gain and food consumption, in the dam were noted in the 125 mg/kg bw/day dose group.

Moreover, at 125 mg/kg bw/day there was a statistically significant reduction in the mean foetal weight also observed. This corresponded with a statistically significant increased incidence of foetuses showing incomplete ossification of thoracic vertebra centrum or supernumerary short 14th rib.

Prenatal developmental toxicity (rat) NOAEL for maternal toxicity and embryo-foetal development is 20 mg/kg bw/day.

In a developmental toxicity study, rats were exposed to 0, 50, 100, 200 mg/kg bw/day of the analogue chemical. In the 200 mg/kg bw/day dose groups, there was a significant dose related increase in the incidence of skeletal anomalies and skeletal variants. Lower litter weights and foetal mean weight were also observed at this dose. Clinical signs of toxicity, such as salivation, fur loss and reduced body weight gain, in the dam were noted in the 200 mg/kg bw/day dose group.

In another developmental toxicity trial, mice were exposed to 15, 150, 1500 mg/kg bw (dermal application) of the analogue chemical. No teratogenic effects, no significant difference in skeletal development compared to negative controls were observed.

Observation in humans

Not supplied.

Public exposure

Salon application

Some of the products containing 2,4-diaminophenoxyethanol sulfate are designed for the salon market and intended for one application per bottle. For such products, public exposure to hair colorant products containing the notified chemical is likely to be intermittent (based on use pattern) and widespread. In these products, the notified chemical (up to 4 per cent) will be diluted 1:1 to 1:2 with developer, leading to maximal exposure concentrations of up to 2 per cent. The hair dye will be used at a maximum of approximately once per month, at up to 2.6 g of the notified chemical (4 per cent in 65 mL liquid product) each application. It is estimated that consumers will be exposed to these hair dye products for up to one hour daily, 12 days per year primarily by dermal route (mainly on the scalp), with the possibility of accidental ocular and oral exposure.

Home application

Some hair dye products containing the notified chemical (up to 4 per cent) may also be used by members of the public in home settings. The application instructions of products designed for home application typically indicate that gloves must be worn when using the dye, though it is unknown whether the gloves provided are of the most suitable type to ensure minimal breakthrough of the notified chemical. In addition, the instructions indicate that an allergy patch test must be performed 48 hours before use.

The method of application used by consumers is likely to be similar to that used by salon workers. As such, exposure is expected to be similar, though slightly higher, than experienced by consumers when the products are applied in salons, due to the greater potential for dermal (particularly to the hands) and accidental ocular exposure when application takes place by members of the public. Dermal exposure to the notified chemical would reduce if wearing gloves are worn during use.

There are a number of additional types of hair dye products for home use containing 2,4-diaminophenoxyethanol sulfate (up to 4 per cent) with different use instructions to those used by hair salon workers. Examples of products may include shampoo-in hair colour and brush-in colour gels. The products are mainly recommended for grey hair and for use by men. Typically, for each product the colour base containing 2,4-diaminophenoxyethanol sulfate at up to 4 per cent concentration will be diluted with developer (hydrogen peroxide solution) in a ratio of 1:1, so that the final maximum concentration of 2,4-diaminophenoxyethanol sulfate applied will be 2 per cent.

Shampoo-in products

The mixture will be applied to the head and lathered evenly into the hair similarly to shampoo. The quantity used per application will be dependent upon the length of the hair and as such, the entire mixture may not be used. In this case, users are directed to discard any unused mixture. Up to 1.2 g of the notified chemical (4 per cent in 30 mL liquid product) will be used per application. The mixture will be kept in the hair for 5 minutes and then rinsed out, followed by shampooing of the hair. Typically reapplication will occur on a monthly basis. The method of reapplication (i.e. application to grey roots) differs from the first time application described above. The mixture will be applied to the roots only and after 4 minutes it will be combed through the hair followed by rinsing. The mixture may also be used on grey sideburns or hair on the temple by applying for a few seconds and subsequently wiping away.

Brush-in colour gel

Hair

The product containing 2,4-diaminophenoxyethanol sulfate (up to 4 per cent) and the developer will be contained in separate resealable tubes. Up to 1.6 g of 2,4-diaminophenoxyethanol sulfate (4 per cent in 40 g liquid product) will be used per application. It will be squeezed along one side of the applicator brush, with an approximately equal amount of developer on the separate and opposite side of the brush. Mixing with the developer does not occur prior to application to the hair. Rather, the brush will be run through the hair, resulting in some mixing on the hair (though it may not be complete or thorough). As such, the scalp may be exposed to concentrations of the notified chemical up to 4 per cent. It will be kept on the hair for up to 10 minutes, followed by rinsing with warm water. Reapplication is expected to occur approximately once per month.

Facial hair

Up to 0.56 g of 2,4-diaminophenoxyethanol sulfate (4 per cent in 14 g liquid product) will be used per application. The mixed product (containing 2,4-diaminophenoxyethanol sulfate at up to 2 per cent) will be applied to facial hair using an applicator brush, left on the hair for up to 5 minutes, and then rinsed out, followed by shampooing. It is anticipated that reapplication would occur no more than once a week. It is also noted that the product instructions imply that the provided gloves should be reused during subsequent applications when the remaining contents of the tubes are used. This practice may lead to increased levels of exposure to 2,4-diaminophenoxyethanol sulfate due to the possible presence of residues on the gloves.

For each of the above types of products outlined above, exposure to the public will be primarily dermal through the scalp, beard area of face, and hands (if gloves are not used properly), but some accidental ocular or oral exposure is also possible. The public will be exposed to the notified chemical at a concentration of up to 4 per cent from dermal contact with the hair dye during dilution and typically up to a concentration of 2 per cent from contact of the hair dye with the scalp and face (beard area) during the dyeing process (note that there is some potential for the scalp to be exposed to concentrations of up to 4 per cent of 2,4-diaminophenoxyethanol sulfate when using brush-in colour gel designed for the hair, due to possible incomplete mixing with the developer).

International regulations

The European Union Cosmetics Directive lists the chemical in Annex III Part 1 List of substances provisionally allowed, after mixing under oxidative conditions, the maximum concentration applied to hair must not exceed 2 per cent (as hydrochloride).

Scheduling status

2,4-Diaminophenoxyethanol sulfate is not specifically scheduled.

Scheduling history

2,4-Diaminophenoxyethanol sulfate has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

Two submissions were received.

One submission indicated that NICNAS new chemical report is not sufficiently clear as to whether this ingredient is used in any therapeutic goods, as the report pertains to its use in hair dyes. The submission requested that if 2,4-diaminophenoxyethanol sulfate is listed in a schedule, it should exclude therapeutic preparations containing 2,4-diaminophenoxyethanol sulfate.

The other submission indicated that while 2,4-diaminophenoxyethanol sulfate is not specifically scheduled, the Schedule 6 and Appendix C entries of phenylenediamine would capture 2,4-diaminophenoxyethanol sulfate. The submission asserted that as the schedule entry for phenylenediamine adequately address the risks of 2,4 diaminophenoxyethanol sulfate, there is no need for a separate listing for 2,4 diaminophenoxyethanol sulfate. If there is a need for a specific listing for 2,4-diaminophenoxyethanol sulfate, the new schedule entry should clearly indicate that the limitations imposed relate to the on-head concentration of the mixture containing 2,4-diaminophenoxyethanol and not the product containing the substance.

ACCS advice to the delegate

The ACCS recommended that that hair dye preparations containing more than 4 per cent 2,4-diaminophenoxyethanol sulfate be included in Schedule 6 and recommends appropriate Appendix E and F statements.

The ACCS recommended an implementation date of 1 October 2014.

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

The reasons for the recommendation comprised the following:

- The toxicity profile of the substance meets the criteria of Schedule 6. The labelling requirements warrant the specified exemptions.

Delegate's interim decision

The delegate accepts ACCS advice that new entries be created in Schedule 6 and Appendices E & F, to regulate the use of 2,4-diaminophenoxyethanol sulfate 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, and previous recommendations made by the ACCS, an exemption from Schedule 6 has been provided for products that meet specific labelling requirements.

The wording of these proposed entries in Schedule 6 and Appendices E & F is consistent with that used for other hair dye components with a similar toxicological profile. The delegate notes that 2,4-diaminophenoxyethanol may be covered by the existing Schedule 6 entry for hair dyes containing phenylenediamines, but that creating a new specific entry allows for an exemption clause (at 4 per cent) to be included, with similar labelling conditions mandated.

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

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.

Public submissions on the interim decision

One submission was received. The submission noted that although 2,4-diaminophenoxyethanol sulfate is not specifically scheduled, it would be captured by the phenylenediamines schedule entry. As there appear to have been no discussions at the ACCS meeting, nor in the delegate's interim decision on whether 2,4-diaminophenoxyethanol sulfate poses a higher risk than other phenylenediamines, 2,4-diaminophenoxyethanol sulfate's schedule entry therefore should mirror the phenylenediamines schedule entry.

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

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.

The delegate notes that, contrary to the opinion in the public submission that 2,4-diaminophenoxyethanol sulfate would be captured by the phenylenediamines schedule entry, this differs from the advice provided by the ACCS in recommending a separate Schedule 6 entry. Furthermore, the ACCS advice is consistent with advice relating to another hair dye ingredient (2-amino-5-ethylphenol) considered at the November 2013 meeting. The ACCS advice relating to both of these recent decisions allows for the Schedule 6 entry to be specific for use in hair dyes, with a cut-off to exempt at an appropriate concentration (4% in the case of 2,4-diaminophenoxyethanol). The warning statements relating to skin/eye irritation would apply to products both covered by and exempted from Schedule 6.

The later implementation date of 1 July 2015 is intended to allow for orderly re-labelling of products already on the Australian market.

Schedule entry

Schedule 6 - New Entry

2,4-DIAMINOPHENOXYETHANOL in hair dye preparations **except** in preparations containing 4 per cent or less of 2,4-diaminophenoxyethanol when the immediate container and primary pack are labelled with the following:

> KEEP OUT OF REACH CHILDREN
>
> **WARNING** – this product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dying eyelashes and eye brow; to do so may be injurious to the eye.
>
> Written in letters not less than 1.5 mm in height.

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

Appendix E, Part 2 – New Entry

Poisons	Standard statements
2,4-Diaminophenoxyethanol	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E1 - If in eyes, wash out immediately with water.

Appendix F, Part 3 – New Entry

Poisons	Warning statements	Safety direction
2,4-Diaminophenoxyethanol	21 - WARNING – this product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dying eyelashes and eye brow; to do so may be injurious to the eye.	

1.4 2-ETHYLHEXYL 2-ETHYLHEXANOATE OR HEXANOIC ACID, 2-ETHYL-, 2-ETHYLHEXYL ESTER

Scheduling proposal

On 10 December 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) programme requested that the delegate consider a proposal to include cosmetic preparations and/or domestic preparations containing hexanoic acid, 2-ethyl-, 2-ethylhexyl ester in Schedule 6 entry with a low concentration exemption cut-off for cosmetic preparations and/or domestic preparations containing hexanoic acid, 2-ethyl-, 2-ethylhexyl ester.

The delegate's reason for referring this scheduling proposal to the ACCS is that, the NICNAS IMAP report focuses on the potential for reproductive toxicity associated with the hydrolysis of this ester to known reproductive toxicants, 2-ethylhexanol and 2-ethylhexanoic acid. The NICNAS report notes its potential use in leave-on cosmetic products with a concentration level up to 8.3 per cent, and that the use of such products is associated with a relatively small Margin of Exposure (MOE) estimate. The issues raised have much in common with current Schedule 6 arrangements for ethylene glycol monoalkyl ethers and their acetates. In view of the potential impact on existing products, the delegate considers that advice is needed from the ACCS, with an appropriate public notice alerting the industry to the proposed scheduling action.

The delegate asked the following specific questions:

- Since the current Schedule 6 entry for ethylene glycol monoalkyl ethers and their acetates does not appear to specifically capture the 2-ethylhexyl 2-ethylhexanoate, does the ACCS support the creation of a separate Schedule 6 entry for this chemical?

- Is the Schedule 6 listing decision on hexyloxyethanol from the July 2013 ACCS meeting a suitable template for the schedule wording, with the associated recommendations for entries in Appendices E & F?
- Should the listing of 2-ethylhexyl 2-ethylhexanoate in Schedule 6 be specific to cover use in cosmetics only?
- What is the preferred name for listing in the Schedules?
- Should the exemption cut-off be set at 10 per cent, consistent with the other ethylene glycol monoalkyl ethers, or at 8.3 per cent (the putative upper limit in cosmetics products), or at some lower level, given the adverse findings of the MOE calculation?
- What weight should be given to the NICNAS comment on the Cosmetics Ingredient Review (CIR) 2013 proposal that the reproductive toxicity potential of the ester may be limited by the rate of hydrolysis?

Substance summary

Please refer to the NICNAS IMAP Human Health Tier II Assessment Reports for hexanoic acid, 2-ethyl-, 2-ethylhexyl and hexanoic acid, 2-ethyl-. These reports are publically available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=827 and http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=787, respectively.

Scheduling status

2-Ethylhexyl 2-ethylhexanoate is not specifically scheduled.

Scheduling history

2-Ethylhexyl 2-ethylhexanoate has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

Two submissions were received.

One submission indicated that the EU and the USA had extensively considered the risks posed by the substance and had not imposed any restriction on the use of the substance. The submission asserted that there was no need to schedule 2-ethylhexyl 2-ethylhexanoate.

The second submission indicated that there does not appear to be an entry in TGA e-BS. It was unclear from the scheduling proposal whether the proposed scheduling of the substance may have impact on therapeutic goods, noting that the wording of the scheduling proposal did not exclude therapeutic goods. The submission requested that the schedule listing should exclude therapeutic preparations containing the substance.

ACCS advice to the delegate

The ACCS recommended that preparations containing more than 10 per cent of 2-ethylhexyl 2-ethylhexanoate be listed in Schedule 6. The committee, in addition to recommending a Schedule 6 listing, also recommended appropriate Appendix E and F statements for 2-ethylhexyl 2-ethylhexanoate.

The ACCS recommended an implementation date of 1 October 2014.

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

The reasons for the recommendation comprised the following:

- Potential reproductive toxicity consistent with criterion for Schedule 6.

Delegate's interim decision

The delegate accepts the advice of the ACCS to include 2-ethylhexyl 2-ethylhexanoate in Schedule 6, with an exemption cut-off at 10 per cent. While its acute oral toxicity is low and there is sparse information on skin-eye irritancy and sensitisation potential, the critical toxicological endpoint is reproductive/developmental toxicity associated with its ready hydrolysis to the known reproductive toxicants, 2-ethylhexanol and 2-ethylhexanoic acid. The NICNAS risk assessment suggests that a Margin of Exposure (MoE) estimate (26) associated with use in leave-on cosmetics (at 8.3 per cent) to be unacceptable. However, this MoE estimate was not based on studies using 2-ethylhexyl 2-ethylhexanoate and includes conservative assumptions (rapid and complete hydrolysis, 100 per cent absorption and a LOAEL-derived additional 3x safety factor). The delegate concludes that the 10 per cent cut-off to exempt recommended by the ACCS is appropriate in these circumstances, and that it is consistent with Schedule 6 exempt cut-offs for compounds with similar reproductive toxicity potential (e.g. ethylene glycol monoalkyl ethers).

The delegate welcomes further comment on the suitability of the proposed 10 per cent exemption cut-off, and whether a lower cut-off (e.g. 2 per cent) should be developed to be specifically applied to leave-on cosmetics.

The delegate also supports the ACCS recommendation to require an Appendix F warning statement (No. 53) relating to this reproductive toxicity potential. This warning statement would only apply to products that meet Schedule 6 criteria.

The delegate proposes a more extended implementation date 1 July 2015 to allow for further consultation on the proposed exemption cut-off (including referral back to the November 2014 ACCS meeting if necessary), and to allow an appropriate time for product re-labelling to occur.

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[5];
- Other relevant information.

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

Public submissions on the interim decision

One submission was received. The submission noted that although the delegate's proposed schedule entry for the substance would capture its salts and derivatives, the metabolites of 2-ethylhexyl 2-ethylhexanoate, such as 2-ethylhexanol and 2-ethyhexanoic acid may not be captured by this entry. The submission requested the delegate defer the final decision on this substance and re-consult a proposal for the two separate schedule entries, i.e. 2-ethylhexanol and 2-ethyhexanoic acid.

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

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.

The delegate notes the proposal in the public submission that consideration be given to developing separate schedules for 2-ethylhexanol and 2-ethyhexanoic acid, the hydrolysis products of 2-ethylhexyl hexanoate in which the developmental toxicity potential resides. This is a matter that could be considered at a future meeting of the ACCS, although there is no indication that either of these chemicals is included in the *Australian Inventory of Chemical Substances* (AICS) and should therefore not be available in Australia.

No specific comment has been received on the proposed cut-off to exempt at 10%.

The delegate confirms the proposed implementation date 1 July 2015 to allow an appropriate time for product re-labelling to occur.

Schedule entry

Schedule 6 – New Entry

2-ETHYLHEXYL 2-ETHYLHEXANOATE **except** in preparations containing 10 per cent or less of 2-ethylhexyl 2-ethylhexanoate.

Appendix E, Part 2 – New Entry

Poisons	Standard statements
2-Ethylhexyl 2-ethylhexanoate	A – For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).

Appendix F, Part 3 – New Entry

Poisons	Warning statements	Safety direction
2-Ethylhexyl 2-ethylhexanoate	53. CAUTION – 2-ethylhexyl 2-ethylhexanoate should not be used by pregnant women.	

1.5 BENZOIC ACID, 2-HYDROXY-, (3Z)-1-METHYL-3-HEXEN-1-YL ESTER

Scheduling proposal

On 29 August 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) under its New Chemicals Assessment process, requested that the delegate consider a proposal to create a new Schedule 6 and Appendix F listing for benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester. This proposal was first notified to the delegate in September 2013 at which time it was determined that expert advisory committee advice may not be required for this proposal. However, due to the complexity of the proposal, expert advice on this substance is being sought.

The reasons for this recommendation include:

- Benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester is a moderate to severe skin sensitiser and meets the Scheduling Policy Framework's Schedule 6 factors.
- A quantitative risk assessment for dermal sensitisation indicated that an acceptable risk to the public was associated with use of the chemical at no more than 0.2 per cent in deodorants, 0.37 per cent in fine fragrances, 0.51 per cent in other leave on cosmetic products and 0.96 per cent in rinse-off cosmetic, fabric care and household cleaning products.

The delegate's reason for referring this scheduling proposal to the ACCS is that, while the NICNAS evaluation report proposes listing this new chemical in Schedule 6, the ACCS advice is needed on whether inclusion in the SUSMP is the most appropriate control measure, given its proposed use in low concentrations in fragrances, cosmetics, household cleaners and fabric care products.

The delegate asked the following specific questions:

- The pure chemical has relatively low acute toxicity, is weakly positive as a skin/eye irritant and is a sensitiser in animal studies, but not in human studies. Public exposure is only likely to occur through its use as a fragrance containing up to 4.8 per cent, in cosmetics containing up to 1 per cent and household cleaning products containing up to 0.12 per cent. Does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and can the ACCS recommend a low cut-off concentration to exempt?
- Should there be different cut-off concentrations for different product classes (e.g. fragrances; leave-on and rinse-off cosmetics; deodorants; household cleaners)?
- If scheduled, what name should be used in the listing – the chemical name - benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester, or an alternative name, such as (Z)-hept-4-en-2-yl 2-hydroxybenzoate?
- Are Appendix E & F statements required?

Substance summary

Benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester is intended to be used as a component of fragrances for a variety of cosmetic and household cleaning products (proposed usage concentration: ≤4.8 per cent in fine fragrances, ≤0.96 per cent in other cosmetic products and ≤0.12 per cent in fabric care and household cleaning products).

The end-use products (containing ≤4.8 per cent benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester) may be used by consumers and professionals, such as hairdressers, workers in beauty salons or cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

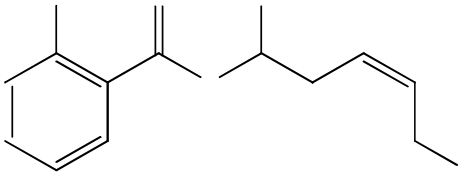

Figure 3. Structure of benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester

Acute toxicity

The acute toxicity end-points for the chemical are listed in the below table.

Toxicity	Species	Benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester	SPF* classification
Oral LD_{50} (mg/kg bw)	Rat	>2000	Schedule 5
Dermal LD_{50} (mg/kg bw)	Rat	>2000	Schedule 5
Inhalational LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Slight irritant	
Eye irritation	Rabbit	Slight irritant	
Skin sensitisation (Local lymph node assay and Modified Local lymph node assay)	Mouse	Sensitiser	
Skin sensitisation (Repeat insult patch test [15 per cent])	Human	Non-sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

Repeat-dose toxicity

In a 28-day oral toxicity study, rats (5/sex/dose) were administered benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester at 0, 100, 300 or 1000 mg/kg bw/day. There were no mortalities during the study and the treatment related effects were, in general, limited to increased liver weights and minimal to mild hepatocellular hypertrophy in 1000 mg/kg bw/day males (2/5) and females (2/5), and in 300 mg/kg bw/day males (2/5). There was slight-moderate salivation and dyspnea in one subject at 1000 mg/kg bw/day. The liver effects were not considered to be adverse, thus the NOAEL established by the study authors was 1000 mg/kg bw/day.

Mutagenicity

Benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester was not mutagenic in a bacterial reverse mutation assay and was not clastogenic in an *in vitro* chromosome aberration assay in Chinese hamster V79 cells.

Genotoxicity

The substance was non genotoxic in an *in vitro* chromosome aberration assay.

Carcinogenicity

Information not supplied.

Reproduction and developmental toxicity

Information not supplied.

Observation in humans

Information not supplied.

International regulations

No known international restrictions identified.

Scheduling status

Benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester is not specifically scheduled.

Scheduling history

Benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

Two submissions were received.

One submission indicated that the information provided in the scheduling proposal and in the NICNAS report was not sufficiently clear as to whether this ingredient was used in any therapeutic goods. The submission requested that if the substance was listed in a schedule, consideration be given to specifically exclude therapeutic good preparations containing benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester.

The other submission noted that NICNAS assessment report indicates that this substance had a low toxicity profile therefore it did not support a schedule listing for this substance.

ACCS advice to the delegate

The ACCS recommended benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester does not require a schedule listing.

The reasons for the recommendation comprised the following:

- The fragrance ingredient based on the evidence before the committee do not require scheduling.

Delegate's interim decision

The delegate accepts ACCS advice that the fragrance ingredient benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester does not require scheduling.

The delegate notes that sensitisation potential is the toxicological finding that could justify inclusion in the schedules, and that the ACCS has made similar recommendations at this and previous meetings on the need to schedule fragrance chemicals where sensitisation potential is the main driver. The delegate also notes that there was extensive discussion at ACCS on the interpretation of positive *in vivo* rodent-based sensitisation tests, such as the Local Lymph Node Assay (LLNA),

particularly where human studies fail to confirm a sensitisation. This information has been supplemented by NICNAS, including information on how the tests may be quantitatively interpreted to determine sensitisation potency and to derive a possibly useful estimate of an appropriate scheduling cut-off. Using this approach, benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester could be classified as a weak sensitiser, possibly explaining why it proved negative in a human study with a limited number of subjects. Since there were no other toxicological factors that would justify scheduling, and the use of benzoic acid, 2-hydroxy-, (3Z)-1-methyl-3-hexen-1-yl ester as a fragrance ingredient in products on the Australian market is likely to be at concentrations of no more than 1 per cent, the delegate confirms that no schedule listing is proposed.

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 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[6];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

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.

1.6 DIBUTYL PHTHALATE

Scheduling proposal

On 10 December 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS), under the Priority Existing Chemical (PEC) program, requested that the delegate consider including cosmetic and personal care preparations containing dibutyl phthalate (DBP) in Appendix C.

The reasons for this recommendation are:

- Estimate of margin of exposure (MoE) for use of DBP in cosmetics indicates that the risk of reproductive toxicity for the general population from the use of cosmetics containing DBP is unacceptable. Repeat-dose toxicity studies on multiple generations of rodents showed testicular

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

toxicity. Both fertility and development are affected in the parents and following generations. The toxicity in male rodents involves overt effects on the reproductive tract organs. DBP also affects testosterone synthesis in male rodents;

- Reproductive toxicity induced by DBP might have serious long-term health effects and affect the development and reproduction of future populations if the exposure is within a critical window of human health development;
- A cautious approach to the potential risks associated with DBP is warranted, given the level of uncertainty regarding both the health effects and levels of exposure for different population groups; and
- Currently there are no restrictions in Australia on the use of DBP in cosmetics and there is a potential for introduction and widespread use of cosmetic products containing DBP.

The delegate referred the proposal to the ACCS. The reason for referring the proposal to the ACCS is that NICNAS recommended specific uses of DBP, i.e. cosmetics and personal care products, be restricted by listing in Appendix C. The Scheduling Policy Framework (SPF) indicates that advice from the ACCS should be sought for such restrictive scheduling. Since the proposal is specific for cosmetic and personal care products, it should have no impact on therapeutic goods regulated by the TGA, so there appears to be no need to refer the matter to a joint meeting of the ACCS-ACMS.

The delegate asked the following questions.

- Noting the difficulties and uncertainties associated with the assignment of a NOAEL for reproductive toxicity and the exposure estimates, does the ACCS agree that the relatively small margin of exposure (MoE) calculations associated with the uses of DBP in cosmetic and personal care products warrant restrictive scheduling?
- Based on similar toxicological concerns, previous decisions of the NDPSC and ACCS in relation to restrictions on the use of diethyl phthalate (DEP), dimethyl phthalate (DMP) and diethylhexyl phthalate (DEHP) have resulted in listing in Appendix C for various products deliberately applied to human skin. Does the ACCS support a parallel entry for DBP?
- The NICNAS exposure calculations indicate that the products contributing most to estimates of DBP systemic exposure would fit the definition of ‘cosmetics’. This suggests that a parallel entry for DEHP could act as a template. Is there a need to expand the proposed Appendix C entry to include sunscreens, personal insect repellents and body lotions, with a cut-off at 0.5 per cent, as in the current DMP and DEP entries?
- None of the phthalate esters currently listed in Appendix Care separately listed in any schedules of the SUSMP. While the NICNAS evaluations only recommend controls on the use of some phthalate esters in cosmetics and personal care products, do other use patterns of the more toxic phthalates suggest a need to consider scheduling to control a broader range of products?

Substance summary

Please refer to the NICNAS PEC assessment report for dibutyl phthalate and its related compounds. This report is publically available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/pec-assessments. The report number is PEC/26.

Scheduling status

Dibutyl phthalate is not specifically scheduled. Other phthalates such as diethylhexyl phthalate, diethylphthalate and dimethylphthalate are listed in Appendix C. Diethylhexyl phthalate for cosmetic use is listed in Appendix C and dimethylphthalate and diethylphthalate in sunscreens or

personal insect repellents for human use (except in preparations containing 0.5 per cent or less of dimethylphthalate and diethylphthalate) is currently listed in Appendix C.

APPENDIX C

DIETHYLHEXYL PHTHALATE for cosmetic use.

APPENDIX C

DIETHYLPHTHALATE in sunscreens, personal insect repellents or body lotion preparations for human use except in preparations containing 0.5 per cent or less of diethylphthalate.

APPENDIX C

DIMETHYLPHTHALATE in sunscreens, personal insect repellents or body lotion preparations for human use except in preparations containing 0.5 per cent or less of dimethylphthalate.

Scheduling history

In August 2001, the National Drugs and Poisons Scheduling Committee (NDPSC) considered foreshadowed proposal (from August 2000) including dimethylphthalate (DMP) and diethylphthalate (DEP) in Appendix C when used in insect repellents or sunscreens for human use. The committee agreed that the potential reproductive hazard to males of the short-chain phthalates, dimethyl- and diethylphthalate when applied to large areas of the skin, warranted prohibition of these substances in products such as sunscreens and insect repellents. A cut-off limit of 0.5% was also supported as dermal exposure at or below this level was unlikely to present a risk.

In June 2011, the chemicals scheduling delegate decided to list diethylhexyl phthalate in Appendix C when in preparations for cosmetic use.

Pre-meeting public submissions

Two submissions were received.

One submission indicated that dibutyl phthalate is listed in TGA e-BS site with use as an active ingredient restricted to topical prescription preparations, and use allowed as an excipient in registered and listed medicines. The submission requested that only cosmetic preparations containing dibutyl phthalate should be listed in a schedule.

The other submission indicated that cosmetic preparations containing dibutyl phthalate be included in Appendix C. The submission noted that dibutyl phthalate is listed in Annex II (substances banned in cosmetics) of the EU Cosmetics Directive.

ACCS advice to the delegate

The ACCS recommended that cosmetic preparations containing dibutyl phthalate be included in Appendix C.

The ACCS recommended an implementation date of 1 October 2014.

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

The reasons for the recommendation comprised the following:

- The potential for irreversible reproductive toxicity warrants banning in cosmetic preparations.

Delegate's interim decision

The delegate accepts ACCS advice that a new Appendix C entry be created to restrict dibutylphthalate use in cosmetics. Reproductive toxicity is the toxic effect noted in animal studies that drives the risk assessment and the Margin of Exposure (MoE) estimate for this specific use is considered unacceptable. Inclusion of such products in Appendix C is considered to be the most effective way to prevent the use of dibutylphthalate in cosmetic products, and it is consistent with the listing of other phthalate esters with similar reproductive toxicity potential in Appendix C.

The delegate agrees with the implementation date being 1 October 2014. An early implementation date is warranted since the objective is to remove any such products from the Australian market on safety grounds.

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 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[7];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

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 proposed new entry in Appendix C is consistent with that proposed in the interim decision.

Schedule entry

Appendix C – New Entry

DIBUTYLPHTHALATE for cosmetic use.

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

1.7 2-PHENOXYETHANOL OR ETHANOL, 2-PHENOXY-

Scheduling proposal

On December 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) process requested that the delegate consider including cosmetic preparations containing more than 1 per cent of ethanol, 2-phenoxy- in Schedule 5.

The delegate's reason for referring this scheduling proposal to the ACCS is that 2-phenoxyethanol is an ethylene glycol aryl ether, so it would not be captured by the current Schedule 6 entry for monoalkyl ethers. Its toxicity profile, as summarised in the IMAP report, does not appear to include the reproductive toxicity potential of some of the monoalkyl ethers, but its potential for eye irritancy and sensitisation warrants consideration for listing in the SUSMP schedules. The IMAP report draws particular attention to its use in cosmetics, and proposes a Schedule 5 entry, with an exemption cut-off in cosmetics at 1 per cent. In view of the potential impact on existing products, the delegate considers that advice is needed from the ACCS, with an appropriate public notice alerting the industry to the proposed scheduling action.

The delegate asked the following specific questions:

- Does the ACCS support the creation of a Schedule 5 entry for 2-phenoxyethanol? If so, should the listing name be: 2-phenoxyethanol, phenylglycol ether, or ethylene glycol monophenyl ether?
- Should the listing be specific to cover use in cosmetics or domestic products only? Such specific scheduling may be needed if there are uses (as noted by the Secretariat) in veterinary products.
- Should there be separate cut-offs to exempt for different product classes? – e.g. 1 per cent for cosmetics and 15 per cent for other domestic products?
- Is the Schedule 6 listing decision on hexyloxyethanol from the July 2013 ACCS meeting a more suitable template for the schedule wording, with the associated recommendations for entries in Appendices E & F?

Substance summary

Please refer to the NICNAS Inventory Multi-tiered Assessment Prioritisation (IMAP) Human Health Tier II Assessment Report for ethanol, 2-phenoxy-. This report is publically available on the NICNAS website at: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=529.

Scheduling status

2-Phenoxyethanol is not specifically scheduled.

Ethylene glycol monoalkyl ethers and their acetate are listed in Schedule 6 and Appendices E, F and I.

In October 2013, the delegate decided to create a new Schedule 6 entry for preparations containing 10 per cent or less of hexyloxyethanol. The delegate also included hexyloxyethanol in Appendix E and F entries.

Scheduling history

Scheduling history of ethylene glycol monoalkyl ethers and their acetates.

In November 1984, the Poisons Schedule (Standing) Committee (PSC) considered scheduling of ethylene glycol monoalkyl ethers and their acetates. The PSC noted that ethylene glycol monomethyl- and monoethyl ethers were the most toxic of the series which demonstrated significant testicular effects, reproductive toxicity and haematological effects and were toxic at inhalation levels at the threshold limit value (TLV). The PSC also noted that other alkyl ethers of demonstrated haematological effects which increased with chain lengths. The PSC therefore decided to include preparations containing 5 per cent or less of ethylene glycol monoalkyl ethers and their acetates in Schedule 6.

In February 1985, the PSC reconsidered the November 1984 decision and decided to raise the Schedule 6 ethylene glycol monoalkyl ethers and their acetates exemption cut-off from 5 per cent to 10 per cent.

In October 2013, the delegate, based on ACCS advice and public submission received in regards to the delegate's proposal, decided to create a new Schedule 6 entry for preparations containing 10 per cent or less of hexyloxyethanol. The delegate also included hexyloxyethanol in Appendix E and F entries. The delegate's decision to include hexyloxyethanol in Schedule 6 was based on its toxicity profile, in particular, hexyloxyethanol's moderate to high acute oral (LD_{50} 738 mg/kg bw) and dermal toxicity (LD_{50} 721 mg/kg bw), and its potential corrosivity to skin.

Pre-meeting public submissions

Three submissions were received.

The first submission indicated that the delegate's scheduling proposal refers to cosmetic preparations containing the substance. The submission indicated that it supports a clear distinction between cosmetics/personal care products and therapeutic goods in the drafting of scheduling proposals.

The second submission indicated that EU Cosmetic Directive allows cosmetic preparations containing up to 1 per cent of 2-phenoxyethanol as a preservative. In Australia, up to 1 per cent of 2-phenoxyethanol was used in cosmetics preparations. The submission requested that consideration therefore be given to include cosmetic preparations containing more than 1 per cent of 2-phenoxyethanol in a schedule.

The third submission indicated that it would make further submission based on delegate's interim decision.

ACCS advice to the delegate

The ACCS recommended that cosmetic preparations containing more than 1 per cent of 2-phenoxy-ethanol and other preparations containing more than 15 per cent of 2-phenoxy- ethanol be included in Schedule 6.

The ACCS recommended an implementation date of 1 October 2014.

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

The reasons for the recommendation comprised the following:

- The acute oral toxicity profile is consistent with the SPF factors for Schedule 6.

Delegate's interim decision

The delegate accepts the advice of the ACCS to include 2-phenoxyethanol in Schedules 5 and 6. The critical toxicological endpoints driving this categorisation (potential for acute oral and dermal

toxicity, skin/eye irritancy and sensitisation) are consistent with SPF criteria for listing in Schedule 6, with the public health risk sufficiently ameliorated for products containing 15 per cent or less, and cosmetic products containing 1 per cent or less.

The delegate agrees with the implementation date being 1 October 2014. An early implementation date is proposed, based on advice that there should be minimal impact on products currently in the Australian market.

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 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[8];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

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.

Schedule entry

Schedule 6 – New Entry

2-PHENOXYETHANOL **except:**

(a) in cosmetic preparations containing 1 per cent or less of 2-phenoxyethanol; or

(b) in other preparations containing 15 per cent or less of 2-phenoxyethanol.

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

Appendix E, Part 2 – New Entry

Poisons	Standard statements
2-Phenoxyethanol	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 eye, wash out immediately with water.

Appendix F, Part 3 – New Entry

Poisons	Warning statements	Safety direction
2-Phenoxyethanol	5. Irritant	1. Avoid contact with eyes.

1.8 HEXAMINE OR 1, 3, 5, 7-TETRAAZATRICYCLO [3.3.1.1^{3,7}] DECANE

Scheduling proposal

On 10 December 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) under the Inventory Multi-tiered Assessment Prioritisation (IMAP) process, requested that the delegate consider a proposal to include 1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane in Schedule 5 with potential low concentration cut-off.

The chemical is not specifically listed. However, specific uses may be included in the following general group entry in Schedule 5 (AMINES for use as curing agents for epoxy resins except when separately specified in these Schedules).

The NICNAS IMAP report recommends that the chemical in cosmetics/personal care products and domestic products should be restricted through poisons scheduling. Exemptions to scheduling may be applicable at low concentrations (up to 0.15 per cent, see Overseas Regulation in the IMAP report).

The IMAP report notes that the matters to be taken into consideration include skin and respiratory sensitisation effects of the chemical (including release of formaldehyde under acidic conditions) and the maximum concentrations authorised in cosmetics overseas.

The delegate's reason for referring this scheduling proposal to the ACCS is that, in accordance with section 4.2 of the Scheduling Policy Framework (SPF), advice is required to be obtained from an expert advisory committee for all rescheduling proposals.

The delegate raised the following specific questions:

- Does the ACCS support the creation of a Schedule 5 entry for 1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane?
- If so, should the listing name be: 1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane, hexamethylene tetramine or methanamine? Note that a related tetramine derivative (hexamethylmelamine) is an anti-cancer drug currently listed in Schedule 4. The structural similarities are not such that the two listings should be confused.

- Is the purported sensitisation potential sufficient to warrant Schedule 5 scheduling, for a chemical that appears to have minimal acute and repeated dose toxicity?
- If the ACCS supports scheduling, should the entry be specific for cosmetic use, with a cut-off at 0.15 per cent? Cosmetic-specific scheduling may be needed if there are potential uses (as noted in the NICNAS IMAP report) in AgVet and therapeutic products.
- Noting the Secretariat's comment that there are generic Appendix E & F statements for 'AMINES for use as curing agents for epoxy resins', or does the ACCS consider that this generic entry already includes 1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane, or does its use pattern (as described in the NICNAS IMAP report) and a proposal to schedule only the cosmetic uses of this chemical indicate that these statements are inappropriate?

Substance summary

Please refer to the NICNAS IMAP Human Health Tier II Assessment Report for 1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane. This report is publically available on the NICNAS website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=119.

Scheduling status

1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane is not specifically scheduled.

Scheduling history

1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

Two public submissions were received.

One submission indicated that as it did not oppose the scheduling of methenamine in cosmetic preparations on the basis of international harmonisation. Methenamine is used as a camp stove fuel tablet (hexamine tablets). Any scheduling decision should understand the impact on this and other potential sectors.

The other submission indicated that the TGA's e-BS site and the ARTG has hexamine listed in the ARTG ingredient list. Hexamine hippurate is also an active ingredient in an OTC medicine widely used to treat urinary tract infection (hexamine hippurate 1g tablets), and this substance could be regarded as a salt or derivative of hexamine. The submission indicated that the scheduling proposal would therefore capture a TGA registered therapeutic product and requested that the schedule listing of the substance be specifically exempted from scheduling for therapeutic goods.

ACCS advice to the delegate

The ACCS recommended that cosmetic preparations containing more than 0.15 per cent of hexamine be included in Schedule 5. The committee also recommended that there be a cross reference between hexamine and methenamine.

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

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

The reasons for the recommendation comprised the following:

- Toxicity profile (skin sensitisation) warrants cosmetic preparation above 0.15 per cent be included in Schedule 5.

Delegate's interim decision

The delegate accepts the advice of the ACCS to include the substance in Schedules 5. While the chemical has a very low toxicity profile (acute oral/dermal toxicity, no skin/eye irritancy) and this profile is inconsistent with any of the SPF scheduling criteria, its sensitisation potential warrants inclusion of cosmetic products containing it in Schedule 5. The risk is sufficiently ameliorated for cosmetic products containing 0.15 per cent or less, and this is consistent with international cosmetic restrictions.

The schedule 5 entry should be restricted to use in cosmetics, the name is an issue. The IUPAC name is 1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane, while other common names are hexamine and hexamethylenetetramine. While the latter names appear to be in common use in Australia, neither appears to have status as an Australian approved name, as outlined in Part 1 of the SUSMP. Accordingly, it is proposed to use the IUPAC name in the listing, with SUSMP index cross-references to hexamine and hexamethylenetetramine.

The delegate agrees with the implementation date being 1 October 2014. An early implementation date is proposed, based on advice that there should be minimal impact on products currently in the Australian market.

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 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.

Public submissions on the interim decision

No public submissions were received.

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.

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

Schedule entry

Schedule 5 – New Entry

1,3,5,7-TETRAAZATRICYLO[3.3.1.1^{3,7}] DECANE in cosmetic preparations, **except** in preparations containing 0.15 per cent or less of 1, 3, 5, 7-tetraazatricyclo [3.3.1.1^{3,7}] decane.

Index – New Entry

HEXAMINE

See 1, 3, 5, 7-TETRAAZATRICYCLO [3.3.1.1^{3,7}] DECANE

HEXAMETHYLENETETRAMINE

See 1, 3, 5, 7-TETRAAZATRICYCLO [3.3.1.1^{3,7}] DECANE

1.9 LAMBDA-CYHALOTHRIN

Scheduling proposal

On 9 November 2013, the Office of Chemicals Safety (OCS) requested that the delegate consider a proposal to amend the Schedule 6 entry for lambda-cyhalothrin to increase the concentration cut-off for (b) other preparations containing lambda-cyhalothrin from 1 per cent or less to 1.5 per cent or less of lambda-cyhalothrin. The OCS's request is based on an application to the Australian Pesticides and Veterinary Medicines Authority (APVMA) to register a new insecticide product, containing lambda-cyhalothrin and an organophosphate (OP) component. The product is emulsion oil in water (EW) formulation for control of certain pests in wheat, barley, canola, pulses, lucerne and pastures.

The reason for this recommendation is that a product containing lambda-cyhalothrin and OP component has:

- Moderate acute oral toxicity in rats;
- Low acute dermal toxicity in rats;
- Low acute inhalational toxicity in rats;
- Moderate irritant of the skin in rabbits;
- Moderate eye irritant in rabbits; and
- Not a skin sensitiser in mice (local lymph node assay).

The delegate noted that the acute inhalational toxicity values align with the Scheduling Policy Framework (SPF) Schedule 6 factors, i.e. moderate to high toxicity.

The OCS considers that due to the scheduling history for lambda-cyhalothrin and the acute toxicity profile of the product, that amendment of the current Schedule 6 entry for lambda-cyhalothrin would be appropriate.

The OCS recommended to the scheduling delegate that the entries for lambda-cyhalothrin be amended to read:

SCHEDULE 7 entry – no change

SCHEDULE 6 – Amendment

LAMBDA-CYHALOTHRIN – amend entry to read:

LAMBDA-CYHALOTHRIN

(a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or

(b) in other preparations containing 1.5 per cent or less of lambda-cyhalothrin

except when included in Schedule 5.

SCHEDULE 5 entry – no change.

The delegate referred this matter to the ACCS. The reason for referring this matter to the ACCS is, although the proposal was a relatively straightforward re-scheduling proposal that may not need advice from the ACCS, the scheduling history of products containing lambda-cyhalothrin is more complex. ACCS advice is therefore requested to ensure that the re-scheduling application incorporates correct wording.

The delegate asked the following questions:

- The toxicity profile of the product under consideration is clearly consistent with Scheduling Policy Framework (SPF) criteria for Schedule 6. However, the contribution of the organophosphate component masks any potential acute toxicity difference between the 1.5 per cent concentration of lambda-cyhalothrin and the 1 per cent permitted in 'other' preparations in the current Schedule 6 entry.

- The scheduling is further complicated by the fact that the current Schedule 6 entry permits a concentration of lambda-cyhalothrin up to 25 per cent when in a microencapsulated formulation, while the Schedule 5 entry allows for up to 1 per cent lambda-cyhalothrin in aqueous preparations and up to 2.5 per cent in microencapsulated formulations.

- The applicant makes a case that the formulation of the product under consideration could be considered to be a form of microencapsulation. If this is the case, amendment of either the Schedule 5 or Schedule 6 entries is not needed to accommodate this product in Schedule 6, where the organophosphate component requires regulation as a Schedule 6 product.

- Does the ACCS advise that the simple solution to amend clause (b) of the current Schedule 6 entry by extending the limit from 1 to 1.5 per cent, as proposed in the OCS evaluation report, is the more effective re-scheduling approach, or should a more specific clause be added to the current Schedule 6 entry to accommodate this product? The delegate notes that extending the cut-off to 1.5 per cent is insufficient to cover the actual formulation under consideration, and the delegate proposes to make this 1.6 per cent if the ACCS advice supports amendment of the Schedule 6 entry.

- Would extending the Schedule 6 cut-off from 1 to 1.6 per cent for 'other' preparations have any unintended consequences for lambda-cyhalothrin products currently regulated as Schedule 7 products?

Substance summary

Lambda-cyhalothrin is a synthetic pyrethroid insecticide. It consists of two of the four enantiomers which constitute cyhalothrin. Cyhalothrin comprises approximately 50 per cent lambda-cyhalothrin (cis 1RαS and cis 1SαR enantiomers, enantiomeric pair B) and 50 per cent R157836 (cis 1RαR and

cis 1SαS enantiomers, enantiomeric pair A)[10]. Pyrethroid insecticides disrupt the normal functioning of the nervous system in an organism, which may cause paralysis or death. It is a non-systemic insecticide with contact and stomach action, and repellent properties.[11]

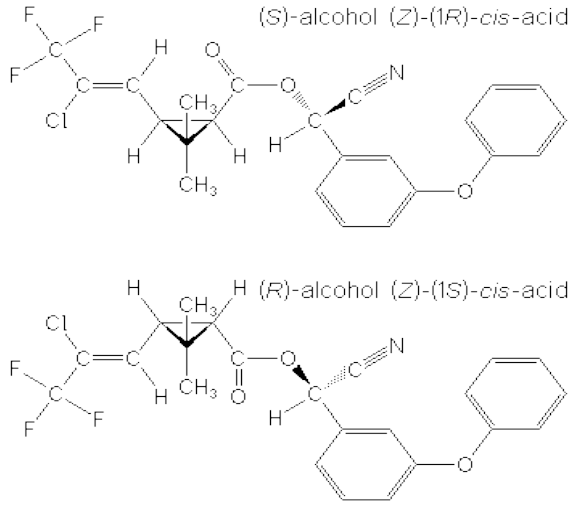

Figure 4. Structures of lambda-cyhalothrin

Acute toxicity

The acute toxicity end-points for the chemical are listed in the below table.

Toxicity	Species	Lambda-cyhalothrin	SPF* classification
Oral LD_{50} (mg/kg bw)	Rats	56	Moderate to high toxicity
Dermal LD_{50} (mg/kg bw)	Rats	632	Moderate to high toxicity
Inhalational LC_{50} ($mg/m^3/4h$)	Rats	65	High to extremely high toxicity
Skin irritation	Rabbits	Slight irritant	
Eye irritation	Rabbits	Slight irritant	
Skin sensitisation (Magnusson and Kligman method)	Guinea pigs	Not a skin sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

The OCS report noted that the acute toxicity symptoms in rats were typical of pyrethroid toxicity, consisting of gait abnormalities, decreased activity, salivation, and piloerection.

[10] Lambda-cyhalothrin (146) by Christian Sieke. Available at [http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Evaluation08/Lambda-cyhalotrhin.pdf]

[11] Lambda-cyhalothrin. Available at [http://www.awhhe.am/downloads/eu_project_presentations/chemicals_eng/lambda-cyhalothrin.pdf]

Repeat-dose toxicity

In a 90-day dietary study in rats with 0, 0.5, 2.5, or 12.5 mg/kg bw/d lambda-cyhalothrin (~10, 50, or 250 ppm), large increases in relative liver weights and aminopyrine demethylase activity were seen in males at 2.5 mg/kg bw/d and in females at 12.5 mg/kg bw/d, but in the absence of accompanying histological changes the effects were considered to be adaptive. The no observed effect level (NOEL) was 2.5 mg/kg bw/d, based on decreased bodyweight gain at 12.5 mg/kg bw/d in both sexes.

Chronic toxicity studies

In a 1-year oral dosing study, dogs in groups of 6/sex/dose received gelatin capsules containing 0.1, 0.5, or 3.5 mg/kg bw/d lambda-cyhalothrin dissolved in corn oil. Slight increases in vomiting in the first weeks of the study were seen at 3.5 mg/kg bw/d, which partially reduced in frequency over the study period. Neurotoxicity symptoms in the form of incoordination (unsteady gait, straddled gait/recumbency), and tremors were seen at 3 to 7 hours post-dosing at 0.5 mg/kg bw/d and above, and were dose dependent. Muscle tremors and convulsions were also seen at 0.5 (2/12 animals) and 3.5 mg/kg bw/d (4/12 animals), but the time of onset and duration was not specified. Most animals recovered from these effects in the intervals between each dosing, and the effects were considered to be non-accumulative. An exception was a male at 3.5 mg/kg bw/d, which developed persistent convulsions and ataxia at week 46 and after two more days was humanely sacrificed in extremis. An incident of ataxia of mild severity was seen in one animal at 0.1 mg/kg bw/d, but was considered to be incidental to treatment.

Decreased food consumption was seen at 3.5 mg/kg bw/d, but bodyweight gain was unaffected. Trends for increased levels of triglycerides, decreased sodium, and (males only) decreased levels of protein and creatine kinase in plasma, were also seen at this dose. Levels of ALP, ALT, and AST in plasma were not measured in the study. Slight but ‘obvious’ increases in the absolute weights of liver and kidney were seen at 3.5 mg/kg bw/d, with trends for increases at lower doses. Necropsy findings, including histopathological, were otherwise unremarkable in all animals. Levels of radiolabel remaining in tissues were not analysed in the study. The NOEL was 0.1 mg/kg bw/d, based on dose-dependent increases in incoordination (unsteady gait, straddled gait/recumbency), muscle tremors and convulsions at 0.5 mg/kg bw/d and above. The OCS (1990) concluded that the neurotoxicity effects of lambda-cyhalothrin could be considered to be short-lasting and reversible. For the purposes of the current assessment, this NOEL can therefore be considered both to be short-term and protective of other effects from long-term exposures.

Mutagenicity

No mutagenic effects were detected using lambda-cyhalothrin in a Salmonella typhimurium reverse mutation assay, with and without metabolic activation.

Genotoxicity

No genotoxic effects were detected.

Carcinogenicity

No information provided.

Reproduction and developmental toxicity

No information provided.

Toxicology of the product

The OCS report noted that the acute toxicity data for lambda-cyhalothrin and an organophosphate (OP) component in the product formulation did not differ markedly from the acute toxicity findings for the product formulation. Therefore, based on a comparison of the acute toxicity profiles of the individual active constituents and the combined product formulation, the information does not appear to indicate the presence of synergism or potentiation resulting from the two active constituents in combination.

The acute toxicity of the product containing OP component and lambda-cyhalothrin are listed in the below table.

Toxicity*	Product	OP component**	Lambda-cyhalothrin
Oral LD_{50} (mg/kg bw)	114 (females, with deaths) (99 - 175)	96-475	56
Dermal LD_{50} (mg/kg bw)	>5000	>2000	632
Inhalational LC_{50} (mg/m^3)	>2450 (males, with deaths) 2070 females, with deaths)	>200	65
Skin irritation	Moderate irritant	slight irritant	Slight irritant
Eye irritation	Moderate irritant	Slight irritant	Slight-irritant
Skin sensitisation	Not sensitising	Not sensitising	Not sensitising

* Oral, dermal and inhalational data from rats; skin and eye irritation data from rabbits; skin sensitisation data from mice or guinea pigs.

** Organophosphate (OP)

Scheduling status

Lambda-cyhalothrin is listed in Schedules 5, 6 and 7.

Other similar substances such as gamma-cyhalothrin is listed in Schedules 5 and 7, and cyhalothrin is listed in Schedule 7.

These three substances differ only in the composition of the stereoisomers present. Cyhalothrin is comprised of 4 stereoisomers (1R, cis, Z-S; 1S, cis, Z-R; 1R, cis, Z-R and 1S, cis, Z-S). Lambda-cyhalothrin is formed from the enantiomer pair (1R, cis, Z-S; 1S, cis, Z-R). Gamma-cyhalothrin has just one isomer (1R, cis, Z-S) which provides almost all the biological activity among the 4 stereoisomers of cyhalothrin.

SCHEDULE 5

LAMBDA-CYHALOTHRIN:

(a) in aqueous preparations containing 1 per cent or less of lambda-cyhalothrin; or

(b) in aqueous preparations containing 2.5 per cent or less of microencapsulated lambda-cyhalothrin.

SCHEDULE 6

LAMBDA-CYHALOTHRIN:

(a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or

(b) in other preparations containing 1 per cent or less lambda-cyhalothrin,

except when included in Schedule 5.

SCHEDULE 7

LAMBDA-CYHALOTHRIN **except** when included in Schedule 5 or 6.

Scheduling history

In November 1987, the Drugs and Poisons Schedule Committee (DPSC) decided to include first aid and safety directions for lambda-cyhalothrin.

In August 1990, the DPSC decided to include preparations containing 1% or less of lambda-cyhalothrin in Schedule 6 and all other preparations containing lambda-cyhalothrin in Schedule 7, based on the toxicity profile of lambda-cyhalothrin.

In November 1991, the DPSC decided to include aqueous preparations containing 1% or less of lambda-cyhalothrin in Schedule 5. The reason for this decision was that the water-based product containing 1% or less of lambda-cyhalothrin would be used by pest control operators therefore registration mechanism would be applicable.

In November 1994, the NDPSC considered toxicological data on microencapsulated suspensions containing 2.5% or less of lambda-cyhalothrin and decided to include it in Schedule 5.

In August 1999, the NDPSC decided to include microencapsulated preparations containing 25% or less of lambda-cyhalothrin in Schedule 6.

Pre-meeting public submissions

One submission was received.

The submission indicated that as lambda-cyhalothrin was used as an insecticide therefore it would be unlikely that the proposed scheduling amendment would have any impact on therapeutic goods.

ACCS advice to the delegate

The ACCS recommended that the Schedule 6 lambda-cyhalothrin entry be amended to increase the concentration cut-off for (b) other preparations containing lambda-cyhalothrin from 1 per cent or less to 1.6 per cent or less of lambda-cyhalothrin.

The ACCS recommended an implementation date of 1 October 2014.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (c) the toxicity of a substance. The reasons for the recommendation comprised the following:

- Toxicity profile of the product is consistent with SPF factors for Schedule 6.

Delegate's interim decision

The delegate accepts the advice tendered by the ACCS, and proposes that the lambda-cyhalothrin entry in Schedule 6 be amended to extend exemption clause (b) from 1 to 1.6 per cent. The toxicity

profile of the product proposed for registration is consistent with SPF criteria for Schedule 6. The delegate also accepts advice that the product formulation is not microencapsulated and therefore it is not covered by the current Schedule 5 and Schedule 6 entry clauses describing such formulations. Increasing the allowed concentration from 1.5 to 1.6 per cent is ensure that the product formulation, when expressed in grams per 100 millilitre (as per Part I of the SUSMP), is covered by the amended entry.

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

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 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.

Public submissions on the interim decision

No public submissions were received.

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.

Schedule entry

Schedule 6 – Amendment

LAMBDA-CYHALOTHRIN – Amend entry to read:

LAMBDA-CYHALOTHRIN:

(a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or

(b) in other preparations containing 1.6 per cent or less of lambda-cyhalothrin

except when included in Schedule 5.

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

1.10 METHYL ISOBUTYL KETONE OR 2-PENTANONE, 4-METHYL

Scheduling proposal

On December 2013, the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) under its Inventory Multi-tiered Assessment Prioritisation (IMAP) process requested that the delegate consider a proposal to delete the current Schedule 5 methyl isobutyl ketone (MIBK) entry and create a new Schedule 6 entry for MIBK.

The reasons for NICNAS' recommendation include:

- carcinogenicity under conditions of high dose repeated inhalation exposure,
- acute inhalation toxicity,
- eye and respiratory irritation,
- flaking and drying of skin following repeated exposure.

The NICNAS report also notes that, although specific cosmetic and domestic uses have not been identified in Australia, the chemical has reported overseas uses for cosmetic and domestic purposes. Overseas reports have identified concentrations of the chemical up to 12 per cent (aerosol) for use in automotive products at home and a concentration of up to 35 per cent (liquid) for home maintenance uses (US Household Products Database).

The delegate's reason for referring this scheduling proposal to the ACCS is that, the IMAP report recommends re-scheduling MIBK (named as 2-pentanone, 4-methyl in the NICNAS IMAP report) from its current Schedule 5 entry to Schedule 6. This requires advice from the ACCS.

The delegate raised the following specific matters:

- MIBK is currently listed in Schedule 5, with a cut-off to exempt at 25 per cent. There are relevant entries in Appendices E & F, and it is also listed in Part 1 as a 'designated solvent'. These SUSMP entries are quite old, and it appears that they may have been unchanged since the 1960s – 1970s.
- The IMAP report draws attention to the recent (2012) IARC classification (2B) of MIBK. The carcinogenicity findings were in liver and kidneys (α-2μ-globulin-induced nephropathy in a recent inhalation toxicity study in rats. The carcinogenicity findings appear to be the primary reason for the NICNAS recommendation to re-schedule MIBK to Schedule 6, although the respiratory and eye irritancy, along with CNS depressant inhalation toxicity could be other reasons.
- Does the ACCS support the re-scheduling proposal to Schedule 6? If so, is the 25 per cent cut-off to exempt still appropriate? Does a schedule change impact on the designation of MIBK as a 'designated solvent'? Note: some 'designated solvents' have their primary listing in Schedule 6.
- Can the ACCS identify the potential regulatory impacts on products currently regulated as Schedule 5?
- Since the NICNAS IMAP report identifies a major overseas use in paints (up to 12 per cent in aerosol form and 35 per cent in liquid form), does the ACCS consider that listing in Appendix I (Uniform Paint Standard) is warranted? If so, in which schedule of the UPS?

Substance summary

Please refer to the NICNAS IMAP Human Health Tier II Assessment Report for MIBK (named as 2-pentanone, 4-methyl- in the IMAP report). This report is publically available on the NICNAS

website: http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=88.

Scheduling status

MIBK is currently listed in in Part 1, interpretation (as a 'Designated Solvent'), in Schedule 5 and Appendices E and F.

PART 1, INTERPRETATION

"Designated solvent" means the following:

methyl isobutyl ketone

SCHEDULE 5

Methyl isobutyl ketone **except** in preparation containing 25 per cent or less of designated solvents.

APPENDIX E

Poisons	Standard statements
Methyl isobutyl ketone	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.

APPENDIX F

Poisons	Warning statements	Safety direction
Methyl isobutyl ketone		1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist

Scheduling history

MIBK was first considered by the Poisons Schedule Sub-Committee (PSSC) in February 1971 as a result of a working party addressing the scheduling of solvents. The PSSC decided to include preparations containing more than 25 per cent MIBK when packed in containers of 5 gallons or less in Schedule 5.

In February 1984, the Poisons Schedule (Standing) Committee (PSC) considered amending the Schedule 5 MIBK entry to provide clarity as a result of broader amendments associated with the introduction of warning statements for hazardous substances in bulk distribution. As a consequence of this, the PSC decided to exempt from the Schedule 5 listing for preparations containing 25 per cent or less of ketones and in containers having a capacity of more than 20 litres, provided the containers are marked with the name and proportion of ketones included in Schedule 5.

In February 1986, the Drugs and Poisons Scheduling Committee (DPSC), based on the Working Party on Safety Directions and First Aid Instructions recommendations, decided to include MIBK in Appendix F (Warning Statements) with a statement indicating "Flammable". The DPSC also decided to delete the exemption references for bulk packs.

Pre-meeting public submissions

Two submissions were received.

One submission indicated that it did not support the scheduling proposal. The submission noted that the NICNAS recommendation to up-schedule MIBK appears to be on the basis of the substance's carcinogenic potential. Both the USA and the EU should also be aware of carcinogenicity potential of MIBK and there were no restrictions in the EU or the USA on the use of this substance in cosmetics. The submission further indicated that the NICNAS had not provided any evidence that the current scheduling of MIBK was inadequate therefore there was no need to up-schedule MIBK or to remove the exemption from scheduling.

The second submission indicted that the TGA e-BS website contains an ARTG ingredient listing for MIBK, with the use not specified. The submission therefore requested that the wording of any proposed Schedule 6 entry should be consistent with the existing Schedule 5 entry, i.e. "Methyl isobutyl ketone except in preparations containing 25 per cent or less of designated solvents." This wording would exclude therapeutic goods from Schedule 5 or 6, as per the existing entry.

ACCS advice to the delegate

The ACCS recommended that the current scheduling of methyl isobutyl ketone remains appropriate.

The reasons for the recommendation comprised the following:

- There are no compelling grounds on the basis of toxicity and carcinogenicity provided to the committee for a change in scheduling.

Delegate's interim decision

The delegate accepts the advice of the ACCS and has decided not to make any change to the current listings of methyl isobutyl ketone (MIBK) in Schedule 5 and Appendices E & F, nor to alter its status as a 'designated solvent' in Part 1 of the SUSMP. The toxicity profile of MIBK is generally consistent with SPF criteria for listing in Schedule 5, but the key issue in the submission seeking re-scheduling to Schedule 6 is its potential for carcinogenicity. The delegate notes the different opinions of the human relevance of carcinogenicity findings in recent inhalation toxicity studies in rats and mice. The ACCS advice downplayed the significance of the findings in rats as possibly related to male rat-specific α-2μ-globulin-induced nephropathy, while the NICNAS report and IARC evaluations have placed less weight on this mechanism and concluded that MIBK is possibly carcinogenic to humans. Findings of non-genotoxicity for MIBK suggest that the carcinogenic findings at high inhalation doses do not appear to be related to a genotoxic mechanism. There is some precedent in that stronger evidence of carcinogenic potential relevant to humans is usually required to support more restrictive scheduling.

The ACCS also noted that, in the absence of information that MIBK is used in any paints on the Australian market, there is no need to amend Appendix I at this time. The delegate accepts this advice.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: 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[13];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

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 METHYLATED SPIRIT(S)

Scheduling proposal

On 15 November 2013, the Australian Competition and Consumer Commission (ACCC) requested the delegate consider including a label warning statement (stated below) alerting consumers regarding the serious burn hazard that methylated spirits may pose when refuelling ethanol burners.

'WARNING: DO NOT attempt to refill methylated spirit burner while it is in use or still warm; it could lead to serious burn injury or death.'

The delegate's reason for referring this scheduling proposal to the ACCS is that the ACCC's proposal to include a mandatory warning statement regarding the risk of burns when used with methylated spirit burners is relatively straightforward. However, the potential regulatory impacts need to be considered by the ACCS and alerted to industry though an appropriate public notice.

The delegate asked the following specific questions:

- Does the ACCS support the ACCC's recommendation that the proposed warning statement be a mandatory inclusion on labels for products regulated under the Schedule 5 entry for methylated spirit?
- Would this be best implemented via a sub-clause in the Schedule 5 entry, or by inclusion of a new Warning Statement in Appendix F?
- In view of the potential regulatory impact, what implementation date does the ACCS recommend for any scheduling action?

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

- Since historical aspects of the scheduling of methylated spirit appear to be incomplete, can any member of ACCS shed any light on how the current entry was promulgated, with the earlier exemption for preparations containing <20 per cent changed to exemption of all 'preparations and admixtures'?

Substance summary

Methylated spirit is ethanol denatured with approximately 5 per cent of methanol. Methanol is commonly used additive in denatured ethanol because of its boiling point is close to that of ethanol, its toxicity and it makes ethanol extremely bad tasting to discourage recreational use of denatured alcohol. Methylated sprit, which is also known as denatured ethanol, ethanol, denatured alcohol, is a clear, colourless, mobile liquid. It is miscible with water in all proportions[14]. Methylated spirit is used as a fuel for spirit burners and camping stoves and also as a solvent for cleaning preparations.

Ethanol is a volatile, flammable, colourless liquid. An ethanol-water solution that contains 40 per cent alcohol by volume will catch fire if heated to about 26°C and if an ignition source is applied to it. The flash point of pure ethanol is 16.60°C, less than average room temperature. Ethanol is a versatile solvent, miscible with water and with many organic solvents, including acetic acid, acetone, benzene, carbon tetrachloride, chloroform, diethyl ether, ethylene glycol, glycerol, nitromethane, pyridine, and toluene. It is also miscible with light aliphatic hydrocarbons, such as pentane and hexane, and with aliphatic chlorides such as trichloroethane and tetrachloroethylene.

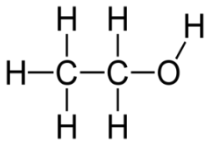

Figure 5. Structure of ethanol

Issues raised in the application

Methanol is commonly used as an additive in the methylated spirit because its boiling point is close to that of ethanol.

Methylated spirit is classified as a Schedule 5 poison and the products' label includes the signal word "CAUTION". It is available from supermarkets, hardware stores and camping/outdoors stores.

Work Safe Australia has classified methylated spirit as a hazardous substance. Methylated spirit is also classified as a dangerous good according to the criteria of the Australian Dangerous Goods (ADG) Code. The products' label includes the following information:

- 'Highly Flammable' symbol and risk phrase;
- 'Keep out of reach of children', 'Keep container tightly closed'; and
- 'Keep away from ignition source – No smoking' safety phrases.

Since the introduction of ethanol burners into the Australian market, methylated spirit has also been used as a common fuel for these products. The product is suitable to use as 'burner fuel' and provides instructions of use of filling the product into the burners. However, the labels of other brands do not have this information.

[14] Safe handling and storage of methylated spirit. Department of Transport and Main Roads, Queensland. Available at [http://www.tmr.qld.gov.au/sitecore/content/TMRInternet/business-industry/Technical-standards-publications/Laboratory-Chemical-Handling-Manual/Methylated-Spirits.aspx]

The ACCC noted that from May 2010 until now, it is aware of twenty-seven incidents relating to ethanol burners, in which twenty-two resulted in burn injuries ranging from minor burns and up to serious burns to 55 per cent of the body. Most of the injuries required hospitalisation. Five of the reported incidents resulted in injuries to child and elderly bystanders.

The majority (64 per cent) of burn injuries reported occurred during the refilling of the burner while it was still lit or warm. The number and severity of injuries related to ethanol burners suggest that ethanol burners pose a hazard to the Australian consumers due to the following reasons:

- Lack of safety warnings on fuel packaging; and
- Lack of safety warnings on burners and burners' packaging.

Additional information

On 19 February 2014, the a member of ACCS sent an email directly to the Scheduling Secretariat indicating that it has been alleged that there are products being sold for "eco fuel" spirit burners present in many households, camping trailers/caravans etc. that are ethanol denatured with (only) 0.25 per cent methyl isobutyl ketone. Apparently these are NOT required to be packed and labelled as Schedule 5 poisons, nor controlled under excise legislation, despite being if anything more dangerous than methylated spirits as defined in the SUSMP as they don't contain a bittering agent but do contain methyl isobutyl ketone which is quite poisonous (and colourless and has a pleasant odour), as noted by the National Industrial Chemicals and Notification Assessment Scheme (NICNAS) in its Inventory Multi-tiered Assessment Prioritisation (IMAP) report. The Excise Act determination indicates that *"Denatured Spirits"* which are exempted from control under the Excise Act includes ethanol denatured with 0.25% methyl isobutyl ketone only. Should the SUSMP definition of methylated spirit be amended to reflect the Excise Act determination?

Methylated sprit is listed in Schedule 5 and Appendix E. It is also listed in Part 2, Labels and Containers under Child-resistant closures.

Scheduling status

SCHEDULE 5

METHYLATED SPIRIT(S) (being ethanol denatured with denatonium benzoate, methyl isobutyl ketone and fluorescein) **except**:

(a) when included in preparations or admixtures; or

(b) when packed in containers having a capacity of more than 5 litres.

APPENDIX E

Poisons	Standard statements
Methylated spirit	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.

PART 2, LABELS AND CONTAINERS

Column 1 Name of the poison	Column 2 Nominal capacity
Methylated spirit excluding preparations or admixtures	5 litres or less

Scheduling history

Methylated spirit was first considered in May 1956 by the Poisons Schedules Committee (PSC). The PSC decided to include methylated spirits and all substances containing more than 20 per cent of methylated sprit in Schedule 5.

In July 1963, the PSC decided to amend the methylated spirit entry to exempt 20 per cent or less of methylated spirit which are labelled in accordance with the then Appendix I (prescribed letter weights).

In February 1978, the Poisons Schedule Sub-Committee (PSSC) decided to amend the Schedule 5 methylated spirit entry to exempt containers having capacity of more than 5 litres and preparations containing 75 per cent or less of methylated spirit.

In November 1978, the PSSC decided to amend the Schedule 5 methylated spirit entry to exclude its preparations and admixtures and methylated spirits in containers having a capacity of more than 5 litres.

Pre-meeting public submissions

Six submissions (including one late submission) were received.

One submission indicated that the application sought an amendment to the Schedule 5 entry rather an Appendix F entry (as proposed by the delegate) for methylated spirits. As Appendix F is not adopted across all jurisdictions, the submission requested to consider the best option for achieving nationally adopted consistent warnings for methylated spirits, perhaps for example, via an amendment to Part 2. The submission also argued that as methylated spirit products are marketed to consumers for use as fuel for burners under a range of names including methylated spirits, bio-fuel and bio-ethanol and therefore the proposed warning statement should apply to all such methylated spirit products.

The second submission indicated that it supports the delegate's proposal to include the additional warning statement to the labelling of methylated spirits.

The third submission questioned whether the current flammability warning is not considered effective, and if it is not, why a new warning would be considered to be effective. The submission argued that labelling proposals need to be demonstrated to be effective before they are imposed.

The fourth (late submission) noted that methylated spirits have multiple uses of which only one is for use in burners. Uses such as disinfecting and cleaning do not result in it being heated. The submission indicated that the proposed warning statement should be applied to the appliance or burner itself, particularly considering such appliances may also have alternate fuel options (which may not contain the proposed warning if such a warning is only applied to methylated spirit containers).

The fifth submission indicated it supports the delegate's proposal to include a warning statement. The submission noted that the appliances themselves have never been referenced as having a

‘methylated spirits burner’ and therefore referring to it in this manner may create confusion or inadequately manage the opportunity for change in line with industry standards and the continuing stable growth of the category. It is absolutely beneficial to both consumers and the category to have appropriately and adequately labelled fuel available as opposed to unlabelled methylated spirits bottles.

The sixth submission indicated that as the methylated spirits label already carries information on flammability, that any additional warning statement may be better placed on the burner itself to warn of the dangers of refilling methylated spirit burners when the burner is still warm or still lit. If there is a need for additional warning labels on methylated spirits, sufficient time should be given (at least two years) to amend the label and transition to the newly labelled products.

ACCS advice to the delegate

The ACCS recommended that the delegate refers this matter back to the ACCC on the grounds that the suggested scheduling of methylated spirits will be potentially ineffective in reducing burn injuries. Labelling maybe better considered on the burner devices.

The committee recommends that the delegate consider the current scheduling definition of methylated spirits be based on denaturing chemicals used.

Delegate’s interim decision

The delegate notes the advice from the ACCS and the difficulties in achieving, through a schedule entry amendment, the requested outcome of warning consumers of the fire risks associated with using methylated spirits to refill burners while alight or hot. The delegate agrees that there are already appropriate flammability warnings on product labels as seen under current requirement in the SUSMP Part 2, Clause 7(h) and that there are a range of other uses for methylated spirit where the applicant’s proposed warning statements would not be applicable. The delegate agrees with ACCS advice that the ACCC be advised to consider attaching the suggested warning statement to the burners, rather than to the fuel. Accordingly, the delegate does not propose to include the requested warning statements by amending the current Schedule 5 entry for methylated spirit, nor by amending Part 2 Clause 7(h), nor by creating a specific Appendix F entry.

The delegate notes the information relating to possible misalignment of the wording of the current Schedule 5 entry with the definition in the Excise Act. Accordingly, the delegate proposes to refer to a future meeting of the ACCS, with appropriate information sought from industry, the specific matter of whether methylated spirits must contain all three denaturing agents (denatonium benzoate, methylisobutyl ketone and fluorescein) or any combination thereof.

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

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[15];
- Other relevant information.

Public submissions on the interim decision

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

The other submission indicated that the efficacy of warning statement is a key factor in the development of effective and efficient responses to product hazards. The current warning statements do not address a specific hazard and that individuals are being injured though lack of understanding of the nature of the risk. The submission requested that delegate consider amending the current methylated spirit(s) entry to provide a prominent new warning statement as follows:

> **'WARNING: DO NOT ATTEMPT TO REFILL A METHYLATED SPIRIT BURNER WHILE IT IS IN USE OR STILL WARM; IT COULD LEAD TO SERIOUS BURN INJURY OR DEATH',** (or similar)

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

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.

The delegate notes the serious nature of burns that have occurred through misuse of fuels that already have prominent flammability warnings and that the ACCC research on the proposed more explicit warning statement suggests the potential for greater awareness of the dangers and possible preventive actions. The delegate intends to seek further information on the practicality of attaching the suggested warning statements to either/both the burners and/or the fuels. The delegate also notes that, under the current schedule 5 entry for METHYLATED SPIRIT(S), some fuels would not be captured even if a warning statement were to be included in the schedule entry (e.g. those in containers containing 5 litres of more and those biofuels not meeting the current specification for methylated spirits).

The delegate had already noted the need to refer back to the ACCS, the matter of which ingredients may be used to denature alcohol, and to better align the methylated spirits definition with current industry practice.

Accordingly, the delegate will refer the matter back to the ACCS for further advice, and also to seek further input from industry and the ACCC. This would include advice on the practicality of limiting the proposed warning statements to methylated spirits in products specifically packaged as biofuels for use in spirit burners and on the need to adjust the schedule entry so that warnings could be applied to the larger containers that are currently exempt from the Schedule 5 listing.

1.12 OXALIC ACID

Scheduling proposal

The chemicals scheduling delegate considered a proposal to amend the current Schedule 6 oxalic acid entry to exempt from scheduling preparations containing 8 per cent or less oxalic acid for household and domestic cleaning.

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

The delegate referred the proposal to the ACCS as the submission sought amendment of the current Schedule 6 entry for oxalic acid, to exempt a specific range of cleaning products containing up to 8 per cent oxalic acid. The Scheduling Policy Framework (SPF) suggests that proposals for re-scheduling require advice from an advisory committee. Furthermore, the history of scheduling of oxalic acid is somewhat obscure and there appears to have been little or no contemporary consideration given to exempting products containing low concentrations of oxalic acid.

The delegate asked the following specific questions to the ACCS:

- The scheduling history for oxalic acid is not very informative. It was first listed in the (then) schedules Schedule 2 and Schedule 5 in May 1956, when the schedules were first being established. The original wording for these entries was:

  Schedule 2: *Substances which are dangerous to human life if misused or carelessly handled*

  OXALIC ACID and metallic oxides, except in laundry blue and polishes.

  Schedule 5: *Domestic poisons*

  OXALIC ACID AND METALLIC OXALATES IN POLISHES.

- There are no records of when the current Schedule 6 entry was promulgated. The only records of further consideration are in November 1985 when the (then) Schedule 6 entry was amended to clarify the status of sodium salts and in February 1986, when a submission to require child resistant closures was considered, and rejected. It appears that the intent of the original scheduling was to exempt some types of cleaning products, but this appears to have been lost during subsequent re-organisation of the schedules.

- The current submission seeks to exempt a range of cleaning products containing up to 8 per cent oxalic acid. The submission acknowledges that oxalic acid is systemically toxic, despite being formed as a normal metabolite within the body, with some dietary intake also contributing to oxalate concentrations in the body. Current label warning statement emphasise the corrosive potential associated with high concentrations of oxalic acid.

- Can the ACCS advise on whether a cut-off clause should be added to the current Schedule 6 entry (to either exempt or to Schedule 5) to address this submission seeking re-scheduling of cleaning products containing up to 8 per cent oxalic acid? If so, what specific wording changes to the current entry are suggested?

- Current SUSMP Appendix E First Aid statement emphasise the risks of skin, eye and respiratory irritancy. Are these still suitable for cleaning products containing up to 8 per cent oxalic acid?

- Current SUSMP Appendix F entries for oxalic acid require safety warning statement 2 (*corrosive*) and safety directions 4 (*attacks eyes – protect eyes when using*) and 8 (*avoid breathing dust (or) vapour (or) spray mist*) while the entry for metallic oxalates requires only safety directions 4 and 8. There is no record of when either the Appendix E or F entries were promulgated, and they appear inconsistent with the range of label warning statements used on the applicant's cleaning products sold overseas. Does the ACCS consider that the current Appendix E and F entries for oxalic acid should be modified, and are there different Appendix entries required if the recommendation is to down-schedule these cleaning products to Schedule 5?

- Can the ACCS advise on whether there might be inadvertent implications for other types of products containing oxalic acid if scheduling changes are recommended?

Substance summary

Oxalic acid is an odourless, colourless powder or granular solid that is slightly soluble in water[16]. It is present in many plants and vegetables, notably in those of the Oxalis and Rumex families, where it occurs in the cell sap of the plant as the potassium or calcium salt[17].

Oxalic acid is endogenously produced in humans and excreted at amounts of about 25 mg daily via urine. Normal concentrations of oxalates in plants were in the range of 5 to 200 000 mg/kg dry weight[18].

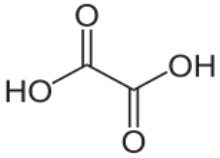

Figure 6. Structure of oxalic acid

Acute toxicity

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

Toxicity	Species	Oxalic acid	SPF* classification
Oral LD_{50} (mg/kg bw)	Rat	475 to 375	Moderate to high toxicity
Dermal LD_{50} (mg/kg bw)	Not supplied	Low toxicity	Unable to assess
Inhalational LC_{50} (mg/m^3/4h)	Not supplied	Not supplied	Unable to assess
Skin irritation	Not provided	Irritant	
Eye irritation	Not provided	Irritant	
Skin sensitisation	Not provided	Not provided	
Skin sensitisation	Non-sensitiser	Sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

The US EPA (2005) indicates that acute oral exposure (LD_{50} = 300 mg/kg in gravid rats and 7500 mg/kg in rats) in rats and dogs causes gastric haemorrhage, central nervous system depression, convulsion, coma and kidney damage in experimental animals.

The US EPA (1992) notes that it is corrosive to the eyes, skin and has been placed in Toxicity Category I (indicating the highest degree of toxicity) for acute eye and skin irritation effects. Moreover, oxalic acid is also highly irritating and damaging to the respiratory system if inhaled. Acute exposure also cause stomach irritation, lowered calcium levels, effects to the nervous system and kidney damage in humans. The Merck Index also indicates that oxalic acid is caustic and corrosive to the human skin and mucous membranes.

[16] The United States Environmental Protection Agency's (US EPA, 2005) Inert Reassessment - Oxalic Acid.
[17] The Merck Index (1996) An encyclopedia of chemicals, drugs and biologicals – 7043. Oxalic acid. Twelfth Edition, pp 10 330.
[18] European Agency for the Evaluation of the Medicinal Product's (EMEA, 2003) Oxalic acid summary report (EMEA/MRL/891/03-final).

Repeat-dose toxicity

In two studies, groups of male and female rats were fed diets supplemented with 0, 25 and 50 g/kg (equivalent to 0, 2000 and 5000 mg/kg bw/day) oxalic acid for 70 days. The high dose levels depressed the growth rate. This was accompanied by renal toxicity (increased water intake, increased kidney weight, abnormal gross appearance of kidneys at necropsy and stone formation) and reduced thyroid function. In a non-invasive screening test for the detection of renal disease, sodium oxalate administrated subcutaneously to rats at 25, 50 and 75 mg/kg bw/day for 2, 3 and 1 weeks respectively, caused mainly haematuria, with increase in the excretion into urine of white blood cells, epithelia and casts. Histopathological examination of kidneys indicated a small number of oxalate deposits in animals treated with sodium oxalate. The report indicated that these effects were indicative of a mild nephrotoxicity due to tubular obstruction following the administration of subcutaneous doses of oxalic acid greater than or equal to 25 mg/kg bw/day, for 5 days a week for 2 weeks.

The US EPA (1992) notes that a subchronic inhalation study in rats showed decreased body weights, restricted growth and disrupted oestrous cycles. At the highest dose, the test animals also had reduced thyroid weights and changes in iodine and hormone levels. Metabolism studies show that excess levels of oxalic acid cause kidney damage in mammals. Chronic oral intake in animals produces kidney damage and disturbances in the metabolism of calcium. A multi-generation mouse reproduction study showed reproductive effects and parental toxicity at the highest dose level.

Mutagenicity

There are no studies which address the mutagenic potential of oxalic acid *in vivo*. The negative results of the relevant *in vitro* studies and the data from a chronic toxicity study suggests that oxalic acid has no carcinogenic potential in rats. Therefore further mutagenic studies are not required for a risk assessment of residues of the compound.

Genotoxicity

The results of the various Ames test indicate that oxalic acid is clearly negative in the Salmonella typhimurium assay.

Carcinogenicity

In a carcinogenicity study, male and female rats were administered with 1000, 5000, 8000 and 12 000 ppm (corresponding to 50 to 600 mg/kg bw/day) of oxalic acid for 2 years. There were no effects of the treatment on body weight, body weight gain and food consumption during the first 52 weeks. There was no significant difference between the mortality rate at any dosage level in the treated groups and in the controls. The report indicated that within limitations of the study, which did not meet the criteria of current guidelines, there was no evidence of carcinogenicity in rats given approximately 50 to 600 mg/kg bw/day.

Reproduction and developmental toxicity

In a reproductive toxicity study, mice were exposed to dietary doses of 0, 0.05, 0.1 and 0.2 per cent (89, 162 and 275 mg/kg bw/day) oxalic acid. In the F0/F1 generations the number of litters in fertile pairs, live pup weight and prostate gland weight decreased significantly at 0.2 per cent in the diet, while all other parameters were unaffected. In the F1-generation the total number of live pups decreased, and prostate gland weight decreased significantly. Decreased water consumption was induced in the F1 0.1 and 0.2 per cent dose groups. Relative kidney weight of F2 females and the incidence of abnormal sperm in F2 males were increased. The report concluded that oxalic acid is a weak reproductive toxicant in mice at dose of 0.2 per cent in drinking water corresponding to about 275 mg/kg bw/day.

Oxalic acid did not induce overt teratogenic effects or postnatal toxicity. A no observed effect level (NOEL) was not determined since the data from the 0.05 and 0.1 per cent dose level groups were not recorded for the second generation.

Two teratogenicity studies were conducted in rats and sheep. In the rat study 10 females were administered with 0, 159, 205 mg/kg bw/day by gavage from day 7 post conception up to the day of parturition. Higher doses of 227 and 272 mg/kg bw/day had proven fatal within 7 days in a pilot study, while 136 mg/kg bw/day had led to marked vacuolation in cells of proximal tubules and tubular nephrosis in the pups. Neither gross malformation nor tubular nephroses was observed in offspring in the main study.

Observation in humans

Intravenous doses of 25 mg/kg bw oxalic acid inadvertently administered to human patients have led to kidney failure, cardiac arrest and death in spite of intensive care. High oral intake via a diet rich oxalic acid has also occasionally led to severe poisoning and deaths. Oral fatal doses of oxalic acid were reported to range from 3 to 30 g/person. The susceptibility of individuals varies greatly, depending on prior kidney damage, certain intestinal disease states or genetic abnormalities such as primary hperoxaluria.

Determination of individual oxalate intake of 3 volunteers maintaining food records over days suggest high average ingestion (152 ± 83 mg/day, range 44 to 351 mg/day) of normal consumers. On the basis of huge variations of oxalic acid content in the diet it may be assumed that occasional intake may reach and exceed 1 g/day, in particular in vegetarians. The report noted that it is believed, that similar to rodents and ruminants, bacterial decomposition of oxalic acid in the human intestine may largely increase with high prolonged oxalate exposure via diet, leading to reduced bioavailability and consequently lowered toxicity. Therefore adverse reactions are not common in humans in spite of daily intake occasionally reaching potentially dangerous levels.

Public exposure

The US EPA (1992) indicates that the potential for significant eye and dermal exposure exists when homeowners apply bathroom disinfectant products containing oxalic acid and other active and inert ingredients. These products are liquid and granular formulations applied using brushes, swabs or mops. Exposure, especially to the concentrated formulations, can cause chemical burns to the skin and severe to permanent damage to the eyes.

Although they contain only a small amount of oxalic acid and a much greater amount of other active and inert ingredients, oxalic acid products as formulated and registered for use as bathroom disinfectants can be highly irritating and damaging to the eyes, skin and mucous membranes. Exposure to the concentrated formulations can result in chemical burns to the skin and severe to permanent eye damage. However, these risks should be low as long as product label directions and precautions are followed.

International regulations

An internet search regarding international regulation of oxalic acid did not provide comprehensive information. Various Material Safety Data Sheets (MSDS) for products marketed in European Union have relevant label warning statements, such as ‘Harmful’, ‘Harmful in contact with skin and if swallowed’, ‘Keep out of reach of children’ and ‘Avoid contact with skin and eyes’. These MSDS also notes: “Classification and labelling have been performed according to EU directives 67/548/EEC, 88/379/EEC”.

Scheduling status

Oxalic acid is listed in Schedule 6, Appendices E and F.

SCHEDULE 6

OXALIC ACID **except** its derivatives and insoluble salts.

APPENDIX E

Poisons	Standard statements
Oxalic 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). E2 - If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes. G3 - If swallowed, do NOT induce vomiting. S1 - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

APPENDIX F

Poisons	Warning statements	Safety direction
Oxalic acid		1. Avoid contact with eyes. 4. Avoid contact with skin. 8. Avoid breathing dust (or) vapour (or) spray mist

Scheduling history

Oxalic acid was first considered in May 1956 by the Poisons Schedule Committee (PSC) and PSC decided to include oxalic acid and metallic oxalates in Schedule 5.

In November 1985, the PSC decided to amend the Schedule 6 oxalic acid entry to exempt its derivatives and insoluble salts from the Schedule 6 entry.

Pre-meeting public submissions

Four submissions were received.

The first submission requested that consideration of this proposal be broadened in such a way to exclude therapeutic mouthwash preparations containing less than 3 per cent of potassium oxalate.

The second submission noted that it did not object to the delegate's proposal in principle. The submission suggested that the current Schedule 5 listing of the oxalic acid entry should remain the same (i.e. "oxalic acid except its derivatives and insoluble salts") so that it excludes the oxalate salt of some registered medicines, such as escitalopram oxalate (which is in Schedule 4).

The third submission indicated that it supports the delegate's proposal to exempt from scheduling oxalic acid in domestic cleaning preparations containing 8 per cent or less oxalic acid. The

submission requested that the ACCS and the delegate consider exempting from scheduling dental products including mouthwashes containing 3 per cent or less of soluble salts of oxalic acid.

The fourth submission requested that mouth wash preparations, intended for use in the symptomatic relief treatment of sensitive teeth, containing up to 3 per cent of oxalic acid's salt potassium oxalate be exempted from scheduling.

ACCS advice to the delegate

The ACCS recommended that the current scheduling of oxalic acid remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (c) the toxicity of a substance. The reasons for the recommendation comprised the following:

- Insufficient evidence to change the scheduling of the chemical.

Delegate's interim decision

The delegate confirms that the toxicity profile of oxalic acid is consistent with SPF Schedule 6 criteria and accepts ACCS advice that the current listing of oxalic acid in Schedule 6 remains appropriate. The label signal heading, First Aid statements (Appendix E), Safety Directions and Warning Statements (Appendix F) remain appropriate for the type of cleaning products in the re-scheduling submission. The delegate also notes ACCS advice that the available information is insufficient to develop an exemption threshold for the Schedule 6 entry at this time. The delegate notes the proposals in public submissions that scheduling therapeutic goods containing oxalates is not appropriate, but concludes that the current entry (excepting derivatives and insoluble salts) should not apply to derivatives used in medicines. The matter of providing an exemption threshold for the use of soluble oxalates in mouthwashes requires further consideration and it will be referred back to a future meeting of the ACCS/ACMS.

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 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[19];
- Other relevant information.

Public submissions on the interim decision

One submission was received. The submission indicated that mouthwash preparations containing potassium oxalate is currently marketed in the UK and several other European countries as a Class

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

IIa medical device for dental sensitivity. It requested that consideration be given to specifically exempt from scheduling for mouthwash preparations containing oxalic acid and if deemed necessary with an appropriate concentration cut-off to enable this preparation to be supplied in Australia.

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

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 current Schedule 6 listing for oxalic acid in relation to its use in cleaning products. The delegate has confirmed that the reasons for the final decision are in keeping with those for the interim decision.

However, the delegate also confirms the need to consider whether mouthwashes or other therapeutic goods containing soluble oxalates should be captured by the current entry. In accordance with SPF guidance that such re-scheduling matters be referred to an advisory committee, and that advice on this matter was not provided by the ACCS, the delegate proposes to refer this specific issue back to a joint meeting of the ACCS/ACMS.

1.13 PPG-1-PEG-9 LAURYL GLYCOL ETHER OR GLYCOLS, 1,2-, C12-16, ETHOXYLATED PROPOXYLATED

Scheduling proposal

On 29 August 2013, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under its New Chemicals Assessment process, requested that the delegate consider a proposal to include PPG-1-PEG-9 lauryl glycol ether in Schedule 5 and Appendix F.

The basis for this recommendation is that:

- PPG-1-PEG-9 lauryl glycol ether is a slight to moderate skin and eye irritant therefore the substance meets the factors in the Scheduling Policy Framework (SPF) for Schedule 5.
- Repeat dose toxicity data indicate PPG-1-PEG-9 lauryl glycol ether is unlikely to produce irreversible toxicity therefore the substance meets the factors in the SPF for Schedule 5.

This proposal was first notified to the delegate in September 2013 at which time it was determined that expert advisory committee advice may not be required for this proposal. However, due to the complexity of the proposal, expert advice on this substance is being sought.

The delegate considered that although this is a reasonably straightforward proposal to create a parent entry for this chemical polymer in Schedule 5, with appropriate exemption for low concentration products, it requires ACCS advice in relation to whether scheduling is the most appropriate control mechanism, and what cut-offs to apply if the chemical is to be listed.

The delegate asked the following specific questions:

- The chemical has a relatively low acute and chronic toxicity profile, with minimal skin/eye irritancy and no evidence of sensitisation potential. Public exposure is only likely to occur through its use as an emulsifier for fragrances in cosmetic products. Does the ACCS consider that listing in the SUSMP is appropriate? If so, is Schedule 5 the most appropriate?
- The proposed use pattern suggests that 2-3 per cent is the likely concentration in products, but 10 per cent is the possible maximum level. At these concentrations, the polymer appears to be sufficiently non-toxic to warrant exemption from Schedule 5. If the ACCS recommends

inclusion of the pure chemical in a schedule, does the ACCS support a cut-off concentration to exempt at 10 or 3 per cent?

- The Margin of Exposure calculations suggest that the estimated maximum daily dose (3.8 mg/kg/d) for products containing 10 per cent is well within the rat 90-day NOAEL of 80 mg/kg/d, although less than 100. Does this add support for an exemption cut-off of 10 per cent?
- If scheduled, what name should be used in the listing – the INCI name of PPG-1-PEG-9 lauryl glycol ether, or the chemical name - glycols, 1,2-, C12-16, ethoxylated propoxylated?
- If the ACCS recommends inclusion in a Schedule, does the toxicity profile warrant development of entries in either Appendices E or F?

Substance summary

PPG-1-PEG-9 lauryl glycol ether will be used as a component of cosmetic products at up to 10 per cent concentration (with a typical usage concentration of 2-3 per cent). PPG-1-PEG-9 lauryl glycol ether is intended for use as a fragrance emulsifier and will therefore be used in cosmetic products that require addition of a fragrance.

The finished products containing PPG-1-PEG-9 lauryl glycol ether (at up to 10 per cent concentration) may be used by consumers and professionals such as hairdressers or beauty salon workers. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or by spray.

Acute toxicity

The acute toxicity end-points for the chemical are listed in the below table.

Toxicity	Species	PPG-1-PEG-9 lauryl glycol ether	SPF* classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	2560	Schedule 5 classification
Acute dermal toxicity LD_{50} (mg/kg bw)	Not provided	Not provided	Unable to assess
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbit	Slight irritant	
Eye irritation	Rabbit	Slight irritant	
Skin sensitisation (non-adjuvant test)	Guinea pig	Non-sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

Repeat-dose toxicity

Repeated dose toxicity information on PPG-1-PEG-9 lauryl glycol ether was not provided. Upon repeated oral (gavage) exposure of rats (90 day exposure period) to an analogue polymer, the NOAEL was established by the authors as 80 mg/kg bw/day, based on the main findings (at the high dose, 150 mg/kg bw/day) of lesions present in the stomachs at histopathology, reduced weight

gain and reduction in food intake, in combination with findings such as nasal respiratory epithelium lesions and organ weight effects (in-particular on the kidneys, thymus and spleen). While effects were noted at lower doses (50 and 80 mg/kg bw/day; especially the effects on the nasal respiratory epithelium), they were considered by the study authors to be due to a local irritant effect of the analogue polymer and/or were not considered to be adverse at the lower dosage levels.

Mutagenicity

PPG-1-PEG-9 lauryl glycol ether was reportedly not mutagenic in a bacterial reverse mutation test in the presence and absence of metabolic activation.

Genotoxicity

No information provided.

Carcinogenicity

No information provided.

Reproduction and developmental toxicity

A reproduction test on Daphnia magna using 0.15, 0.47, 1.5, 4.8 and 15.4 mg/L of PPG-1-PEG-9 lauryl glycol ether did not have long lasting harmful effects on aquatic invertebrates.

Observation in humans

No information provided.

Public exposure

The general public will be repeatedly exposed to PPG-1-PEG-9 lauryl glycol ether during the use of cosmetic products containing PPG-1-PEG-9 lauryl glycol ether (proposed to be used at up to 10 per cent concentration, noting that the typical usage concentration will be 2-3 per cent).

Local effects

Based on the information available, PPG-1-PEG-9 lauryl glycol ether is considered to be a skin and eye irritant. However, PPG-1-PEG-9 lauryl glycol ether will be present in cosmetic products at concentrations ≤10 per cent, skin and eye irritation effects are considered much less likely. Based on the limited available repeated dose toxicity data on an analogue polymer, the risk of adverse nasal irritancy effects cannot be ruled out.

Systemic effects

The potential systemic exposure to the public from the use of PPG-1-PEG-9 lauryl glycol ether in cosmetic products was estimated to be 3.80 mg/kg bw/day. Using a NOAEL of 80 mg/kg bw/day, which was derived from a repeated dose toxicity study on an analogue polymer, the margin of exposure (MOE) was estimated to be 21. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences, therefore, the MOE is considered to be unacceptable.

Reducing the concentration of PPG-1-PEG-9 lauryl glycol ether in leave-on cosmetic products to 2 per cent and in rinse-off products to 3 per cent gives a recalculated combined internal dose of 0.78 mg/kg bw/day. An acceptable MOE of 102 is then estimated.

Therefore, based on the information available, the risk to the public associated with the use of PPG-1-PEG-9 lauryl glycol ether at ≤2 per cent in leave-on cosmetic products and ≤3 per cent in rinse-off cosmetic products is not considered to be unreasonable.

International regulations

No international regulations identified.

Scheduling status

PPG-1-PEG-9 lauryl glycol ether is not specifically scheduled.

Scheduling history

PPG-1-PEG-9 lauryl glycol ether has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

Two submissions were received.

One submission questioned the basis for NICNAS's proposed restrictions on the substance and indicated that there is no need to schedule this substance. The toxicity profile and its use pattern does not warrant a schedule listing, particularly when only a maximum of 1000kg of the polymer is allowed in Australia per year. The submission asserted that if scheduling is deemed necessary, it should align with other scheduled surfactants such as sodium lauryl sulfate.

The second submission indicated that PPG-1-PEG-9 lauryl glycol ether is listed in TGA eBS website, with the synonym Eumulgin LG. The concentration of this ingredient is not to exceed 5 per cent in the final finished product and is not to be included in topical products intended for use on the eye. The compound is also found in the International Cosmetic Ingredient Dictionary as an emulsifying agent/surfactant. The submission requested that, if the delegate decides to schedule the substance, therapeutic preparations containing the substance be excluded from the schedule listing.

ACCS advice to the delegate

The ACCS recommended that that PPG-1-PEG-9 lauryl glycol ether does not require a schedule listing.

The reasons for the recommendation comprised the following:

- Low toxicity profile coupled with the use pattern does not warrant scheduling control.

Delegate's interim decision

The delegate accepts ACCS advice that PPG-1-PEG-9 lauryl glycol ether does not require a schedule listing.

The delegate notes that the ACCS considered the NICNAS calculation deriving a Margin of Exposure (MoE) of 21 to be overly conservative. The MoE was based on exposure estimates from simultaneous multiple product use, it used a reduced dermal absorption factor (15.6 per cent), partly based on read-across from a different lauryl glycol ether, and the NOAEL used was from a 90-day rat study with an analogue glycol ether. The delegate also notes ACCS advice that other PPG-1-PEG-9 lauryl ether analogues (none of which are scheduled in the SUSMP) have been used widely in cosmetic and other products (including therapeutic goods) for some time without apparent adverse health effects. The delegate notes that the slight skin/eye irritancy potential and low acute oral toxicity are consistent with SPF criteria for listing in Schedule 5, but concludes that public health concerns associated with proposed uses in products at quite low concentrations are insufficient to warrant scheduling the chemical.

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

substance is to be used and the extent of use of a substance, c) the toxicity of a substance and d) the dosage, formulation, labelling, packaging and presentation of a substance.

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[20];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

Delegate's final decision

The delegate 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 4,4-DIMETHYL-1-CYCLOHEXENE-1-PROPANAL

Scheduling proposal

On 29 August 2013 the National Industrial Chemicals and Notification Assessment Scheme (NICNAS), under its New Chemicals Assessment process, requested that the delegate consider a proposal to include 4,4-dimethyl-1-cyclohexene-1-propanal in Schedule 6 and Appendix F.

The reasons for this request are:

- 4,4-dimethyl-1-cyclohexene-1-propanal has moderate to high acute oral toxicity which may cause death or severe injury if taken internally which meets the Scheduling Policy Framework's (SPF) Schedule 6 factors.
- It is a severe eye irritant with corneal opacity noted in all treated eyes which meets the factors in the SPF for Schedule 6.
- It is a moderate to severe skin sensitiser which meets the factors in the SPF for Schedule 6.
- A quantitative risk assessment determined that the risk from repeated exposure to the chemical, skin irritation, eye irritation and skin sensitisation is acceptable at concentrations no more than 1.0 per cent in fine fragrances, 0.1 per cent in other leave-on cosmetic products, 0.5 per cent in rinse-off cosmetic products and 0.9 per cent in household products.

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

This proposal was first notified to the delegate in September 2013 at which time it was determined that expert advisory committee advice may not be required for this proposal. However, due to the complexity of the proposal, expert advice on this substance is being sought.

The delegate considered that while the NICNAS evaluation report proposes listing this new chemical in Schedule 6, ACCS advice is needed on whether inclusion in the SUSMP is the most appropriate control measure, given its proposed use in low concentrations in fragrances, cosmetics and household products.

The delegate asked the following questions:

- Given the relatively moderate toxicity profile of this chemical, and the fact that public exposure is only likely to occur through its use as a fragrance in cosmetic and household cleaning products containing up to 5 per cent, does the ACCS consider that listing in the SUSMP is appropriate? If so, in which schedule should it be listed, and can the ACCS recommend a low cut-off concentration to exempt?

- Noting that the pure chemical is a skin/eye irritant and a potential sensitiser, but there is limited information on these toxicities at the low concentrations proposed for consumer products, is this toxicity potential sufficient to warrant inclusion of the substance in Schedule 6? Are Appendix E & F statements required?

Substance summary

The substance is intended to be used as a component of fragrances for a variety of cosmetic and household products (proposed usage concentration: ≤1.15 per cent concentration in fine fragrances, ≤2.5 per cent in other cosmetic products and ≤5 per cent in household products).

The finished products containing the substance may be used by consumers and professionals such as hairdressers, workers in beauty salons or cleaners. Depending on the nature of the product, these could be applied in a number of ways, such as by hand, using an applicator or sprayed.

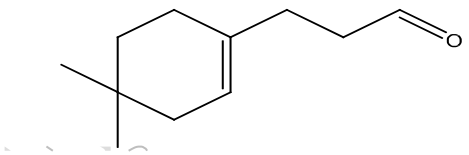

Figure 7. Structure of 4,4-dimethyl-1-cyclohexene-1-propanal

Acute toxicity

The acute toxicity end-points for the chemical are listed in the below table.

Toxicity	Species	4,4-dimethyl-1-cyclohexene-1-propanal	SPF* classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	300 - 2000	Consistent with Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	>2000	Consistent with Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	Unable to assess
Skin irritation	Rabbits	Irritant	
Eye irritation	Rabbits	Severe irritant	
Skin sensitisation (local lymph node assay)	Mice	Sensitiser	

*Scheduling Policy Framework for Medicines and Chemicals (2010)

Repeat-dose toxicity

A 28-day repeat-dose study by oral gavage was conducted in rats. There were no overt clinical signs of toxicity noted for animals at up to 300 mg/kg bw/day. However, organ weight and histopathological changes were noted in animals treated at this dose.

There were no treatment related macroscopic findings in any organ at necropsy. However, absolute and relative liver and kidney weights were increased in males in the low, mid and high dose groups and females in the high dose group only. While liver weights returned to normal following the recovery period, kidney weights remained elevated for males receiving 300 mg/kg bw/day (the only dose measured in the recovery group). The organ weight effects in both sexes to be non-adverse due to increased water intake, resulting in an adaptive response in organ weights.

Gastro-intestinal tract lesions and inflammation were noted in males receiving 300 mg/kg bw/day. Chronic ulceration was also noted at the conclusion of the study (following the recovery period) in one animal. These effects were attributed to 4,4-dimethyl-1-cyclohexene-1-propanal. Based on the adverse gastro-intestinal results of this study, a no observed adverse effect level (NOAEL) of 150 mg/kg bw/day was derived.

Mutagenicity

4,4-dimethyl-1-cyclohexene-1-propanal was not mutagenic in a bacterial reverse mutation study and was not clastogenic in an *in vitro* mammalian chromosome aberration test.

Genotoxicity

4,4-dimethyl-1-cyclohexene-1-propanal was a not genotoxic in *in vitro* mammalian chromosome aberration.

Carcinogenicity

No information provided.

Reproduction and developmental toxicity

No information provided.

Observation in humans

Irritation

An *in vitro* skin irritation study conducted using a reconstituted human epidermis model (EpiSkin), indicated that 4,4-dimethyl-1-cyclohexene-1-propanal was borderline non-irritating.

An *in vitro* eye irritation study conducted using a reconstituted human corneal epithelium model (SkinEthic) indicated that 4,4-dimethyl-1-cyclohexene-1-propanal was non-irritating to the eyes.

Public exposure

Repeated-dose toxicity

Members of the public may experience repeated exposure to 4,4-dimethyl-1-cyclohexene-1-propanal (at ≤5 per cent concentration) through the use of the cosmetic and household products. The principal route of exposure will be dermal. Ocular and inhalation exposure is also possible, particularly if products are applied by spray.

The repeat-dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of 4,4-dimethyl-1-cyclohexene-1-propanal using the worst case exposure scenario from use of multiple products of 7.3 mg/kg bw/day and the NOAEL of 150 mg/kg bw/day, which was established in a 28-day repeated dose toxicity study on 4,4-dimethyl-1-cyclohexene-1-propanal. A MoE value ≥300 is considered acceptable to account for intra- and inter-species differences, and to account for long-term exposure (noting that the NOAEL was derived from a 28-day study). Using the abovementioned NOAEL, a MoE of 21 was estimated, which is considered to be unacceptable.

Reducing the concentration of 4,4-dimethyl-1-cyclohexene-1-propanal in fine fragrances to 1.0 per cent, all other leave-on cosmetic products to 0.1 per cent, rinse-off cosmetic products to 0.5 per cent and household products to 0.9 per cent allows recalculation of the combined internal dose to 0.5 mg/kg bw/day. An acceptable MoE of 300 is then estimated.

Irritation

4,4-dimethyl-1-cyclohexene-1-propanal is considered to be a skin irritant and cause serious damage to eyes. Skin irritation effects are not expected from use of the notified chemical at the revised (lowered) concentrations in cosmetic and household products. However, the potential for eye irritation (namely, from use of household products and fine fragrances, which will contain a higher concentration of the notified chemical) is of concern.

Ocular exposure is only expected to occur in the unlikely event of an accident, and, in the case of household products, the products may be diluted with water at the time of eye contact. The potential for eye irritation may be further minimised by the inclusion of appropriate labelling and directions for use to warn against eye contact.

Sensitisation

4,4-dimethyl-1-cyclohexene-1-propanal is considered to have the potential to cause skin sensitisation. Methods for the quantitative risk assessment of dermal sensitisation have been proposed and been the subject of significant discussion. Using a fine fragrance (containing 1.0 per cent notified chemical) as an example product that may contain 4,4-dimethyl-1-cyclohexene-1-

propanal, as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 37.5 µg/cm2. When tested in an LLNA study, 4,4-dimethyl-1-cyclohexene-1-propanalwas a skin sensitiser with an EC3 value of 54.6 per cent. Consideration of the study details and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 41.8 µg/cm2. In this instance, the factors employed included an inter-species factor (3.16), intra-species factor (10), a matrix factor (3.16) and a use and time factor (3.16), giving an overall safety factor of >300 (300 used for calculations).

As the AEL>CEL, the risk to the public of the induction of sensitisation that is associated with the use of fine fragrances (a worst case example of a leave-on cosmetic product) at ≤1.0 per cent concentration is not considered to be unreasonable. Based on the significantly lower expected exposure level from other leave-on cosmetic products (containing ≤0.1 per cent 4,4-dimethyl-1-cyclohexene-1-propanal), rinse-off products (containing ≤0.5 per cent 4,4-dimethyl-1-cyclohexene-1-propanal) and household products (≤0.9 per cent of 4,4-dimethyl-1-cyclohexene-1-propanal), by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing 4,4-dimethyl-1-cyclohexene-1-propanal and a quantitative assessment based on the aggregate exposure has not been conducted.

Therefore, based on the information available, the risk to the public associated with the use of 4,4-dimethyl-1-cyclohexene-1-propanal at ≤1.0 per cent in fine fragrances, ≤0.1 per cent in other leave-on cosmetic products, ≤0.5 per cent in rinse-off cosmetic products and ≤0.9 per cent in household products, is not considered to be unreasonable.

International regulations

A search on the internet did not provide any information on the international regulation of 4,4-dimethyl-1-cyclohexene-1-propanal or the substance.

Scheduling status

4,4-dimethyl-1-cyclohexene-1-propanal is not specifically scheduled.

Scheduling history

4,4-dimethyl-1-cyclohexene-1-propanal has not been previously considered for scheduling therefore scheduling history is not available.

Pre-meeting public submissions

Two submissions were received.

One submission questioned the dermal absorption value used in the NICNAS assessment report (i.e. 100 per cent dermal absorption was assumed), and the use of the worst case scenario i.e. the use of 4,4-dimethyl-1-cyclohexene-1-propanal by a single person in maximum concentrations in 10 product types (body lotion, face cream, hand cream, fine fragrances, deodorant spray, shampoo, conditioner, shower gel, hand soap and hair styling products). Further, the submission argued that the use of 300 as the acceptable Margin of Exposure (MoE) value for 4,4-dimethyl-1-cyclohexene-1-propanal when 100 was used for PPG-1-PEG-9 lauryl glycol ether. The submission requested that the ACCS and the delegate to determine whether the methods and data used by NICNAS to derive the acceptable use pattern of 4,4-dimethyl-1-cyclohexene-1-propanal is appropriate. If the ACCS and delegate consider it is necessary to schedule 4,4-dimethyl-1-cyclohexene-1-propanal, a further consultation which includes the proposed exemption cut-off from scheduling is required.

The second submission indicated that 4,4-dimethyl-1-cyclohexene-1-propanal is used as a fragrance in cosmetic and household products. The submission also indicated that 4,4-dimethyl-1-cyclohexene-1-propanal is not appears to be listed on the ingredient list of the ARTG.

ACCS advice to the delegate

The ACCS recommended that preparations containing more than 1 per cent of 4,4-dimethyl-1-cyclohexene-1-propanal/4,4-dimethyl-1-cyclohexene-1-propanal, be listed in Schedule 6 and that the substance requires inclusion in Appendix E and F.

The ACCS recommended an implementation date of 1 October 2014.

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

The reasons for the recommendation comprised the following:

- Toxicity profile (skin sensitisation, eye irritation and acute oral toxicity) consistent with criteria of Schedule 6 above 1 per cent.

Delegate's interim decision

The delegate accepts ACCS advice that 4,4-dimethyl-1-cyclohexene-1-propanal should be listed in Schedule 6. While the acute toxicity profile (oral and dermal lethal dose estimates) is reasonably low, the severe eye-irritancy is consistent with SPF criteria for Schedule 6. This is reinforced by evidence of sensitisation potential (categorised as weak with EC3 value of 54.6 per cent).

The delegate notes that NICNAS has calculated Margin of Exposure (MoE) estimates for systemic toxicity based on conservative exposure factors and using an additional 3x factor to account for the limited data on repeated dose toxicity (NOAEL of 150 mg/kg bw/d in a 28 day study in rats). The delegate notes the point made in a public submission that such an additional factor was not used in estimating the MoE for another chemical considered by the ACCS at the meeting (where a the NOAEL from a 90-day rat study was used), but the delegate accepts that inclusion of the additional 3x factor is consistent with standard toxicological practice and reasonable in these circumstances. The NICNAS MoE estimate of 21 based on multiple product exposure and the highest estimated product concentrations was considered unacceptable. Considering both the risk assessment calculations for both sensitisation and systemic toxicity, NICNAS estimated that an acceptable MoE could only be achieved where the concentration of 4,4-dimethyl-1-cyclohexene-1-propanal was restricted to 0.9 per cent in household products, 0.5 per cent in rinse-off cosmetics and 0.1 per cent in leave-on cosmetics.

Accordingly, while the delegate accepts ACCS advice that a cut-off to exempt at 1 per cent would be reasonable for most products, the delegate proposes lower cut-offs for cosmetic products, as recommended in the NICNAS report.

Since there may already be products containing 4,4-dimethyl-1-cyclohexene-1-propanal on the Australian market, the delegate proposes a longer implementation time (1 July 2015) to allow for product-re-labelling and for more extensive consultation on the proposed exemption cut-offs.

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

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[21];
- Other relevant information.

Public submissions on the interim decision

No public submissions were received.

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 confirms the longer implementation time (1 July 2015) to allow for product-re-labelling, since there may already be products containing 4,4-dimethyl-1-cyclohexene-1-propanal on the Australian market.

Schedule entry

Schedule 6 – New Entry

4,4-DIMETHYL-1-CYCLOHEXENE-1-PROPANAL **except**:

(a) in leave-on cosmetic preparations containing 0.1 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal;

(b) in rinse-off cosmetic preparations containing 0.5 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal; or

(c) in other preparations containing 1 per cent of less of 4,4-dimethyl-1-cyclohexene-1 propanal.

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

Appendix E, Part 2 – New Entry

Poisons	Standard statements
4,4-Dimethyl- 1-cyclohexene-1-propanal	A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). E2 - If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.

Appendix F, Part 3 – New Entry

Poisons	Warning statements	Safety direction
4,4-Dimethyl-1-cyclohexene-1-propanal	5. Irritant. 28. (Over) (Repeated) exposure may cause sensitisation.	1. Avoid contact with eyes. 2. Avoid contact with skin.

Part B - Final decisions on matters not referred to an expert advisory committee

2. Agriculture and Veterinary Chemicals

2.1 PROPOXUR

Scheduling proposal

In June 2014, the Australian Pesticides and Veterinary Medicines Authority (APVMA) through the Agriculture and Veterinary Chemicals Assessment Team (AVCAT) of the Office of Chemicals Safety (OCS) indicated the Secretariat that:

- The current propoxur Schedule 5(d) entry does not specify the concentration ratio that should be present in a spray pack containing propoxur. As the concentration ratio is not provided, it is not clear whether the propoxur concentration in the spray pack should be g/kg or % and therefore this entry needs clarification.

Substance summary

Propoxur is a non-systemic insecticide which was introduced in 1959. Propoxur is not used on food crops. It is used against mosquitoes in outdoor areas, for flies in agricultural settings, for fleas and ticks on pets, as an acaricide, on lawns and turf for ants, on flowering plants, and in private dwellings and public buildings. It is also used as a molluscicide. It is effective against cockroaches, aphids and leafhoppers[22, 23].

Propoxur is one of the chemicals that have, to a large extent, replaced DDT in the control of black flies and mosquitoes. It is a nonsystemic insecticide with contact and stomach action that has longstanding residual poisonous or toxic activity when it is in direct contact with the target pest. Many formulations are available including ready-to-use liquids and aerosols, emulsifiable concentrates, wettable powders, granular baits, dusts and impregnated pet collars and strips.

Propoxur is one of a family of carbamate insecticides. These chemicals block the production and action of cholinesterase, an essential nervous system enzyme. These materials quickly paralyze the nervous systems of insects, gaining them a reputation of having a rapid "knockdown" effect.

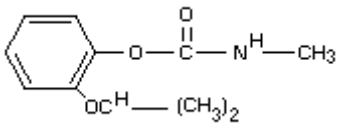

Figure 8. Structure of propoxur

[22] Propoxur (Baygon), Technology Transfer Network. United States Environmental Protection Authority. Available at [http://www.epa.gov/ttn/atw/hlthef/propoxur.html]
[23] Propoxur, Pesticide Information Network, Extension Toxicology Network. Available at [http://pmep.cce.cornell.edu/profiles/extoxnet/metiram-propoxur/propoxur-ext.html]

Acute toxicity

No toxicity studies have been provided. Secretariat has obtained the following information from the World Health Organisation's report on propoxur[24].

The acute toxicity end-points for this chemical are listed in the below table.

Toxicity	Species	Propoxur	SPF* classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	89.7	Moderate to high toxicity
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	> 5000	Low toxicity
Acute inhalational toxicity LC_{50} (mg/m^3)	Rat	654	Moderate to high toxicity
Skin irritation	Rabbit	Non-irritant	
Eye irritation	Rabbit	Minor-irritant	
Skin sensitisation (Magnusson and Kligman test)	Guinea pig	Non-sensitiser	

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

Repeat dose toxicity

Not provided. Secretariat has obtained the following information, including mutagenicity, carcinogenicity and reproduction toxicity, from the United States Extension Toxicology Network's report on propoxur[25].

Prolonged or repeated exposure to propoxur may cause symptoms similar to acute effects. Propoxur is very efficiently detoxified (transformed into less toxic or practically nontoxic forms), thus making it possible for rats to tolerate daily doses approximately equal to the LD_{50} of the insecticide for long periods, provided that the dose is spread out over the entire day, rather than ingested all at once.

Mutagenicity

No information provided.

Propoxur did not cause mutations in six different types of bacteria. The evidence indicates that propoxur is not mutagenic.

Genotoxicity

No information provided.

Carcinogenicity

No information provided.

[24] Propoxur. WHO specifications and evaluations for public health pesticides. Available at [http://www.who.int/whopes/quality/en/propoxur_eval_spec_WHO_October_2005.pdf]
[25] Propoxur, Extension Toxicology Network, Pesticide Information Profiles. Available at [http://extoxnet.orst.edu/pips/propoxur.htm]

Reproduction and developmental toxicity

No information provided.

In female rats given high dietary doses of approximately 18 mg/kg bw/day of propoxur as a part of a three-generation reproduction study, reduced parental food consumption, growth, lactation, and litter size were observed. At 25 mg/kg bw/day administered to pregnant rats there was a decrease in the number of offspring. Dietary doses of approximately 2.25 mg/kg bw/day did not affect fertility, litter size, or lactation, but parental food intake and growth were depressed in the exposed group. This evidence suggests that reproductive effects in humans are unlikely at expected exposure levels.

Observation in humans

No information provided. Secretariat obtained the following information from the International Program on Chemical Safety (IPCS).[26].

In a study undertaken to develop an oral administration of 110 and 116 mg/person produced no signs of illness. The level of urinary phenols reached 140 ppm in the absence of clinical signs of poisoning.

In persons engaged in spraying or other occupation exposure, urinary levels of 80 ppm are uniformly associated with illness.

In another study, 135 mg/person was administered to a male volunteer (1.5 mg/kg bw) and within 20 minutes after ingestion described clinical signs of poisoning due to the carbamate. Significant erythrocyte cholinesterase depression was evident coinciding with clinical signs of poisoning, while plasma cholinesterase depression was not observed. Two hours after the ingestion of propoxur, there were no signs of poisoning and the rapid disappearance of symptoms was consistent with the rapid recovery of erythrocyte cholinesterase activity. Absorption and excretion of propoxur was very rapid as evidenced by measurement of urinary phenols which reached a maximum value within four hours of almost 200 ppm. Of the total phenol content excreted, 81% was found within five hours after administration. In another experiment, a single dose of 0.36 mg/kg again produced a rapid fall of erythrocyte cholinesterase to 57% of normal within 10 minutes. Cholinesterase recovered to its normal value within three hours. Within 10 minutes of the administration of propoxur, short-lasting stomach discomfort, blurred vision, and moderate facial redness and sweating were evident in the volunteer.

A number of experiments were carried out to study the effect of storage or build-up of propoxur in the body. Human volunteers took doses of either 0.15 or 0.2 mg/kg at half-hour intervals for a total of five doses. In each subject a symptomless depression of erythrocyte cholinesterase to about 60% of normal was observed. At the cessation of dosing, enzyme recovery was rapid, being complete within two hours. Similarly pronounced and as a rule symptomless daily depression and reactivation of cholinesterase was observed in persons who are occupationally exposed to propoxur. Studies in humans have shown that depression of erythrocyte cholinesterase (rather than plasma cholinesterase) is a significant indicator of exposure to propoxur.

Public exposure

Not provided. Secretariat has obtained the following information from the Centers for Disease Control and Prevention's website.[27].

[26] Propoxur, JMPR 1973. Available at [http://www.inchem.org/documents/jmpr/jmpmono/v073pr19.htm]
[27] Bio monitoring Summary, Carbamade insecticides – Propoxur, Centers for Disease Control and Prevention. Available at [http://www.cdc.gov/biomonitoring/Propoxur_BiomonitoringSummary.html]

General population exposure to propoxur through the diet is likely to be limited because of usage restrictions. Estimated human intakes have been below recommended intake limits. Pesticide applicators are likely to have the highest exposures. Propoxur can be absorbed through the skin, lungs, and gastrointestinal tract. Propoxur does not accumulate in blood or tissues and is eliminated rapidly from the body.

International regulations

Not provided. Secretariat has obtained the following information.

In the US, the use of currently registered products containing propoxur in accordance with approved labeling will not pose unreasonable risks of adverse effects to humans.

Scheduling status

Propoxur is currently listed in Schedules 5 and 6.

SCHEDULE 5

PROPOXUR:

(a) when impregnated in plastic resin strip material containing 10 per cent or less of propoxur;

(b) in dust preparations containing 3 per cent or less of propoxur;

(c) in granular sugar-based fly baits containing 1 per cent or less of propoxur, a dark colouring agent and a separate bittering agent;

(d) in pressurised spray packs containing 10 g or less of propoxur; or

(e) in printed paper sheets for pest control containing 0.5 per cent or less of propoxur and in any case not more than 100 mg of propoxur per sheet.

SCHEDULE 6

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

Scheduling history

Propoxur was first considered by the Poisons Schedule Sub-committee (PSC) in August 1974 when it was included in Schedule 6. In August 1975, the PSC decided based on the toxicity profile of propoxur to list dust preparations containing 3% or less of propoxur in Schedule 5 and all other preparations containing propoxur in Schedule 6.

In February 1978, the PSC considered an application to reschedule preparations containing 20% or less of propoxur from Schedule 6 to Schedule 5. The PSC decided not to reschedule propoxur due to insufficient information on the safety of the concentration level had been provided.

In November 1979, the PSC decided to create a Schedule 2 entry for preparations containing propoxur intended for external human therapeutic use. At this meeting, the PSC also considered an application to amend the Schedule 5 entry to include aerosol preparations containing 2% or less of propoxur and rejected this request.

In November 1981, the PSC decided to amend the Schedule 5 entry to include granular sugar-based fly baits containing 1% or less of propoxur. This amendment was based on the conditions that the preparation must also contains a dark colouring agent and a separate bittering agent.

In August 1983, the PSC considered a re-scheduling request, this time included with 2-year rat, dog and mouse studies, for surface sprays containing 20 g/L of propoxur. It was proposed to be included

in Schedule 5. The committee decided to support the proposal and the Schedule 5 entry was amended to include: c) in aerosol packs containing 10 g or less of propoxur.

In November 1983, the PSC decided to include propoxur in Schedule 4.

In February 1985, the PSC decided to amend the Schedule 5 entry to include printed paper sheets for pest control containing 0.5% or less of propoxur and in any case not more than 100 mg of propoxur.

In November 1986, the Drugs and Poisons Scheduling Sub-committee (DPSC) decided to include propoxur in Appendix E with a statement 'If sprayed on skin, wash thoroughly. If sprayed in mouth, give milk or water'.

In August 1995, the National Drugs and Poisons Schedule Committee (NDPSC) noted that the then new acute oral LD_{50} studies in rat for propoxur, not previously considered by NDPSC, indicated an oral LD_{50} of 39 mg/kg, somewhat less than the previous LD_{50} of 90 mg/kg. Based on this information, the NDPSC foreshadowed a decision to move Schedule 6 entry to Schedule 7 and decided to delete the Schedule 6 entry. The NDPSC also decided to review the Schedule 5 listing.

In May 1996, the NDPSC decided to amend the Schedule 5 entry to include 'when impregnated in plastic resin strip material containing 10 per cent or less of propoxur'.

In May 1999, the NDPSC decided to delete the Schedule 4 entry.

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[28];
- Other relevant information.

Delegate-only final decision

The current wording of clause (d) in the Schedule 5 entry for propoxur allows pressurised spray products to contain up to 10g of propoxur, without specifying the pack size or the final concentration. The scheduling history relating to this clause is unclear, however it would appear to allow any pressurised spray product containing 10g propoxur or less in Schedule 5, irrespective of the pack size of concentration of active ingredient. Given the toxicity profile of propoxur, this is clearly inappropriate and an unintended outcome of a previous scheduling decision. Accordingly, the delegate proposes to make an editorial amendment to clause (d) to restrict the concentration of propoxur to 2%. This will have no regulatory impact on an existing product in the APVMA Pubcris list and ensures that any future pressurised spray product conforms to the SPF toxicological criteria for Schedule 5.

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

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 a substance.

Schedule entry

Schedule 5 – Amendment

PROPOXUR – Amend entry to read:

d) in pressurised spray packs containing 2 per cent ~~10 g~~ or less of propoxur; or